Appendix 1. Overview of all CAs, CECs and LECs consulted

Country	CA/CEC/LEC	CA address / CE address / LEC address	Tel Number	Fax Number	E-mail Address
Belgium	CA	Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten – FAGG Galileelaan 5/03 1210 Brussel Belgium	+32 2 528 40 00		CT.RD@fagg.be
Belgium	CEC	Commissie Medische Ethiek az groeninge President Kennedylaan 4 8500 Kortrijk Belgium	+32 56 63 62 88		commissie.medische.ethiek@azgroeninge.be
France	CA	Agence nationale de Sécurité du Médicament et des Produits de Santé (ANSM) 143-147 bd Anatole France FR-93285 Saint Denis Cedex France	+33 1 55 87 30 00	+33 1 55 87 36 42	BPC@ansm.sante.fr
France	LEC	CPP Sud-EST III Comité de Protection des Personnes Ile de France 10 Hôtel Dieu - Porte 161, place de l'Hôpital - 69288 Lyon cedex 02 France	+33 4 78 42 94 48	+33 4 78 42 94 69	cppsudest3@yahoo.fr

Germany	CA	Paul-Ehrlich-Institut (PEI) Paul-Ehrlich-Str. 51-59 63225 Langen Germany	+49 6103 771813	+49 6103 771277	ct@pei.de
Germany	CEC	Ethik-Kommission der **Friedrich-Schiller-Universität Jena** Bachstraße 18 07740 Jena Germany	+49 3641-933770	+49 3641-933771	ethikkommission@med.uni-jena.de
Germany	LEC	Ethik-Kommission bei der **Ärztekammer Schleswig-Holstein** Bismarckallee 8-12 23795 Bad Segeberg	+ 49 4551 803152	+49 4551 803214	ethik@aeksh.org
Germany	LEC	Ethik-Kommission des **Landes Berlin (LaGeSo)** Fehrbelliner Platz 1 10707 Berlin	+49 30 902291220	+49 30 90283383	ethik-kommission@lageso.berlin.de
Germany	LEC	Ethik-Kommission an der **Technischen Universität Dresden** Fetscherstr. 74 01307 Dresden	+49 351 458 29 92	+49 351 45843 69	ethikkommission@mailbox.tu-dresden.de
Germany	LEC	Ethik-Kommission der **Ärztekammer Nordrhein** Tersteegenstraße 9 40474 Düsseldorf	+49 211 4302 22 72	+49 211 43 0222 79	ethik@aekno.de

Germany	LEC	Ethik-Kommission der **Ärztekammer Hamburg** Weidestrasse 122 b 22083 Hamburg	+49 40 2022 992 40	+49 40 2022994 10	ethik@aekhh.de
Germany	LEC	Ethik-Kommission bei der **Ärztekammer Niedersachsen** Berliner Allee 20 30175 Hannover	+49 511 38 022 08	+49 511 38021 19	ethikkommission@aekn.de
Germany	LEC	Ethik-Kommission der **Bayerischen Landesärztekammer** Mühlbaurstraße 16 81677 München	+49 89 4147-0	+49 89 4147 280	ethikkommission@blaek.de
Germany	LEC	Ethik-Kommission bei der **Landesärztekammer Baden-Württemberg** Jahnstraße 40 70597 Stuttgart	+49 711 76989 60	+49 711 769898 56	patricia.hager@laek-bw.de
Germany	LEC	**Ethik-Kommission der Universität Ulm** Helmholtzstraße 20 89081 Ulm	+49 731 500 220 52	+49 731 500 220 36	ethik-kommission@uni-ulm.de
Germany	LEC	**Ethikkommission bei der LMU München** Pettenkoferstr. 8 80336 München	+49 89 4400 55191	+49 89 4400 55192	ethikkommission@med.uni-muenchen.de

Germany	LEC	**Ethik-Kommission der Medizinischen Fakultät der Friedrich-Alexander-Universität Erlangen-Nürnberg** Krankenhausstraße 12 91054 Erlangen	+49 9131 852 2270	+49 9131 852 6021	ethikkommission@fau.de
Germany	LEC	**Ethikkommission am Universitätsklinikum Tübingen** Gartenstraße 47 72074 Tübingen	+49 7071 297 7661	+49 7071 29 5965	ethik.kommission@med.uni-tuebingen.de
Germany	LEC	**Ethik-Kommission der Universität zu Lübeck** Ratzeburger Allee 160, Haus 2 23562 Lübeck	+49 451 500 4639	+49 451 500 3026	ethikkommission@uni-luebeck.de
Netherlands	CEC	Centrale Commissie Mensgebonden Onderzoek (CCMO) PO Box 16302 2500 BH The Hague The Netherlands	+31 70 340 7527	+31 70 340 6737	ccmo.nl@ccmo.nl
Netherlands	LEC	CMO Regio Arnhem-Nijmegen p/a Raboudumc Huispostnummer 548 Postbus 9101 6500 HB Nijmegen The Netherlands	+31 24 361 31 54		commissiemensgebondenonderzoek@radboudumc.nl

Spain	CA	Registro de la Agencia Espanola de Medicamentos Y Productos Sanitarios Parque Empresarial Las Mercedes. Edif. 8 c/Campezo, 1 28022 Madrid Spain	+34 918225073	+31 918225043	smhaem@aemps.es
Spain	CEC	Ethic Committee Hospital Universitario La Paz Pº de la Castellana, 261 Madrid. 28046 Paz Lavilla Spain	+34 914532502 +34 914532559 +34 914532534	+34 914532502	ceic.hulp.@salud.madrid.org

Appendix 2 Patient Information and Informed Consent Form

EAU RF nr 2008-01 Version 6 January 7th , 2019.

The European Association of Urology Research Foundation (EAU RF) is conducting a study on patients who have a disease similar to yours. The study will be conducted at the European level under the supervision of physicians recognized as experts in this area of expertise. We would like to invite you to participate in this project after you have been given full information about this study.

In order to be able to take a knowledge-based decision whether or not you should participate in this study, you should be informed about its possible risks and benefits. This process is known as informed consent. This patient information form gives detailed information about the research study which your physician will discuss with you. Once you understand the study, you will be asked to sign the informed consent form if you wish to participate. When you have signed the form, you will receive a copy to keep as a record.

The research study being proposed to you is entitled:
"Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG.
A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAU RF number 2008-01 (AUO-Studie AB37/10)".

Introduction:
Your doctor has discovered that you have a high grade non-muscle invasive bladder tumor(s). This means that the tumor is not yet invading the urinary bladder muscle. The tumor is limited to the superficial part of the urinary bladder inside wall. The standard treatment consists of an operation through the urethra, the canal through which urine is discharged from the bladder (TUR-Bladder) where the tumor(s) are removed completely. A separate information folder supplied by employees of the department of urology will be used to inform you about the risks of this operation.
However, there is chance of over 50% that the disease may recur in the near future. It could also become more malignant. In order to avoid recurrence, an adjuvant treatment after the operation is necessary. This therapy consists of repeated bladder instillations through the urethra with a drug called Bacillus Calmette Guèrin (BCG). This drug was originally developed as a vaccine against lung tuberculosis. Independent from this indication, BCG has been found one of the best drugs to prevent recurrence of non-muscle invasive bladder cancer. Other known drugs that are used for instillation are chemotherapeutic drugs like Mitomycin, Doxorubicin and Epirubicin. However, these chemotherapeutic drugs are not used as standard of care to prevent recurrence of high grade non-muscle invasive bladder tumor(s). Unfortunately, it is unknown how many bladder instillations with BCG are necessary. Scientific evidence prones to the fact that the standard number of instillations can be reduced for a proper immune response resulting in similar clinical efficacy and potentially less side-effects and costs. In this study, we investigate the efficacy of BCG standard number versus BCG reduced number of bladder instillations. Moreover, we look carefully at the symptoms and side effects that may be caused by the drug or by the instillation procedure. A total of 824 patients will be asked to participate and the study duration will be in total 9 years. The incidence and severity of side effects may bother you and affect your quality of life during the treatment period. The symptoms and quality of life aspects have to be filled in by you in simple questionnaires. If this is difficult for you, ask us, we can help or advise you.

What do we expect from you ?
1. You will be examined clinically and undergo blood tests and urine examinations as usual. These tests do not differ from patients who do not participate in this study.
2. Specific care is taken that all tumors are completely resected. Four to eight weeks after the first surgical resection a control cystoscopy is performed where the site of the initial tumor will again be biopsied.
3. Randomization will decide which treatment will be given to you (standard number of instillations or the reduced number of instillations. The randomization is made by a computer after you have been registered onto the trial. Neither you nor your physician can anticipate which treatment you will receive. If you are randomized for the standard number of instillations, you will start with 6 weekly instillations with BCG (cycle 1) followed by 3 weekly instillations at months 3, 6 and 12 (cycles 2,3 and 4) after the operation – in total 15 instillations.
If you are randomized for the reduced frequency arm you will receive instillations at weeks 1, 2 and 6 (cycle 1) followed by instillations on week 1 and 3 at months 3, 6 and 12 (cycles 2,3 and 4) after the operation – in total 9 instillations.
Questionnaires are to be completed before the first and last instillation of each cycle which is in total 2 times in each of the four cycles – in total 8 times.
4. You will receive no payment for your participation. All medical examinations and analyses are standard and reimbursable by the health insurance as they are part of the normal routine.

After entering the study, you will be followed at fixed time periods: every three months the first 2 years and bi-annually until maximal the 6th year, when your physician will do a control cystoscopy. If your physician diagnoses a recurrence of your bladder tumor(s), the tumor will again be removed and further treatment will be decided at the discretion of you and your physician. Your study participation will end after a maximum of 5 years of follow up or earlier, when a recurrence is observed.
Your participation is entirely voluntary. You may decline from participating or withdraw your consent at any time. This will not affect your further treatment.

Are there risks, side-effects or discomforts when you decide to participate ?
The burden and risks associated with participation in the study is considered minimal and acceptable. The number of visits to the clinic and treatments is equal to or less compared with what patients with these criteria is offered when they are treated on a standard way which is BCG intravesical instillation therapy. Extra in this study are the lower urinary tract symptoms questionnaires (13 questions for females and 14 for males) and quality of life questions (30 questions) that need to be completed. This will take you an additional 15-20 minutes to complete.

A potential risk for patients in the reduced frequency arm is that the treatment is less effective with respect to the prevention of recurrence compared to the standard frequency arm. A potential benefit is that side effects, both in quantity and quality, are expected to be less in the reduced frequency arm compared to the standard frequency arm. The risks related to the expected treatment outcome and quality and quantity of side effects of the BCG treatment can be considered as low and acceptable.

Side effects that are common when using BCG instillations in the bladder are: fever, chills, malaise, flu-like symptoms, increased fatigue or an increase in urinary symptoms, (such as burning or pain on urination). You are advised to notify your physician if any of these symptoms last more than 48 hours or increase in severity. You should also notify your physician immediately if you experience any of the following less frequent occurring symptoms: joint pain, eye complaints (such as pain, irritation or redness), an increase in urinary symptoms (such as urgency, frequency of urination, blood in urine), cough, skin rash, jaundice, nausea or vomiting.

BCG contains live mycobacterium, that may be excreted with the urine. Therefore, you are advised to follow appropriate hygienic procedures to protect family and close contacts from infection. When you live with or in close quarters to persons who are immune-compromised (on chemotherapy, etc.), you should exercise special caution to avoid inadvertently transmitting BCG infection to such susceptible persons. After the instillation, BCG is retained in the bladder for as long as possible (up to 2 hours) and then voided. To avoid transmission of BCG to others, for 6 hours after treatment you should void while seated to avoid splashing of urine. Urine voided during this time should be disinfected with an equal volume of household bleach for 15 minutes before flushing or disposal. Unless medically contraindicated, you should increase fluid intake to “flush” the bladder for several hours following treatment with intravesical BCG. You may experience pain or burning with the first void after treatment. <u>During the first week after BCG treatment a condom should be used during sexual intercourse.</u>

The possible risks of BCG treatment to a pregnant woman and foetus are not known. Female patients capable of childbearing will be asked to take appropriate precautions to avoid pregnancy during the whole period of treatment administration (at least 30 days prior to the first treatment and up to three months after the last administration). Pregnant women may not participate at any time in the study, and, if applicable, pregnancy tests will be done to make sure that you are not pregnant at study entry and during the study.

<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
For selected centres which participate in the immunological substudy, the following should be added:

As part of the study you are invited to take part in optional research to better understand the immunological response to the BCG instillation. Therefore, we ask you to collect one urine sample prior to each installation and one urine sample between 4 and 8 hours after each instillation during the entire instillation process of the study. Collected samples will be transferred to the EAU RF or other laboratories working with the EAU RF where these urine samples are used to measure immunological important substances in the urine. The EAU RF will require anyone who works with your sample to hold the information and any results in confidence. These urine samples are extra and should not take place in case you should decide not to participate in this optional research. You will not have any individual benefit of the collection of urine samples.
<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
Additional laboratory and radiological evaluations are not foreseen in the study and are performed at the investigators discretion for monitoring eventual recurrence or progression of disease.

<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
For selected centres which participate in the DNA substudy, the following should be added:
As part of the study you are invited to take part in optional research to better understand why some patients react favourably to BCG instillations and others experience a recurrence. Therefore, we ask you 10 ml of your blood in order to be able to investigate your DNA specifics. Collected samples will be transferred to the EAU RF or other laboratories working with the EAU RF where these blood samples are used to measure DNA specifics. The EAU RF will require anyone who works with your sample to hold the information and any results in confidence. This blood sample is extra and should not take place in case you should decide not to participate in this optional research. You will not have any individual benefit of the collection of your of your blood sample.
<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
Possible benefit for the patient is that the patient is treated according to the latest standards and guidelines of the treatment of non-muscle invasive bladder tumor(s).

For all patients participating in this study an insurance policy covers any damage that may occur during the course of this study.
Name of the insurer:
Policy number:
Contact person:
Telephone number contact person:

Together with this information sheet, you will receive a copy of the insurance details for your attention and consideration. See the attachment.

Privacy statement
For this study, the data related to your disease and your date of birth will be, dependent on the reason for collection, processed anonymously and only for the purpose of the study. This means that your full name and date of birth are only recognizable in the informed consent form that will be archived only in the hospital where you are treated for possible required verification of your willingness to participate in the study. For every patient that participates in the study the central research office will attribute a patient number that will consequently be used to identify the patient for processing the study data. This patient number cannot lead to the identification of the participant outside the hospital where you are treated. Anonymity of participants is strictly observed. When the study results are published, the anonymity of participants will be maintained.

If you do not have any further questions and you want to participate in this study, you are kindly invited to sign the informed consent form that is attached. You will receive a copy of this patient information as well as a copy of the informed consent for your records.

Thank you for your attention and your willingness to participate.

The study leader:

*Prof. Dr. med. M.-O. Grimm**
Chair dept. of Urology
University Hospital Jena

_____	_____
Place, Date	Signature Participant
_____	_____
Place, Date	Signature Physician
_____	_____
Place, Date (only applicable if the participant cannot read)	Signature Witness

** Italic part is hospital specific and has to be adapted for each of the participating centres.*

Patient Consent Form Standard Version 6, date January 7th, 2019: **Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG.**
A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAU RF number 2008-01.

- I have read and understand the patient information form (Version 6, January 7th , 2019) related to this research study and my physician has answered all my questions regarding the study.

- I had sufficient time to consider my participation in this research study and I am aware that participation is completely voluntary.

- I realize that I may decide to withdraw my participation at any time without affecting the quality of my health care.

- I understand and agree that personal data will be collected from my medical records in a anonymised manner, used and processed by the EAU RF or any other designated third party that is involved in the study (e.g. hospital, physician, regulatory bodies and medical ethics committees).

- I authorize and instruct my physician(s) and institution to release the necessary personal - anonymised - data to the EAU RF and any other designated third party involved in the study.

- The EAU RF and all other designated third parties involved in the study shall maintain the confidentiality of all data provided compliant with all applicable data protection and privacy laws and shall not use my name or other identifying characteristics in publications.

- I have received a copy of the Patient Information and Consent Form and I hereby agree to participate in this study.

  - I hereby consent to my personal and confidential data being:

1. processed by the EAU RF for the purposes as described above;
2. disclosed by the EAU RF to third parties as indicated in point 4 of this page for the purposes as described above.

<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
For selected centres which participate in the immunological substudy, the following should be added:

- I have been given time and opportunity to consider taking part in optional immunological research.

By ticking the appropriate bullet in the next question, I freely give my consent to take part in this optional immunological research, as follows, and understand that if I select 'No' to such testing, it will not affect my participation in the clinical study.

- I agree that my urine samples will be used by the EAU RF or laboratories working with the EAU RF for "optional immunological research".

☐Yes ☐ No *Tick as appropriate*

<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

For selected centres which participate in the DNA substudy, the following should be added:

- I have been given time and opportunity to consider taking part in optional DNA research.

By ticking the appropriate bullet in the next question, I freely give my consent to take part in this optional DNA research, as follows, and understand that if I select ‘No’ to such testing, it will not affect my participation in the clinical study.

- I agree that my blood samples will be used by the EAU RF or laboratories working with the EAU RF for “optional immunological research”.

☐Yes ☐ No *Tick as appropriate*

<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

type/print name

______________________________	______________________________	____________
(Patient)	Signature	Date

I hereby declare that I have fully informed the patient about this research study and explained to him its nature, aim, procedures and duration in full detail. I also declare that I have provided the patient with the information sheet and a dated and signed copy of the informed consent form.

type/print name

______________________________	______________________________	____________
(Physician) (has to sign always)	Signature	Date

type/print name

______________________________	______________________________	____________
(Name of presenter, if applicable) (who presented/explained the document)	Signature	Date

Appendix 3: Overview of all parties involved relevant for the conduct of the study

1. SPONSOR: EUROPEAN ASSOCIATION OF UROLOGY RESEARCH FOUNDATION (EAU RF)

EAU RF Central Office
Mr. E.N. van Kleffensstraat 5
6842 CV Arnhem, The Netherlands
Tel: 026-3890677

Tasks:

- Centralized Project Quality Management
  - The overall management and organization of the study, including coordination of activities in the participating countries
  - Communication with Contract Research Organisations or academic organisations with a similar function and Contract Research Affiliates in the participating countries, and (if needed) with Ethics Committees (EC) and Competent Authorities
  - Design, review and release of the study documentation
  - Organization of investigator meetings, meetings of the Steering Committee, meetings of the Independent Data Monitoring Committee, group meetings and teleconferences
  - Organization of Quality Assurance Audits, possibly by third parties
  - Reporting (e.g., study progress, timelines, budget)
  - Trial Registration
- Data management/Biometrics/IT:
  - Provision of a project-specific web-based data management system for study documents (e.g. electronic Case Report Forms), randomization
  - Design and testing (UAT) database in Marvin
  - Set up and update Data validation plan, Data validation
  - Design of Marvin user manual, Site training Marvin, Helpdesk Marvin
  - Study-specific adaptation and validation of the web-based system
  - Center and User management in Marvin, Marvin reports
  - Examination of the collected data, generation and management of "queries"
  - Preparation of the data for statistical analysis, statistical evaluation
  - Annual reporting and preparation of the final report
  - Establish and maintain the Trial Master File
  - Archiving of trial master file after completion of the Clinical Trial.
- Pharmacovigilance:
  - SAE management
  - Medical examination or confirmatory review of Serious Adverse Event (SAE) / Suspected Unexpected Serious Adverse Reaction (SUSAR) reports
  - Fulfil the legal reporting obligations regarding SAEs, periodic reports, any new safety issue
  - Establish and maintain the safety database, collection of safety data

EAU RF provides the following services for the Clinical Trial in The Netherlands and Belgium:

- Selection, initiation and closure of study centers, establishing Clinical Trial Agreements with Dutch and Belgian study centers
- Obtaining and maintaining Clinical Trial Authorization from the Ethics Committee and Competent Authorities in The Netherlands and Belgium for the conduct of the Clinical Trial and substantial amendments to the Protocol
- Preparation and delivery of Investigator Site Files to the Dutch and Belgian study centers
- Study coordination and support for the Dutch and Belgian study centers throughout the study
- Continuous monitoring of the Dutch and Belgian study centers

Period of time: 2011-2021

Study team members

Scientific and Clinical Research Director	Name	Dr. Wim Witjes
	Tasks	Overall Project Management, Central medical contact for medical issues during the study, Medical review of collected data
	Period of time	2011- 2021
Clinical Project manager	Name	Dr. Raymond Schipper
	Tasks	Project management, Regulatory and Organisational issues
	Period of time	2013 - 2021
Clinical Project manager	Name	Drs. Christien Caris
	Tasks	Back up Project Management, Quality and Safety issues, Data Management, Statistical analyses
	Period of time	2011- 2021
Clinical Data manager	Name	Mrs. Joke van Egmond
	Tasks	Data management
	Period of time	2011- 2021
Clinical Data manager	Name	Mr. Sheik Nurmohamed
	Tasks	Back-up Data Management
	Period of time	2011- May 2015
Data Management Assistant	Name	Mr. Hans Noordzij
	Tasks	Assistance MARVIN system
	Period of time	May 2015-2021
Financial Officer	Name	Mrs. Xandra Helmonds
	Tasks	Financial Management
	Period of time	2013- 2021
Clinical Research Associate	Name	Mrs Ria Janzing
	Tasks	Monitoring activities
	Period of time	2013- Oct 2017
Clinical Research Associate	Name	Mrs Ilse Christ
	Tasks	Monitoring activities
	Period of time	2017- 2020

2. CO-SPONSOR: ZENTRUM FUR KLINISCHE STUDIEN JENA

Salvador-Allende-Platz 29
07740 Jena, Germany
Tel: + 49 3641 93 96664

Tasks:

- Selection, initiation and closure of study centers, establishing Clinical Trial Agreements with German study centers
- Obtaining and maintaining Clinical Trial Authorization from the Ethics Committee and Competent Authorities in Germany for the conduct of the Clinical Trial and substantial amendments to the Protocol
- Take out and maintain Clinical Trial insurance for German patients
- Budget management (budget available from a grant of the Deutsche Krebshilfe)
- Preparation and delivery of Investigator Site Files to the German study centers
- Study coordination and support for the German study centers throughout the study
- Continuous monitoring of the German study centers
- Participation in the meetings of the Steering Committee, investigator meetings, regular teleconferences

Period of time: 2013-2021

Study team members

National coordinator	Name	Prof. Dr. Marc-Oliver Grimm
	Tasks	Overall Project Management
	Period of time	2013- 2021
Clinical Project manager	Name	Dr. Andrea Rößler
	Tasks	Project management, Coordinating monitor
	Period of iime	2013 - 2021
Clinical Research Associate	Name	Mrs. Jana Ziegler
	Tasks	Monitoring
	Period of time	Aug 2013-Dec 2014
Clinical Research Associate	Name	Mrs. Nicole Brillinger
	Tasks	Monitoring
	Period of time	Jan 2015-Dec 2015
Clinical Research Associate	Name	Mrs. Anne Ansorg
	Tasks	Monitoring
	Period of time	Jan 2016- Jan 2017
Clinical Research Associate	Name	Uta Schurigt
	Tasks	Monitoring
	Period of time	Dec 2016- May 2017
Clinical Research Associate	Name	Anne Ruschel
	Tasks	Monitoring
	Period of time	May 2017- Aug 2018
Clinical Research Associate	Name	Julia Müller
	Tasks	Monitoring
	Period of time	Aug 2017- 2020

3. CO-SPONSOR: HOSPICES CIVILS DE LYON (HCL)

Quai des Célestins
69229 Lyon Cedex, France
Tel: +33 472117494

Tasks:

- Selection, initiation and closure of study centers, establishing Clinical Trial Agreements with French study centers
- Obtaining and maintaining Clinical Trial Authorization from the Ethics Committee and Competent Authorities in France for the conduct of the Clinical Trial and substantial amendments to the Protocol
- Take out and maintain Clinical Trial insurance for French patients, if applicable.
- Budget management (grants available from a) private French foundation affiliated with Hospices Civils de Lyon; b) EAU RF
- Preparation and delivery of Investigator Site Files to the French study centers
- Study coordination and support for the French study centers throughout the study
- Continuous monitoring of the French study centers
- Participation in the meetings of the Steering Committee, investigator meetings, regular teleconferences.

Period of time: 2016-2021

Study team members

National coordinator	Name	Prof. Marc Colombel
	Tasks	Overall Project Management
	Period of time	2016- 2021
Project manager	Name	Cécile Gayet
	Tasks	Project management (regulatory affairs)
	Period of time	2016 – 2021
Project manager	Name	Océane Brassart
	Tasks	Project management
	Period of time	May 2018 – 2019
Project manager	Name	Jacques Cussey
	Tasks	Project management
	Period of time	May 2019 – 2020
Study Coordinator (back-up)	Name	Charline Faure
	Tasks	Study coordination
	Period of time	2016-2021
Clinical Research Associate	Name	Micipsa Ait-Mokhtar
	Tasks	Monitoring
	Period of time	Jul 2017- Sep 2018
Clinical Research Associate	Name	Déborah Ligout
	Tasks	Monitoring
	Period of time	Jul 2017- May 2018
Clinical Research Associate	Name	Maria Pezze
	Tasks	Monitoring
	Period of time	2017- 2020
Clinical Research Associate	Name	Camille Jordan
	Tasks	Monitoring
	Period of time	2019- 2020
Parmacist	Name	Carole Dhelens
	Tasks	Service Pharmacie
	Period of time	2017- 2020
Clinical Research Associate	Name	Asma Ben-Amor
	Tasks	Monitoring
	Period of time	2017- 2019
Study Nurse	Name	Alfreda Pages
	Tasks	Nurse study
	Period of time	2017- 2020
Financial Officer	Name	Batoul Tighoula
	Tasks	Study finances
	Period of time	2017- 2021

4. CO-SPONSOR: LA UNIDAD CENTRAL DE INVESTIGACIÓN CLÍNICA Y ENSAYOS CLÍNICOS DEL HOSPITAL LA PAZ (UCICEC)

Paseo de La Castellana, 261
Edificio de Maternidad - 2ª planta
28046 - Madrid
Tel: +34 91 207 14 66/ 91 727 70 00 ext 42485

Tasks:

- Selection, initiation and closure of study centers, establishing Clinical Trial Agreements with Spanish study centers

- Obtaining and maintaining Clinical Trial Authorization from the Ethics Committee and Competent Authorities in Spain for the conduct of the Clinical Trial and substantial amendments to the Protocol
- Budget management (grant available from EAU RF)
- Preparation and delivery of Investigator Site Files to the Spanish study centers
- Study coordination and support for the Spanish study centers throughout the study
- Continuous monitoring of the Spanish study centers
- Participation in the meetings of the Steering Committee, investigator meetings, regular teleconferences.

Study team members

National coordinator	Name	Prof. Dr. Luis Martinez-Pineiro
	Tasks	Overall Project Management
	Period of time	2016- 2021
Project manager regulatory affairs and Clinical Research Associate	Name	Paloma Moraga
	Tasks	Project management
	Period of time	July 2018 – 2020
Project manager regulatory affairs and Clinical Research Associate	Name	Guiomar Rodriguez
	Tasks	Project management
	Period of time	Jan 2018 – 2020
Contract negotiator	Name	Andrea Santos
	Tasks	Negotiation contracts
	Period of time	Jan 2018-2020
Coordinator UCICEC	Name	Alberto M. Borobia
	Tasks	Coordination UCICEC
	Period of time	2017-2020
Clinical Research Associate	Name	Víctor Alelú Hernández
	Tasks	Monitoring
	Period of time	2019-2020
Clinical Research Associate	Name	Elena Pintos Sánchez
	Tasks	Monitoring
	Period of time	2019-2020

Period of time: 2018-2020

5. MEDAC: GESELLSCHAFT FUR KLINISCHE SPEZIALPRAEPARATE GMBH

Theaterstrasse 6
22880 Wedel, Germany
Tel: +49 410380090

Tasks: support the German participating centres with the study medication BCG, Strain RIVM, compatible to the marketed product “BCG Medac” free of charge for patients participating in NIMBUS and randomised for the reduced frequency arm. The study medication was delivered by Medac free of charge directly to the pharmacy of the participating study centre.

Period of time: 2013-2020

6. CENTRAL LABORATORY EXPERIMENTAL UROLOGY RADBOUDUMC

Urology Research Laboratory
Geert Grooteplein 10
6525 GA Nijmegen, The Netherlands
Tel: +31 (0)24 3614907

Tasks: Collect and analyse urine and blood samples Cytokine and DNA substudies of Clinical Trial

Period of time: 2013-2021

7. XCLINICAL GMBH

GmbH Arnulfstraße 19
80335 München, Germany
Tel: +49 8945-2277-5000

Tasks: Provision and support of a web-based data management system for study documents (e.g. electronic Case Report Forms)

XClinical provided the following services for the Clinical Trial:

- MARVIN Instance installation (Live-, Test- and Demo-Instance)
- eCRF structure and item definition: Support & Review
- eCRF edit checks and dynamics (Actions): Support & Review
- Roles & Permissions: Set-up by XClinical
- Randomization set-up: Support and Review
- Randomization import: Support and Review (EAUrf needs to do tests on cloned DB to find seed)
- Customized Data Transformation (ODM export into CIOMS XML format): Set-up by XClinical
- E-Mail workflow with attachments: Set-up by XClinical
- Project management & communication (TC, webcasts, etc.)
- End of study procedures

Period of time: 2014-2020

8. INTERNATIONAL STEERING COMMITTEE

Principal Investigators:

Prof. Levent Turkeri	Acibadem University, Istanbul, Turkey
Prof. Marko Babjuk	Hospital Motol, Praha, Czech Republic

Committee members:

Prof. Dr. Marc-Oliver Grimm	Universitätsklinikum Jena, Germany
Prof. Dr. Peter Mulders	Radboudumc, Nijmegen, The Netherlands
Dr. Toine van der Heijden	Radboudumc, Nijmegen, The Netherlands

Prof. Dr. Marc Colombel	Hôpital Edouard Herriot, Lyon, France
Dr. Tim Muilwijk	UZs Leuven, Belgium
Prof. Dr. Louis Martinez-Pineiro	Hospital Universitario La Paz, Spain
Prof. Dr. Andrea Tubaro	Sapienza Università di Roma, Rome, Italy
Dr. Andrea Gallina	Vita-Salute San Raffaele University, Milan, Italy
Mr. Anup Patel	Spire London East Hospital. London, United Kingdom
Dr. Pedro Costa	Centro Hospitalar Vila Nova de Gaia, Esphino, Portugal

Tasks: to provide overall supervision of the trial, to take steps to reduce deviations from the protocol to a minimum and periodic review of the progress.

Period of time: 2012-2021

9. INDEPENDENT DATA MONITORING COMMITTEE

Prof. Dr. George Thalmann, uro-oncologist, Switzerland
Prof. Dr. Markus Kuczyk, uro-oncologist, Germany
Prof. Dr. Lambertus Kiemeney, epidemiologist, The Netherlands

Tasks: to review interim safety data (prepared by the study statistical data analist, Drs. Christien Caris) and to recommend whether the study needed to be changed or terminated based on this evaluation. The Committee also determined whether and to whom these results were to be released prior to the reporting of study results.

Period of time: 2015-2020

Appendix 4: List of Centres and Investigators NIMBUS Study

Germany

Site nr	Name of PI	Institute	Address	Postal code	City
DE-01	Dr. Jörg Horstmann	Urologische Praxisklinik am Franziskushospital, Standort Aachen I	Sanatoriumsstraße 10	52064	Aachen
DE-02	Dr. Stefan Machtens	MarienKrankenhaus Bergisch Gladbach	Dr.-Robert-Koch-Str. 18	51465	Bergisch Gladbach
DE-03	Dr. Eberhard Mumperow	Urologische Praxis Langenfeld	Hauptstraße 116	40764	Langenfeld
DE-08	Dr. Andreas Al Ghazal	Klinik für Urologie und Kinderurologie	Albert-Einstein-Allee 23	89081	Ulm
DE-09	Dr. Thomas Pulte	Urologische Praxis am Wasserturm	Niederbardenberger Straße 21a	52146	Würselen
DE-11	Dr. Michael Stephan-Odenthal	Praxis Urologie RheinBerg	Am Gesundheitspark 4,	51375	Leverkusen
DE-13	Dr. Georgios Gakis	Universitätsklinikum Tübingen, Klinik für Urologie	Hoppe-Seyler-Str. 3	72076	Tübingen
DE-14	Dr. Mario Kramer	Universitätsklinikum Schleswig-Holstein, Klinik und Poliklinik für Urologie, Campus Lübeck	Ratzeburger Allee 160 (Haus 13)	23538	Lübeck
DE-15	Prof. Dr. Marc - Oliver Grimm	Universitätsklinikum Jena Klinik für Urologie	Am Klinikum 1	07747	Jena
DE-16	Prof. Dirk Zaak	Urologisches Praxiszentrum Traunstein	Wasserburger Straße 1	83278	Traunstein
DE-17	Prof. Dr. Bernd Schmitz-Dräger	Überörtlichen Gemeinschaftspraxis für Urologie	Karlstraße 2	90513	Zirndorf
DE-18	Dr. Holger Schreier	Urologie im SchlossCarrée	Ritterbrunnen 7	38100	Braunschweig
DE-20	Dr. Jan Lehmann	Urologische Gemeinschaftspraxis Prüner Gang	Prüner Gang 15	24103	Kiel
DE-21	Dr. Torsten Werner	Urologie Herzberg	Ziegengasse 2	37412	Herzberg am Harz
DE-22	Dr. Jörg Klier	Urologie Bayenthal/Urologische Partnerschaft Köln	Bernhardstraße 110	50968	Köln
DE-24	Dr. Jan Marin/Dr. Michael Kämmerling	Urologische Gemeinschaftspraxis	Arnoldstrasse 13b	47906	Kempen
DE-25	Dr. Wolfgang Rulf	Überortliche Gemeinschaftspraxis Praxis Erkrath-Hochdahl	Bergstraße 9	40699	Erkrath
DE-26	Dr. Eva Hellmis	Urologicum - Duisburg	Kometenplatz 29-33	47179	Duisburg
DE-27	Dr. Andreas Schneider	Kooperative Gemeinschaftspraxis - Belegabteilung	Friedrich-Lichtenauer-Allee 1b	21423	Salzhausen
DE-28	Dr. Spiegelhalder	Urologie Neandertal - Gemeinschaftspraxis für Urologie (Mettmann)	Adlerstraße 1	40822	Mettmann
DE-30	Prof. Dr. Manfred Wirth	Universitätsklinikum Dresden, Klinik für Urologie	Fetscherstr. 74, Haus 27	01307	Dresden
DE-31	Prof. Dr. Theodor Klotz	Kliniken Nordoberpfalz AG, Klinikum Weiden - Urologische Klinik	Söllnerstraße 16	92637	Weiden
DE-33	Dr. Henrik Suttmann	Urologikum Hamburg Standort Alstertal	Harksheider Str. 3	22399	Hamburg
DE-34	Dr. Michael Siebels	Gemeinschaftspraxis Urologie Pasing	Josef-Retzer-Str. 48	81241	München-Pasing
DE-38	Dr. Gerd Rodemer	Praxisgemeinschaft f. Onkologie & Urologie	Friedrich-Paffrath-Str. 98	26389	Wilhelmshaven
DE-39	Dr. Robert Rudolph	GUT GbR Urologische Gemeinschaftspraxis	Stuttgarter Straße 56	73230	Kirchheim / Teck
DE-44	Dipl. med. Roger Zillmann	Urologische Gemeinschaftspraxis	Garbatyplatz 1	13187	Berlin-Pankow

List Centres Investigators 09/06/2021

The Netherlands

Site nr	Name of PI	Institute	Address	Postalcode	City
NL-01	Dr. M. de Bruin	Laurentius Ziekenhuis	Mgr. Driessenstraat 6	6041 NW	Roermond
NL-04	Dr. S. Bos	Noordwest Ziekenhuisgroep locatie Alkmaa	Wilhelminalaan 12	1815 JD	Alkmaar
NL-06	Prof. dr. R. van Moorselaar	VU Medische Centrum	De Boelelaan 1117	1081 HV	Amsterdam
NL-07	Prof. dr. T de Reijke	Academisch Medische Centrum (AMC)	Meibergdreef 9	1105 AZ	Amsterdam
NL-08	Dr. J. Boormans	Erasmus MC	s-Gravendijkwal 230	3015 CE	Rotterdam
NL-11	Dr. B. Wijsman	EZT Sint Elisabeth Ziekenhuis	Hilvarenbeekseweg 60	5022 GC	Tilburg
NL-12	Dr. H.H.E. van Melick	St. Antonius Ziekenhuis - locatie Nieuweg	Koekoekslaan 1	3430 EM	Nieuwegein
NL-13	Dr. E van Boven	Maasziekenhuis Pantein	Dokter Kopstraat 1	5835 DV	Beugen
NL-14	Dr. R.P. Meijer	UMC Utrecht	Heidelberglaan 100	3584 CX	Utrecht
NL-37	Dr. A. G. van der Heijden	Radboudumc	Geert Grooteplein-Zuid 10	6525 GA	Nijmegen
NL-43	Dr. H. Vergunst	Canisius-Wilhelmina Ziekenhuis	Weg door Jonkerbos 100	6532 SZ	Nijmegen
NL-48	Dr. E. te Slaa	Isala Klinieken - locatie Sophia	Dokter van Heesweg 2	8025 AB	Zwolle/Meppel
NL-49	Dr. A.M. Leliveld-Kors	UMC Groningen (UMCG)	Hanzeplein 1	9713 GZ	Groningen/Winschoten

France

Site nr	Name of PI	Institute	Address	Postalcode	City
FR-01	Prof. Marc COLOMBEL	Hôpital Edouard Herriot, Unité de Recherche Clinique –Service d'Urologie	5, place d'Arsonval	69437	Lyon Cedex 03
FR-02	Prof. Alain RUFFION	Centre Hospitalier Lyon Sud	165, Chemin du Grand Revoyet	69310	Pierre-Bénite
FR-03	Dr. Christian PFISTER	CHU de Rouen	1, rue de Germont	76031	Rouen
FR-04	Prof. Morgan ROUPRET	CHU La Pitié-Salpêtrière, APHP	47-83 Boulevard de l'Hôpital	75013	Paris
FR-05	Prof. Jacques IRANI	APHP Hôpital Bicêtre	78 rue du Général Leclerc	94270	Le Kremlin-Bicêtre
FR-06	Dr. Gabriel STOICA	CHIC Alençon	25 rue Fresnay	61000	Alençon

Belgium

Site nr	Name of PI	Institute	Address	Postalcode	City
BE-01	Dr. Siska Van	AZ Groeninge Kortrijk	President Kennedylaan 4	8500	Kortrijk
BE-02	Dr. Filip Ameye	AZ Maria Middelares Gent	Buitenring-Sint-Denijs 30	9000	Gent
BE-03	Dr. Harm Arentsen	AZ Sint-Jan Brugge-Oostende	Ruddershove 10	8000	Brugge
BE-04	Prof. Dr. Steven Joniau	UZ Leuven	Herestraat 49	3000	Leuven

Spain

Site nr	Name of PI	Institute	Address	Postalcode	City
ES-02	Pastora Beardo	Hospital Universitario de Araba	Calle Jose Atxotegi, s/n	1009	Vitoria-Gastei (Álava)

Appendix 5. Sample of the case report form (unique pages only)

NIMBUS

Blank CRFs *[Individual forms only displayed once]*

NIMBUS

Protocol Name: *NIMBUS*

XC 14

File Information:

Study OID:	*NIMBUS*
File Type:	*Snapshot*
Granularity:	*Metadata*
File OID:	*Export.922135084639683265*
Creation Date and Time:	*2018-02-15T08:24:35+00:00*
As of:	
Date of printout:	*2018-02-15T10:00:26+01:00*
ODM Version:	*1.2*

Metadata Version Information:

Metadata Version OID:	*4.0*
Metadata Version Name:	*4.0*
Metadata Version Description:	*4.0*

Signature Information:

Signature OID:	*sig_001*
Meaning:	*Sig_001 Meaning*
Legal Reason:	_____

Subject Protocol

*Eligibility and Randomisation**

Inclusion and Exclusion Criteria*

Patient ID*

Patient ID*	_ _ _ _ _ _ _ _ _
Center #*	_ _ _ _ _
Patient Initials*	_ _
Date of Birth*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Date of written Informed Consent*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Will the patient participate in the immunological substudy?*	O Yes O No
Will the patient participate in the DNA substudy?*	O Yes O No
Date of written Informed Consent for participation in one or both substudies*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Inclusion Criteria*

1. Is there any presence of high grade* (Ta-T1) urothelial carcinoma of the bladder with or without CIS. Tumors can be primary or recurrent, single or multiple.*	O Yes O No
*Pathological Grading will be done according to WHO/ISUP classification	
2. Has a re-TUR been performed at weeks 4-8 after initial resection, including the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s)?*	O Yes O No
Re-Re-TUR should be performed in case of histological detection of high grade papillary NMIBC in the Re-TUR, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s).	
3. Have all visible tumors been completely resected?*	O Yes O No
4. Has the Patient signed and dated the Informed Consent Form?*	O Yes O No
In case any of the items is NO patient is not eligible	

Exclusion Criteria*

1. Has the patient received any previous intravesical BCG therapy?*	O Yes O No
2. Is there any presence of primary CIS only?*	O Yes O No

Exclusion Criteria*

3. Is there any presence of histopathologically proven muscle invasive urothelial carcinoma of the bladder at the first or re-TUR surgical specimens?*	O Yes O No
4. Is there an incomplete resection of visible tumors?*	O Yes O No
5. Is muscle tissue in the re-TUR specimen(s) absent?*	O Yes O No
6. Presence of any upper urinary tract tumors at any time?*	O Yes O No
7. Presence of any other histological type of resected tumor other than urothelial carcinoma on the first or second resection?*	O Yes O No
8. Presence of another malignancy other than the basal cell carcinoma of the skin?*	O Yes O No
9. Presence of pregnancy or lactation?*	O Yes O No
10. Presence of active tuberculosis, any form of immunodeficiency (eg HIV + serology, transplant recipients) and/or any other contraindication of BCG therapy?*	O Yes O No
11. Presence of WHO performance score of > 2 or ASA grade 4-5?*	O Yes O No
12. Has the patient received any systemic cytostatic agents within the last 3 months?*	O Yes O No
13. Is the patient older than 80 years of age?*	O Yes O No
14. Does the patient have uncontrollable UTI?*	O Yes O No
15. Was the White Blood Count (WBC) below 3.0 x 10E9/L or Platelet count below 100 x 10E9/L at baseline?*	O Yes O No
16. Do the Renal and Hepatic function values exceed two times the upper normal value of the local laboratory?*	O Yes O No
17. Has the patient received any multi-instillation intravesical chemotherapy during the last 3 months prior to randomisation?*	O Yes O No
18. Has single dose postoperative chemotherapy (e.g. Mitomycin C) been given after re-TUR?	O Yes O No

In case any of the items is YES patient is not eligible

Inclusion Criteria (amendment 4)*

1. Is there any presence of high grade* (Ta-T1) urothelial papillary carcinoma of the bladder with or without CIS. Tumors can be primary or recurrent, single or multiple.*	O Yes O No

*Pathological Grading will be done according to WHO/ISUP classification

Inclusion Criteria (amendment 4)*

2. Has a re-TUR been performed at weeks 4-8 after initial resection, including the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s)?* O Yes O No

Re-Re-TUR should be performed in case of histological detection of high grade papillary NMIBC in the Re-TUR, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s).

3. Histopathologically confirmed absence of high-grade papillary NMIBC in the re-TUR specimen and/or re-re-TUR specimen?* O Yes O No

4. Have all visible papillary tumors been completely resected?* O Yes O No

5. Has the Patient signed and dated the Informed Consent Form?* O Yes O No

6. Is patient clinically fit enough to receive BCG bladder instillations?* O Yes O No

In case any of the items is NO patient is not eligible

Exclusion Criteria (amendment 4)*

1. Has the patient received any previous intravesical BCG therapy?* O Yes O No

2. Is there any presence of primary CIS only?* O Yes O No

3. Is there any presence of histopathologically proven muscle invasive urothelial carcinoma of the bladder at the first or re-TUR surgical specimens?* O Yes O No

4. Is there an incomplete resection of visible tumors?* O Yes O No

5. Is muscle tissue in the (re-)re-TUR specimen(s) absent?* O Yes O No

6. Presence of any tumors in upper urinary tract or in the prostatic urethra at any time?* O Yes O No

7. Presence of any other histological type of resected tumor other than urothelial carcinoma on the first or second resection?* O Yes O No

8. Presence of another malignancy other than the basal cell carcinoma of the skin or localised prostate cancer in active surveillance?* O Yes O No

9. Presence of pregnancy or lactation?* O Yes O No

10. Presence of active tuberculosis, any form of immunodeficiency (eg HIV + serology, transplant recipients) and/or any other contraindication of BCG therapy?* O Yes O No

11. Has the patient received any systemic cytostatic agents within the last 3 months?* O Yes O No

12. Does the patient have uncontrollable UTI?* O Yes O No

13. Has the patient received any multi-instillation intravesical chemotherapy during the last 3 months prior to randomisation?* O Yes O No

Exclusion Criteria (amendment 4)*

14. Has single dose postoperative chemotherapy (e.g. Mitomycin C) been given after (re-)re-TUR?* O Yes O No

In case any of the items is YES patient is not eligible

Inclusion Criteria (amendment 5)*

1. Is there any presence of high grade* (Ta-T1) urothelial papillary carcinoma of the bladder with or without CIS. Tumors can be primary or recurrent, single or multiple.* O Yes O No

*Pathological Grading will be done according to WHO/ISUP classification

2a. In case of a Ta high grade tumor in the initial resection, a re-TUR can be performed at the discretion of the investigator. Does initial resection or re-TUR include the deep resection or cold cup biopsy (deep enough to obtain muscle tisssue) of the (initial) tumor site(s)? O Yes O No

2b. In case of a T1 high grade tumor in the initial resection, has a re-TUR been performed at weeks 4-8 after initial resection, including the deep resection or cold cup biopsy (deep enough to obtain muscle tisssue) of the initial tumor site(s)?*

3. Has a re-re-TUR been performed, at weeks 4-8 after re-TUR, in case of histological detection of T1 low grade/high grade tumor in the re-TUR, including the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s)?* O Yes O No

Re-Re-TUR should be performed in case of histological detection of T1 low grade/high grade papillary tumor in the Re-TUR, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s).

4. Histopathologically confirmed absence of T1 low grade/high-grade tumor(s) in the re-TUR specimen and/or re-re-TUR specimen?* O Yes O No

5. Have all visible papillary tumors been completely resected?* O Yes O No

6. If the patient is male, will he use a condom during sexual intercourse during the first week after BCG treatment? If the patient is female and of childbearing potential, does she have a negative pregnancy test and will she practice adequate contraception for 30 days prior to administration of study treatment and will she continue such precautions during all study treatment period and for 3 months after the last BCG treatment?* O Yes O No

7. Has the Patient signed and dated the Informed Consent Form?* O Yes O No

Inclusion Criteria (amendment 5)*

8. Is patient clinically fit enough to receive BCG bladder instillations?*	O Yes O No

In case any of the items is NO patient is not eligible

Exclusion Criteria (amendment 5)*

1. Has the patient received any previous intravesical BCG therapy?*	O Yes O No
2. Is there any presence of primary CIS only?*	O Yes O No
3. Is there any presence of histopathologically proven muscle invasive urothelial carcinoma of the bladder at the first or (re-)re-TUR surgical specimens?*	O Yes O No
4. Presence of any tumors in upper urinary tract or in the prostatic urethra at any time?*	O Yes O No
5. Presence of any other histological type of resected tumor other than urothelial carcinoma on the first or second resection?*	O Yes O No
6. Presence of another malignancy in the 5 years prior to randomisation, other than the basal cell carcinoma of the skin or localised prostate cancer in active surveillance?*	O Yes O No
7. Presence of pregnancy or lactation?*	O Yes O No
8. Presence of active tuberculosis, any form of immunodeficiency (eg HIV + serology, transplant recipients) and/or any other contraindication of BCG therapy?*	O Yes O No
9. Has the patient received any systemic cytostatic agents within the last 3 months?*	O Yes O No
10. Does the patient have uncontrollable UTI?*	O Yes O No
11. Has the patient received any multi-instillation intravesical chemotherapy during the last 3 months prior to randomisation?*	O Yes O No
12. Has single dose postoperative chemotherapy (e.g. Mitomycin C) been given after (re-)re-TUR?*	O Yes O No

In case any of the items is YES patient is not eligible

Randomisation*

Stratification Criteria*

Pathological Papillary Bladder Tumors*	O Ta O T1
In case of multiple tumors, enter the highest T category	
Presence of Bladder Tumors*	O With CIS O Without CIS
Type of BCG strain*	O BCG Tice O BCG Connaught O BCG Medac (other name: BCG RIVM) O Other

Stratification Criteria*

Number of Papillary Tumors*	O Single Tumor O Multiple Tumors
Click 'Save/Next' to Randomise this patient. Algorithm mode applicable for center:*	∇ minimization algorithm ∇ manual entry

Randomisation*

Auxiliary item for switch of randomization: algorithm to apply?	∇ Yes ∇ No
Treatment Schedule (entered)	_ _
Date of randomisation (entered)	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Treatment Schedule (minim. alg.)	_ _
Date of randomisation (minim. alg.)	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Treatment Schedule	_ _
Date of randomisation	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Randomisation Number	_ _ _ _

*Screening**

Demography*

Demography*

Date of visit*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Gender*	O Male O Female
Childbearing status*	O Childbearing potential O Post-menopausal O Surgically sterile
A pregnancy test must be performed within 7 days before start of each BCG cycle and 3 months after the last BCG treatment. Date of pregnancy test*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Result pregnancy test*	O Positive O Negative
Race	O Caucasian O Asian O Black O Oriental O Other
If Other, specify	_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Height	_ _ _ cm
Weight	_ _ _ , _ kg

Medical History*

Medical History (not related to the disease under study)*

Please record all the Concomitant Medications the patient is currently taking in the concomitant treatment section Is there any relevant medical history?*	O Yes O No

If any condition is currently being treated, please complete concomitant treatment section.

Add as many Conditions as needed by clicking on 'Add ItemGroup' [# _ _]*

Condition/Medical History*	_ _
Start Date	_ _ _ _ Year
Ongoing at study start?	O Yes O No
Currently treated	O Yes O No

Previous History of Bladder Cancer*

Previous History of Bladder Cancer*

Current tumor is:*	O Primary O Recurrent

Recurrent*

Date of the first pathological diagnosis of bladder cancer*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Number of previous TUR's at which pathologically proven bladder tumors were present	_ _
Highest pT category of papillary tumor:	O T0 O Ta O T1 O Tis O ≥T2
	O WHO 2004 O WHO 1973
Which WHO grading system would you like to use?	
Highest grade of papillary tumor (WHO 2004)	O Papilloma O PUNLMP O LG O HG O Not available
Highest grade of papillary tumor (WHO 1973)	O Papilloma O Grade 1 O Grade 2 O Grade 3 O Not available
Date of the last TUR before study entry	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Did the patient receive intravesical therapy previously?	O Yes O No

Previous intravesical therapy [# _ _]*

Previous intravesical therapy	∇ BCG ∇ Mitomycin ∇ Epirubicin ∇ Other agent, specify
Other agent, specify	_ _
Total number of instillations	_ _
Date of the last instillation	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Clinical Examination*

Upper Urinary Tract Investigation*

Has the upper urinary tract been investigated for any suspected tumors?*	O Yes O No

Add as many Types of Investigation as needed by clicking on 'Add ItemGroup' [# _ _]*

Date of investigation	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Type of investigation	O CT-Urography O IVU O Other
If other, specify	_ _
Was investigation suspicious for upper urinary tract tumor?*	O Yes O No

Physical Examination*

Has a physical examination been performed?*	O Yes O No
Result	O Normal O Abnormal
Abnormal, specify	_ _
Please add the condition to the Medical History	_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _

WHO Performance Score*

WHO Performance Score*

WHO Performance Score*

O 0. Asymptomatic O 1. Symptomatic but completely ambulatory O 2. Symptomatic, O 3. Symptomatic, >50% in bed during day O 4. Bedbound O 5. Death

ASA Performance Scale*

ASA Performance Scale*

O 1. A normal healthy patient O 2. A patient with mild systemic disease O 3. A patient with severe systemic disease O 4. A patient with severe systemic disease that is a constant threat to life O 5. A moribund patient who is not expected to survive without the operation O 6. A declared brain-dead patient whose organs are being removed for donor purposes

Laboratory Examination*

Laboratory Examination*

Date of examination* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

In case of multiple dates, please enter the most recent date

BUN*

Test done Yes/No* O Yes O No

Result* _ _ , _ _ [ ]mg/dL [ ]mmol/L

Lower range _ _ , _ _

Upper Range _ _ , _ _

Clinically Significant* O Yes O No

If Yes, please add to the Medical History

Creatinine*

Creatinine* O Yes O No

Result* _ _ _ , _ _ [ ]mg/dL [ ]µmol/L

Lower range _ _ _ , _ _

Upper Range _ _ _ , _ _

Clinically Significant* O Yes O No

If Yes, please add to the Medical History

AST*

AST* O Yes O No

Result* _ _ _ , _ U/L

Lower range _ _ , _

Upper Range _ _ , _

AST*

Clinically Significant*	O Yes O No

If Yes, please add to the Medical History

ALT*

ALT*	O Yes O No
Result*	_ _ _ , _ U/L
Lower range	_ _ , _
Upper Range	_ _ , _
Clinically Significant*	O Yes O No

If Yes, please add to the Medical History

Leucocytes*

Leucocytes*	O Yes O No
Result*	_ _ , _ x 10E9/L
Lower range	_ _ , _
Upper Range	_ _ , _
Clinically Significant*	O Yes O No

If Yes, please add to the Medical History

Platelets*

Platelets*	O Yes O No
Result*	_ _ _ x 10E9/L
Lower range	_ _ _
Upper Range	_ _ _
Clinically Significant*	O Yes O No

If Yes, please add to the Medical History

DNA Substudy*

If the patient is participating in the substudy, has a blood sample been collected?*	O Yes O No

Cystoscopy prior to TUR*

Cystoscopy prior TUR*

Date of cystoscopy*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Kind of cystoscopy*	O Flexible O Rigid
Advanced imaging method used?*	O Yes O No
If Yes, please specify: Method:*	O Blue light cystoscopy O NBI O Other, specify
Other, specify*	_ _

Cystoscopy prior TUR*

Lesions with high suspicion for malignancy at cystoscopy*	O Yes O No
If Yes, please specify: Flat*	O Yes O No
Exophytic tumor*	O Yes O No
Aspect*	O Papillary O Solid O Both
Number*	O Single Tumor O Multiple Tumors

TUR at Study Entry*

TUR at Study Entry*

Date of TUR* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Bladdermap

Indicate number and size (maximum diameter) of **pathologically confirmed papillary** tumors at each location

A: Trigone*

Number of tumors:*	_ _
Size 1 (mm):	_ _ _
Size 2 (mm):	_ _ _
Size 3 (mm):	_ _ _
√ if exact size is unknown.	☐
Size 1*	∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA
Size 2	∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA
Size 3	∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

B: Right ureteral orifice*

Number of tumors:*	_ _
Size 1 (mm):	_ _ _
Size 2 (mm):	_ _ _
Size 3 (mm):	_ _ _
√ if exact size is unknown.	☐
Size 1*	∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA
Size 2	∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA
Size 3	∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

C: Left ureteral orifice*

Number of tumors:*	_ _
Size 1 (mm):	_ _ _

C: Left ureteral orifice*

Size 2 (mm): _ _ _

Size 3 (mm): _ _ _

√ if exact size is unknown. ☐

Size 1* ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 2 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 3 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

D: Right wall*

Number of tumors:* _ _

Size 1 (mm): _ _ _

Size 2 (mm): _ _ _

Size 3 (mm): _ _ _

√ if exact size is unknown. ☐

Size 1* ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 2 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 3 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

E: Left wall*

Number of tumors:* _ _

Size 1 (mm): _ _ _

Size 2 (mm): _ _ _

Size 3 (mm): _ _ _

√ if exact size is unknown. ☐

Size 1* ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 2 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 3 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

F: Anterior wall*

Number of tumors:* _ _

Size 1 (mm): _ _ _

Size 2 (mm): _ _ _

Size 3 (mm): _ _ _

√ if exact size is unknown. ☐

Size 1* ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 2 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 3 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

G: Posterior wall*

Number of tumors:* _ _

Size 1 (mm): _ _ _

Size 2 (mm): _ _ _

G: Posterior wall*

Size 3 (mm): _ _ _

√ if exact size is unknown. ☐

Size 1* ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 2 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 3 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

H: Dome=fundus*

Number of tumors:* _ _

Size 1 (mm): _ _ _

Size 2 (mm): _ _ _

Size 3 (mm): _ _ _

√ if exact size is unknown. ☐

Size 1* ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 2 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 3 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

I: Neck*

Number of tumors:* _ _

Size 1 (mm): _ _ _

Size 2 (mm): _ _ _

Size 3 (mm): _ _ _

√ if exact size is unknown. ☐

Size 1* ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 2 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 3 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

J: Prostatic urethra*

Number of tumors:* _ _

Size 1 (mm): _ _ _

Size 2 (mm): _ _ _

Size 3 (mm): _ _ _

√ if exact size is unknown. ☐

Size 1* ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 2 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 3 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

K: Prostatic substance*

Number of tumors:* _ _

Size 1 (mm): _ _ _

Size 2 (mm): _ _ _

Size 3 (mm): _ _ _

K: Prostatic substance*

√ if exact size is unknown. ☐

Size 1* ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 2 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

Size 3 ∇ ≤ 30 mm ∇ > 30 mm ∇ UK ∇ NA

*

Highest pT category of papillary tumor:* O T0 O Ta O T1 O Tis O ≥T2

O WHO 2004 O WHO 1973

Which WHO grading system would you like to use?*

Highest grade of papillary tumor (WHO 2004)* O Papilloma O PUNLMP O LG O HG O Not available

Highest grade of papillary tumor (WHO 1973)* O Papilloma O Grade 1 O Grade 2 O Grade 3 O Not available

In patients with Ta-T1 tumors, was associated CIS present?* O Yes O No

Was muscle present in the specimen?* O Yes O No

Was immediate post TUR intravesical instillation administered?* O Yes O No

If Yes, please specify Agent* ∇ BCG ∇ Mitomycin ∇ Epirubicin ∇ Other agent, specify

Other, specify* _

Dose _ _ mg

Volume _ _ ml

Cytology*

Has a cytology been performed?* O Yes O No

Date of cytology before or during initial TUR* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Material* O Voided urine cytology O Wash-out cytology

Cytology result* O Normal exfoliated cells O Cells showing inflammatory changes or dyscaryosis O Specimen with moderate dysplasia or papillary clusters (suspicious) O Specimen with severe dysplasia O Specimen with evidently malignant cells O Specimen could not be evaluated

Cystoscopy prior to re-TUR*

Cystoscopy prior to Re-TUR*

Has a cystoscopy been performed?* O Yes O No

Date of cystoscopy* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Kind of cystoscopy* O Flexible O Rigid

Advanced imaging method used?* O Yes O No

Cystoscopy prior to Re-TUR*

If Yes, please specify:
Method:* — O Blue light cystoscopy O NBI O Other, specify

Other, specify* — _

Lesions with high suspicion for malignancy at cystoscopy* — O Yes O No

If Yes, please specify:
Flat* — O Yes O No

Exophytic tumor* — O Yes O No

Aspect* — O Papillary O Solid O Both

Number* — O Single Tumor O Multiple Tumors

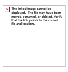
Re-TUR*

Re-TUR date*

Has a re-TUR been performed?* — O Yes O No

Date of re-TUR* — _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Bladdermap



Indicate number and size (maximum diameter) of **pathologically confirmed papillary** tumors at each location

A: Trigone*
- *[Itemgroup already referred to in a previous form!]*

B: Right ureteral orifice*
- *[Itemgroup already referred to in a previous form!]*

C: Left ureteral orifice*
- *[Itemgroup already referred to in a previous form!]*

D: Right wall*
- *[Itemgroup already referred to in a previous form!]*

E: Left wall*
- *[Itemgroup already referred to in a previous form!]*

F: Anterior wall*
- *[Itemgroup already referred to in a previous form!]*

G: Posterior wall*
- *[Itemgroup already referred to in a previous form!]*

H: Dome=fundus*
- *[Itemgroup already referred to in a previous form!]*

I: Neck*

- [Itemgroup already referred to in a previous form!]

J: Prostatic urethra*

- [Itemgroup already referred to in a previous form!]

K: Prostatic substance*

- [Itemgroup already referred to in a previous form!]

---

*

Highest pT category of papillary tumor:*	O T0 O Ta O T1 O Tis O ≥T2
	O WHO 2004 O WHO 1973
Which WHO grading system would you like to use?*	
Highest grade of papillary tumor (WHO 2004)*	O Papilloma O PUNLMP O LG O HG O Not available
Highest grade of papillary tumor (WHO 1973)*	O Papilloma O Grade 1 O Grade 2 O Grade 3 O Not available
In patients with Ta-T1 tumors, was associated CIS present?*	O Yes O No
Was muscle present in the specimen?*	O Yes O No
Was primary CIS present?*	O Yes O No
If Yes, specify Location(s)*	_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Was immediate post TUR intravesical instillation administered?*	O Yes O No
If Yes, please specify Agent*	∇ BCG ∇ Mitomycin ∇ Epirubicin ∇ Other agent, specify
Other, specify*	_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Dose	_ _ mg
Volume	_ _ ml

Cytology*

Has a cytology been performed?*	O Yes O No
Date of cytology before or during re-TUR*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Material*	O Voided urine cytology O Wash-out cytology
Cytology result*	O Normal exfoliated cells O Cells showing inflammatory changes or dyscaryosis O Specimen with moderate dysplasia or papillary clusters (suspicious) O Specimen with severe dysplasia O Specimen with evidently malignant cells O Specimen could not be evaluated

Cystoscopy prior to re-re-TUR*

Cystoscopy prior to Re-Re-TUR*

Cystoscopy prior to Re-Re-TUR*

Has a cystoscopy been performed?*	O Yes O No
Date of cystoscopy*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Kind of cystoscopy*	O Flexible O Rigid
Advanced imaging method used?*	O Yes O No
If Yes, please specify: Method:*	O Blue light cystoscopy O NBI O Other, specify
Other, specify*	_ _
Lesions with high suspicion for malignancy at cystoscopy*	O Yes O No
If Yes, please specify: Flat*	O Yes O No
Exophytic tumor*	O Yes O No
Aspect*	O Papillary O Solid O Both
Number*	O Single Tumor O Multiple Tumors

Re-Re-TUR*

Re-Re-TUR date*

Has a re-re-TUR been performed?*	O Yes O No
Date of re-re-TUR*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Bladdermap

Indicate number and size (maximum diameter) of **pathologically confirmed papillary** tumors at each location

A: Trigone*

- [Itemgroup already referred to in a previous form!]

B: Right ureteral orifice*

- [Itemgroup already referred to in a previous form!]

C: Left ureteral orifice*

- [Itemgroup already referred to in a previous form!]

D: Right wall*

- [Itemgroup already referred to in a previous form!]

E: Left wall*

- [Itemgroup already referred to in a previous form!]

F: Anterior wall*

- [Itemgroup already referred to in a previous form!]

G: Posterior wall*

G: Posterior wall*

- [Itemgroup already referred to in a previous form!]

H: Dome=fundus*

- [Itemgroup already referred to in a previous form!]

I: Neck*

- [Itemgroup already referred to in a previous form!]

J: Prostatic urethra*

- [Itemgroup already referred to in a previous form!]

K: Prostatic substance*

- [Itemgroup already referred to in a previous form!]

*

Highest pT category of papillary tumor:*	O T0 O Ta O T1 O Tis O ≥T2
	O WHO 2004 O WHO 1973
Which WHO grading system would you like to use?*	
Highest grade of papillary tumor (WHO 2004)*	O Papilloma O PUNLMP O LG O HG O Not available
Highest grade of papillary tumor (WHO 1973)*	O Papilloma O Grade 1 O Grade 2 O Grade 3 O Not available
In patients with Ta-T1 tumors, was associated CIS present?*	O Yes O No
Was muscle present in the specimen?*	O Yes O No
Was primary CIS present?*	O Yes O No
If Yes, specify Location(s)*	_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Was immediate post TUR intravesical instillation administered?*	O Yes O No
If Yes, please specify Agent*	∇ BCG ∇ Mitomycin ∇ Epirubicin ∇ Other agent, specify
Other, specify*	_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Dose	_ _ mg
Volume	_ _ ml

Cytology*

Has a cytology been performed?*	O Yes O No
Date of cytology before or during re-re-TUR*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Material*	O Voided urine cytology O Wash-out cytology
Cytology result*	O Normal exfoliated cells O Cells showing inflammatory changes or dyscaryosis O Specimen with moderate dysplasia or papillary clusters (suspicious) O Specimen with severe dysplasia O Specimen with evidently malignant cells O Specimen could not be evaluated

Month 1 Week 1

General Information*

General Information*

Date of visit*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Did the patient complete the ICIQ LUTS questionnaires?*	O Yes O No
Did the patient complete the QLQ-C30 questionnaires?*	O Yes O No
Were there any changes to the Concomitant Treatment including antibiotics?*	O Yes O No

If Yes, please complete the Concomitant Medication form.

Urine Examination*

Urine Examination*

Has an Urine Examination been performed?*	O Yes O No

Nitrite test*

Nitrite test*	O Yes O No
Date	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Result*	O Negative O Positive

Urine culture*

Urine culture*	O Yes O No
Date	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Result*	O Negative O Positive

Mycobacterium DNA PCR

Test done Yes/No	O Yes O No
Date	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Result*	O Negative O Positive

Löwenstein cultures

Löwenstein cultures	O Yes O No
Date	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Result*	O Negative O Positive

Baseline condition grading*

Baseline condition grading prior to instillation*

Has the grading of the baseline condition been assessed?* O Yes O No

Please provide the grade for each baseline condition:
Grade 0: No baseline condition
Grade 1: Moderate
Grade 2: Severe

Local Condition*

Frequency	∇ Grade 0: No baseline condition ∇ Grade 1: Moderate ∇ Grade 2: Severe
Urgency	∇ Grade 0: No baseline condition ∇ Grade 1: Moderate ∇ Grade 2: Severe
Dysuria	∇ Grade 0: No baseline condition ∇ Grade 1: Moderate ∇ Grade 2: Severe
Incontinence	∇ Grade 0: No baseline condition ∇ Grade 1: Moderate ∇ Grade 2: Severe
Macroscopic hematuria	∇ Grade 0: No baseline condition ∇ Grade 1: Moderate ∇ Grade 2: Severe
Bacterial cystitis	∇ Grade 0: No baseline condition ∇ Grade 1: Moderate ∇ Grade 2: Severe
Chemical cystitis	∇ Grade 0: No baseline condition ∇ Grade 1: Moderate ∇ Grade 2: Severe
Other, specify	_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Grading 'Other, specify'	∇ Grade 0: No baseline condition ∇ Grade 1: Moderate ∇ Grade 2: Severe

Systemic Condition*

Fever	∇ Grade 0: No baseline condition ∇ Grade 1: Moderate ∇ Grade 2: Severe
General malaise	∇ Grade 0: No baseline condition ∇ Grade 1: Moderate ∇ Grade 2: Severe
Skin rash	∇ Grade 0: No baseline condition ∇ Grade 1: Moderate ∇ Grade 2: Severe
Lung infection	∇ Grade 0: No baseline condition ∇ Grade 1: Moderate ∇ Grade 2: Severe
Sepsis	∇ Grade 0: No baseline condition ∇ Grade 1: Moderate ∇ Grade 2: Severe
Other, specify	_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Grading 'Other, specify'	∇ Grade 0: No baseline condition ∇ Grade 1: Moderate ∇ Grade 2: Severe

Female LUTS Questionnaires*

Female LUTS Questionnaire*

Many people experience urinary symptoms some of the time. We are trying to find out how many people experience urinary symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

Today's Date* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

2a. During the night, how many times do you have to get up to urinate, on average?* O none O one O two O three O four of more

2b. How much does this bother you?*

Please ring a number between 0 (not at all) and 10 (a great deal)

O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

3a. Do you have a sudden need to rush to the toilet to urinate?* O never O occasionally O sometimes O most of the time O all of the time

3b. How much does this bother you?*

Please ring a number between 0 (not at all) and 10 (a great deal)

O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

4a. Do you have pain in your bladder?* O never O occasionally O sometimes O most of the time O all of the time

4b. How much does this bother you?*

Please ring a number between 0 (not at all) and 10 (a great deal)

O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

5a. How often do you pass urine during the day?* O 1 to 6 times O 7 to 8 times O 9 to 10 times O 11 to 12 times O 13 or more times

5b. How much does this bother you?*

Please ring a number between 0 (not at all) and 10 (a great deal)

O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

F score: sum scores 2a-5a* _ _

6a. Is there a delay before you can start to urinate?* O never O occasionally O sometimes O most of the time O all of the time

6b. How much does this bother you?*

Please ring a number between 0 (not at all) and 10 (a great deal)

O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

7a. Do you have to strain to urinate?* O never O occasionally O sometimes O most of the time O all of the time

7b. How much does this bother you?*

Please ring a number between 0 (not at all) and 10 (a great deal)

O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

8a. Do you stop and start more than once while you urinate?* O never O occasionally O sometimes O most of the time O all of the time

Female LUTS Questionnaire*

8b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

V score: sum scores 6a+7a+8a* _ _

9a. Does urine leak before you can get to the toilet?* O never O occasionally O sometimes O most of the time O all of the time

9b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

10a. How often do you leak urine?* O never O once or less per week O two or three times per week O once per day O several times per day

10b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

11a. Does urine leak when you are physically active, exert yourself, cough or sneeze?* O never O occasionally O sometimes O most of the time O all of the time

11b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

12a. Do you ever leak urine for no obvious reason and without feeling that you want to go?* O never O occasionally O sometimes O most of the time O all of the time

12b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

13a. Do you leak urine when you are asleep?* O never O occasionally O sometimes O most of the time O all of the time

13b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

I score: sum scores 9a-13a* _ _

Male LUTS Questionnaires*

Male LUTS Questionnaires*

Male LUTS Questionnaires*

Many people experience urinary symptoms some of the time. We are trying to find out how many people experience urinary symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

Today's Date* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

2a. Is there a delay before you can start to urinate?* O never O occasionally O sometimes O most of the time O all of the time

2b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

3a. Do you have to strain to continue urinating?* O never O occasionally O sometimes O most of the time O all of the time

3b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

4a. Would you say that the strength of your urinary stream is…* O normal O occasionally reduced O sometimes reduced O reduced most of the time O reduced all of the time

4b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

5a. Do you stop and start more than once while you urinate?* O never O occasionally O sometimes O most of the time O all of the time

5b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

6a. How often do you feel that your bladder has not emptied properly after you have urinated?* O never O occasionally O sometimes O most of the time O all of the time

6b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

VS: sum scores 2-6* _ _

7a. Do you have a sudden need to rush to the toilet to urinate?* O never O occasionally O sometimes O most of the time O all of the time

7b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

8a. Does urine leak before you can get to the toilet?* O never O occasionally O sometimes O most of the time O all of the time

Male LUTS Questionnaires*

8b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

9a. Does urine leak when you cough or sneeze?* O never O occasionally O sometimes O most of the time O all of the time

9b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

10a. Do you ever leak for no obvious reason and without feeling that you want to go?* O never O occasionally O sometimes O most of the time O all of the time

10b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

11a. Do you leak urine when you are asleep?* O never O occasionally O sometimes O most of the time O all of the time

11b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

12a. How often have you had a slight wetting of your pants a few minutes after you had finished urinating and had dressed yourself?* O never O occasionally O sometimes O most of the time O all of the time

12b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

IS: sum scores 7-12*

13a. How often do you pass urine during the day?* _ _ O 1 to 6 times O 7 to 8 times O 9 to 10 times O 11 to 12 times O 13 or more times

13b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

14a. During the night, how many times do you have to get up to urinate, on average?* O none O one O two O three O four of more

14b. How much does this bother you?* O 0 O 1 O 2 O 3 O 4 O 5 O 6 O 7 O 8 O 9 O 10

Please ring a number between 0 (not at all) and 10 (a great deal)

Quality of Life Questionnaires*

Quality of Life Questionnaires-C30*

Quality of Life Questionnaires-C30*

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are not « right » or « wrong » answers. The information that you provide will remain strictly confidential.

Today's Date* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

1. Do you have any trouble doing strenous activities, like carrying a heavy shopping bag or suitcase?*	O Not at all O A little O Quite a bit O Very much
2. Do you have any trouble taking a LONG walk?*	O Not at all O A little O Quite a bit O Very much
3. Do you have any trouble taking a SHORT walk outside the house?*	O Not at all O A little O Quite a bit O Very much
4. Do you need to stay in bed or a chair during the day?*	O Not at all O A little O Quite a bit O Very much
5. Do you need help with eating, dressing, washing yourself or using the toilet?*	O Not at all O A little O Quite a bit O Very much
During the past week: 6. Were you limited in doing either your work or other daily activities?*	O Not at all O A little O Quite a bit O Very much
7. Were you limited in persuing your hobbies or other leisure time activities?*	O Not at all O A little O Quite a bit O Very much
8. Were you short in breath?*	O Not at all O A little O Quite a bit O Very much
9. Have you had pain?*	O Not at all O A little O Quite a bit O Very much
10. Did you need to rest?*	O Not at all O A little O Quite a bit O Very much
11. Have you had trouble sleeping?*	O Not at all O A little O Quite a bit O Very much
12. Have you felt weak?*	O Not at all O A little O Quite a bit O Very much
13. Have you lacked appetite?*	O Not at all O A little O Quite a bit O Very much
14. Have you felt nauseated?*	O Not at all O A little O Quite a bit O Very much
15. Have you vomited?*	O Not at all O A little O Quite a bit O Very much
16. Have you been constipated?*	O Not at all O A little O Quite a bit O Very much
17. Have you had diarrhea?*	O Not at all O A little O Quite a bit O Very much
18. Were you tired?*	O Not at all O A little O Quite a bit O Very much
19. Did pain interfere with your daily activities?*	O Not at all O A little O Quite a bit O Very much
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?*	O Not at all O A little O Quite a bit O Very much
21. Did you feel tense?*	O Not at all O A little O Quite a bit O Very much
22. Did you worry?*	O Not at all O A little O Quite a bit O Very much
23. Did you feel irritable?*	O Not at all O A little O Quite a bit O Very much
24. Did you feel depressed?*	O Not at all O A little O Quite a bit O Very much
25. Have you had difficulty remembering things?*	O Not at all O A little O Quite a bit O Very much
26. Has your physical condition or medical treatment interfered with your family life?*	O Not at all O A little O Quite a bit O Very much
27. Has your physical condition or medical treatment interfered with your social life?*	O Not at all O A little O Quite a bit O Very much
28. Has your physical condition or medical treatment caused you financial difficulties?*	O Not at all O A little O Quite a bit O Very much

Quality of Life Questionnaires-C30*

For the following questions please circle the number between 1 and 7 that best applies to you 29. How would you rate your overall health during the past week?*	O 1 (Very poor) O 2 O 3 O 4 O 5 O 6 O 7 (Excellent)
30. How would you rate your overall Quality of Life during the past week?*	O 1 (Very poor) O 2 O 3 O 4 O 5 O 6 O 7 (Excellent)

BCG Instillation*

BCG Instillation*

Date of instillation*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Date and Time of Instillation*	_ _ /_ _ /_ _ _ _ _ _ :_ _ dd/mmm/yyyy hh:mm
Has the instillation been delayed?*	O Yes O No
Instillation delayed due to*	_ _
Patient restricted fluid prior to attendance for instillation?	O Yes O No
Catheterization*	O Non-traumatic O Traumatic
Size of catheter	_ _ F/Ch
Urine Volume drained from bladder immediately pre-instillation	_ _ _ _ ml
BCG received*	O Not administered because of traumatic catheterization O Full dose O One-third–dose O Reduced dose, specify
Reduced dose, specify*	_ _
BCG Strain*	O BCG Tice O BCG Connaught O BCG Medac (other name: BCG RIVM)
Catheter management after instillation*	O Plugged + Retained O Removed immediately
Postvoided residual urine measured by transabdominal ultrasonography	_ _ _ _ ml

BCG retention*

Duration of retention in bladder	_ _ _ minutes
Was the patient rotated during retention?*	O Yes O No
Provide urine volume drainage at end of instillation	_ _ _ _ ml
Provide urine volume voided at end of instillation	_ _ _ _ ml

Immunological Substudy*

Urine sample collected prior to BCG instillation*

Date and time the urine sample has been collected*	_ _ /_ _ /_ _ _ _ _ _ :_ _ dd/mmm/yyyy hh:mm

Urine sample collected after BCG instillation*

Date and time the urine sample has been collected* _ _ /_ _ /_ _ _ _ _ _ :_ _ dd/mmm/yyyy hh:mm

Month 1 Week 2

General Information*

General information*

Date of visit*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Has an urine examination been done?*	O Yes O No
If Yes, please record only the Positive results on an Unscheduled Urine Examination form.	
Did the patient experience any Adverse Events since last visit/instillation?*	O Yes O No
Were there any changes to the Concomitant Treatment including antibiotics?*	O Yes O No
If Yes, please complete the Concomitant Medication form.	

Treatment Modification*

Treatment Modification*

Has the treatment been modified?*	O Yes O No
If Yes, treatment has been modified due to*	O Side-Effects after previous instillation (Please record as an Adverse Event) O Other, specify
Other, specify*	_ _
Specify the treatment modification*	O Instillation administered too early O BCG dose has been reduced O Instillation was delayed without reducing the BCG dose O Instillation was delayed with reducing the BCG dose O Instillation had to be stopped

In case of early stop of BCG instillations, side effects are to be evaluated and questionnaires are to be completed.

BCG Discontinuation Assessments*

BCG Discontinuation Assessments*

Did the patient complete the ICIQ LUTS questionnaires?*	O Yes O No
Did the patient complete the QLQ-C30 questionnaires?*	O Yes O No

BCG Instillation*

BCG Instillation*

Date of instillation*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Date and Time of Instillation*	_ _ /_ _ /_ _ _ _ _ _ :_ _ dd/mmm/yyyy hh:mm
Patient restricted fluid prior to attendance for instillation?	O Yes O No
Catheterization*	O Non-traumatic O Traumatic
Size of catheter	_ _ F/Ch
Urine Volume drained from bladder immediately pre-instillation	_ _ _ _ ml
BCG received*	O Not administered because of traumatic catheterization O Full dose O One-third–dose O Reduced dose, specify
Reduced dose, specify*	_ _
BCG Strain*	O BCG Tice O BCG Connaught O BCG Medac (other name: BCG RIVM)
Catheter management after instillation*	O Plugged + Retained O Removed immediately
Postvoided residual urine measured by transabdominal ultrasonography	_ _ _ _ ml

BCG retention*

- [Itemgroup already referred to in a previous form!]

Immunological Substudy*

- [Form already referred to in a previous event!]

Side Effects*

Side Effects*

Has the grading of toxicity been assessed?* O Yes O No

Side effects also need to be recorded as (S)AE

Please provide the toxicity grade for each side effect:
Grade 0: No side effect
Grade 1: Moderate and
Grade 2: Severe and/or >48 h (usually requires suspension of instillations until resolution of symptoms)
Grade 3: Local, regional, systemic, and immunoallergic (resumption of instillations must be

evaluated in the light of the benefit-risk ratio with dose reduction)
Grade 4: Systemic BCG reactions (cessation of BCG therapy is required)

Local Side effects*

Frequency*	∇ Grade 0: No side effect ∇ Grade 1: Moderate and ∇ Grade 2: Severe and/or >48 h ∇ Grade 3: Local, regional, systemic, and immunoallergic ∇ Grade 4: Systemic BCG reactions
Urgency*	∇ Grade 0: No side effect ∇ Grade 1: Moderate and ∇ Grade 2: Severe and/or >48 h ∇ Grade 3: Local, regional, systemic, and immunoallergic ∇ Grade 4: Systemic BCG reactions
Dysuria*	∇ Grade 0: No side effect ∇ Grade 1: Moderate and ∇ Grade 2: Severe and/or >48 h ∇ Grade 3: Local, regional, systemic, and immunoallergic ∇ Grade 4: Systemic BCG reactions
Incontinence*	∇ Grade 0: No side effect ∇ Grade 1: Moderate and ∇ Grade 2: Severe and/or >48 h ∇ Grade 3: Local, regional, systemic, and immunoallergic ∇ Grade 4: Systemic BCG reactions
Macroscopic hematuria*	∇ Grade 0: No side effect ∇ Grade 1: Moderate and ∇ Grade 2: Severe and/or >48 h ∇ Grade 3: Local, regional, systemic, and immunoallergic ∇ Grade 4: Systemic BCG reactions
Bacterial cystitis*	∇ Grade 0: No side effect ∇ Grade 1: Moderate and ∇ Grade 2: Severe and/or >48 h ∇ Grade 3: Local, regional, systemic, and immunoallergic ∇ Grade 4: Systemic BCG reactions
Chemical cystitis*	∇ Grade 0: No side effect ∇ Grade 1: Moderate and ∇ Grade 2: Severe and/or >48 h ∇ Grade 3: Local, regional, systemic, and immunoallergic ∇ Grade 4: Systemic BCG reactions
Other, specify	_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Grading 'Other, specify'	∇ Grade 0: No side effect ∇ Grade 1: Moderate and ∇ Grade 2: Severe and/or >48 h ∇ Grade 3: Local, regional, systemic, and immunoallergic ∇ Grade 4: Systemic BCG reactions

Side effects also need to be recorded as (S)AE

Systemic Side Effects*

Fever*	∇ Grade 0: No side effect ∇ Grade 1: Moderate and ∇ Grade 2: Severe and/or >48 h ∇ Grade 3: Local, regional, systemic, and immunoallergic ∇ Grade 4: Systemic BCG reactions
General malaise*	∇ Grade 0: No side effect ∇ Grade 1: Moderate and ∇ Grade 2: Severe and/or >48 h ∇ Grade 3: Local, regional, systemic, and immunoallergic ∇ Grade 4: Systemic BCG reactions

Systemic Side Effects*

Skin rash*	∇ Grade 0: No side effect ∇ Grade 1: Moderate and ∇ Grade 2: Severe and/or >48 h ∇ Grade 3: Local, regional, systemic, and immunoallergic ∇ Grade 4: Systemic BCG reactions
BCG induced lung infection*	∇ Grade 0: No side effect ∇ Grade 1: Moderate and ∇ Grade 2: Severe and/or >48 h ∇ Grade 3: Local, regional, systemic, and immunoallergic ∇ Grade 4: Systemic BCG reactions
Sepsis*	∇ Grade 0: No side effect ∇ Grade 1: Moderate and ∇ Grade 2: Severe and/or >48 h ∇ Grade 3: Local, regional, systemic, and immunoallergic ∇ Grade 4: Systemic BCG reactions
Other, specify	_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Grading 'Other, specify'	∇ Grade 0: No side effect ∇ Grade 1: Moderate and ∇ Grade 2: Severe and/or >48 h ∇ Grade 3: Local, regional, systemic, and immunoallergic ∇ Grade 4: Systemic BCG reactions

Female LUTS Questionnaires*

- [Form already referred to in a previous event!]

Male LUTS Questionnaires*

- [Form already referred to in a previous event!]

Quality of Life Questionnaires*

- [Form already referred to in a previous event!]

Month 1 Week 3

General Information*

- [Form already referred to in a previous event!]

Treatment Modification*

- [Form already referred to in a previous event!]

In case of early stop of BCG instillations, side effects are to be evaluated and questionnaires are to be completed.

BCG Discontinuation Assessments*

- [Form already referred to in a previous event!]

BCG Instillation*

BCG Instillation*

Date of instillation*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Date and Time of Instillation*	_ _ /_ _ /_ _ _ _ _ _ :_ _ dd/mmm/yyyy hh:mm
Patient restricted fluid prior to attendance for instillation?	O Yes O No
Catheterization*	O Non-traumatic O Traumatic
Size of catheter	_ _ F/Ch
Urine Volume drained from bladder immediately pre-instillation	_ _ _ _ ml
BCG received*	O Not administered because of traumatic catheterization O Full dose O One-third–dose O Reduced dose, specify
Reduced dose, specify*	_ _
BCG Strain*	O BCG Tice O BCG Connaught O BCG Medac (other name: BCG RIVM)
Catheter management after instillation*	O Plugged + Retained O Removed immediately
Postvoided residual urine measured by transabdominal ultrasonography	_ _ _ _ ml

BCG retention*

BCG retention*

- [Itemgroup already referred to in a previous form!]

Immunological Substudy*

- [Form already referred to in a previous event!]

Side Effects*

- [Form already referred to in a previous event!]

Female LUTS Questionnaires*

- [Form already referred to in a previous event!]

Male LUTS Questionnaires*

- [Form already referred to in a previous event!]

Quality of Life Questionnaires*

- [Form already referred to in a previous event!]

Month 1 Week 4

General Information*

- [Form already referred to in a previous event!]

Treatment Modification*

- [Form already referred to in a previous event!]

In case of early stop of BCG instillations, side effects are to be evaluated and questionnaires are to be completed.

BCG Discontinuation Assessments*

- [Form already referred to in a previous event!]

BCG Instillation*

BCG Instillation*

Date of instillation*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Date and Time of Instillation*	_ _ /_ _ /_ _ _ _ _ _ :_ _ dd/mmm/yyyy hh:mm
Patient restricted fluid prior to attendance for instillation?	O Yes O No
Catheterization*	O Non-traumatic O Traumatic
Size of catheter	_ _ F/Ch
Urine Volume drained from bladder immediately pre-instillation	_ _ _ _ ml
BCG received*	O Not administered because of traumatic catheterization O Full dose O One-third–dose O Reduced dose, specify
Reduced dose, specify*	_ _
BCG Strain*	O BCG Tice O BCG Connaught O BCG Medac (other name: BCG RIVM)
Catheter management after instillation*	O Plugged + Retained O Removed immediately
Postvoided residual urine measured by transabdominal ultrasonography	_ _ _ _ ml

BCG retention*

BCG retention*

- [Itemgroup already referred to in a previous form!]

Immunological Substudy*

- [Form already referred to in a previous event!]

Side Effects*

- [Form already referred to in a previous event!]

Female LUTS Questionnaires*

- [Form already referred to in a previous event!]

Male LUTS Questionnaires*

- [Form already referred to in a previous event!]

Quality of Life Questionnaires*

- [Form already referred to in a previous event!]

Month 2 Week 5

General Information*

- [Form already referred to in a previous event!]

Treatment Modification*

- [Form already referred to in a previous event!]

In case of early stop of BCG instillations, side effects are to be evaluated and questionnaires are to be completed.

BCG Discontinuation Assessments*

- [Form already referred to in a previous event!]

BCG Instillation*

BCG Instillation*

Date of instillation*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Date and Time of Instillation*	_ _ /_ _ /_ _ _ _ _ _ :_ _ dd/mmm/yyyy hh:mm
Patient restricted fluid prior to attendance for instillation?	O Yes O No
Catheterization*	O Non-traumatic O Traumatic
Size of catheter	_ _ F/Ch
Urine Volume drained from bladder immediately pre-instillation	_ _ _ _ ml
BCG received*	O Not administered because of traumatic catheterization O Full dose O One-third–dose O Reduced dose, specify
Reduced dose, specify*	_ _
BCG Strain*	O BCG Tice O BCG Connaught O BCG Medac (other name: BCG RIVM)
Catheter management after instillation*	O Plugged + Retained O Removed immediately
Postvoided residual urine measured by transabdominal ultrasonography	_ _ _ _ ml

BCG retention*

BCG retention*

- [Itemgroup already referred to in a previous form!]

Immunological Substudy*

- [Form already referred to in a previous event!]

Side Effects*

- [Form already referred to in a previous event!]

Female LUTS Questionnaires*

- [Form already referred to in a previous event!]

Male LUTS Questionnaires*

- [Form already referred to in a previous event!]

Quality of Life Questionnaires*

- [Form already referred to in a previous event!]

Month 2 Week 6

General Information*

General Information*

Date of visit*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Did the patient complete the ICIQ LUTS questionnaires?*	O Yes O No
Did the patient complete the QLQ-C30 questionnaires?*	O Yes O No
Has an urine examination been done?*	O Yes O No
If Yes, please record only the Positive results on an Unscheduled Urine Examination form.	
Did the patient experience any Adverse Events since last visit/instillation?*	O Yes O No
Were there any changes to the Concomitant Treatment including antibiotics?*	O Yes O No
If Yes, please complete the Concomitant Medication form.	

Side Effects*

- [Form already referred to in a previous event!]

Treatment Modification*

- [Form already referred to in a previous event!]

Female LUTS Questionnaires*

- [Form already referred to in a previous event!]

Male LUTS Questionnaires*

- [Form already referred to in a previous event!]

Quality of Life Questionnaires*

- [Form already referred to in a previous event!]

BCG Instillation*

BCG Instillation*

Date of instillation*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Date and Time of Instillation*	_ _ /_ _ /_ _ _ _ _ _ _ :_ _ dd/mmm/yyyy hh:mm
Patient restricted fluid prior to attendance for instillation?	O Yes O No
Catheterization*	O Non-traumatic O Traumatic
Size of catheter	_ _ F/Ch
Urine Volume drained from bladder immediately pre-instillation	_ _ _ _ ml
BCG received*	O Not administered because of traumatic catheterization O Full dose O One-third–dose O Reduced dose, specify
Reduced dose, specify*	_ _
BCG Strain*	O BCG Tice O BCG Connaught O BCG Medac (other name: BCG RIVM)
Catheter management after instillation*	O Plugged + Retained O Removed immediately
Postvoided residual urine measured by transabdominal ultrasonography	_ _ _ _ ml

BCG retention*

- [Itemgroup already referred to in a previous form!]

Immunological Substudy*

- [Form already referred to in a previous event!]

Maintenance Month 3 Week 1

Cytology/Cystoscopy*

Cytology*

Has a cytology been performed?*	O Yes O No
Date of cytology*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Material*	O Voided urine cytology O Wash-out cytology
Cytology result*	O Normal exfoliated cells O Cells showing inflammatory changes or dyscaryosis O Specimen with moderate dysplasia or papillary clusters (suspicious) O Specimen with severe dysplasia O Specimen with evidently malignant cells O Specimen could not be evaluated If abnormal and tumor-free cystoscopy, please complete the Unscheduled UUTI, Biopsies and Wash Cytology form

Cystoscopy*

Has a cystoscopy been performed?*	O Yes O No
Date of cystoscopy*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Kind of cystoscopy*	O Flexible O Rigid
Advanced imaging method used?*	O Yes O No
If Yes, please specify: Method:*	O Blue light cystoscopy O NBI O Other, specify
Other, specify*	_ _
Lesions with high suspicion for malignancy at cystoscopy*	O Yes O No
If Yes, please specify: Flat*	O Yes O No
Exophytic tumor*	O Yes O No
Aspect*	O Papillary O Solid O Both
Number*	O Single Tumor O Multiple Tumors In case of suspicious lesions, please complete the Unscheduled TUR form

General Information*

- [Form already referred to in a previous event!]

Pregnancy Test*

Pregnancy Test*

A pregnancy test must be performed within 7 days before start of each BCG cycle and 3 months after the last BCG treatment.

Date of pregnancy test* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Result pregnancy test* O Positive O Negative

Side Effects*

- [Form already referred to in a previous event!]

Treatment Modification*

- [Form already referred to in a previous event!]

Female LUTS Questionnaires*

- [Form already referred to in a previous event!]

Male LUTS Questionnaires*

- [Form already referred to in a previous event!]

Quality of Life Questionnaires*

- [Form already referred to in a previous event!]

BCG Instillation*

BCG Instillation*

Date of instillation* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Date and Time of Instillation* _ _ /_ _ /_ _ _ _ _ _ :_ _ dd/mmm/yyyy hh:mm

Patient restricted fluid prior to attendance for instillation? O Yes O No

Catheterization* O Non-traumatic O Traumatic

Size of catheter _ _ F/Ch

BCG Instillation*

Urine Volume drained from bladder immediately pre-instillation	_ _ _ _ ml
BCG received*	O Not administered because of traumatic catheterization O Full dose O One-third–dose O Reduced dose, specify
Reduced dose, specify*	_ _
BCG Strain*	O BCG Tice O BCG Connaught O BCG Medac (other name: BCG RIVM)
Catheter management after instillation*	O Plugged + Retained O Removed immediately
Postvoided residual urine measured by transabdominal ultrasonography	_ _ _ _ ml

BCG retention*

- [Itemgroup already referred to in a previous form!]

Immunological Substudy*

- [Form already referred to in a previous event!]

Maintenance Month 3 Week 2

General Information*

- [Form already referred to in a previous event!]

Treatment Modification*

- [Form already referred to in a previous event!]

In case of early stop of BCG instillations, side effects are to be evaluated and questionnaires are to be completed.

BCG Discontinuation Assessments*

- [Form already referred to in a previous event!]

BCG Instillation*

BCG Instillation*

Date of instillation*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Date and Time of Instillation*	_ _ /_ _ /_ _ _ _ _ _ :_ _ dd/mmm/yyyy hh:mm
Patient restricted fluid prior to attendance for instillation?	O Yes O No
Catheterization*	O Non-traumatic O Traumatic
Size of catheter	_ _ F/Ch
Urine Volume drained from bladder immediately pre-instillation	_ _ _ _ ml
BCG received*	O Not administered because of traumatic catheterization O Full dose O One-third–dose O Reduced dose, specify
Reduced dose, specify*	_ _
BCG Strain*	O BCG Tice O BCG Connaught O BCG Medac (other name: BCG RIVM)
Catheter management after instillation*	O Plugged + Retained O Removed immediately
Postvoided residual urine measured by transabdominal ultrasonography	_ _ _ _ ml

BCG retention*

BCG retention*

- [Itemgroup already referred to in a previous form!]

Immunological Substudy*

- [Form already referred to in a previous event!]

Side Effects*

- [Form already referred to in a previous event!]

Female LUTS Questionnaires*

- [Form already referred to in a previous event!]

Male LUTS Questionnaires*

- [Form already referred to in a previous event!]

Quality of Life Questionnaires*

- [Form already referred to in a previous event!]

Maintenance Month 3 Week 3

General Information*

- [Form already referred to in a previous event!]

Side Effects*

- [Form already referred to in a previous event!]

Treatment Modification*

- [Form already referred to in a previous event!]

Female LUTS Questionnaires*

- [Form already referred to in a previous event!]

Male LUTS Questionnaires*

- [Form already referred to in a previous event!]

Quality of Life Questionnaires*

- [Form already referred to in a previous event!]

BCG Instillation*

BCG Instillation*

Date of instillation*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Date and Time of Instillation*	_ _ /_ _ /_ _ _ _ _ _ :_ _ dd/mmm/yyyy hh:mm
Patient restricted fluid prior to attendance for instillation?	O Yes O No
Catheterization*	O Non-traumatic O Traumatic
Size of catheter	_ _ F/Ch

BCG Instillation*

Urine Volume drained from bladder immediately pre-instillation	_ _ _ _ ml
BCG received*	O Not administered because of traumatic catheterization O Full dose O One-third–dose O Reduced dose, specify
Reduced dose, specify*	_ _
BCG Strain*	O BCG Tice O BCG Connaught O BCG Medac (other name: BCG RIVM)
Catheter management after instillation*	O Plugged + Retained O Removed immediately
Postvoided residual urine measured by transabdominal ultrasonography	_ _ _ _ ml

BCG retention*

- [Itemgroup already referred to in a previous form!]

Immunological Substudy*

- [Form already referred to in a previous event!]

Maintenance Month 6 Week 1

Cytology/Cystoscopy*

- [Form already referred to in a previous event!]

General Information*

- [Form already referred to in a previous event!]

Pregnancy Test*

- [Form already referred to in a previous event!]

Side Effects*

- [Form already referred to in a previous event!]

Treatment Modification*

- [Form already referred to in a previous event!]

Female LUTS Questionnaires*

- [Form already referred to in a previous event!]

Male LUTS Questionnaires*

- [Form already referred to in a previous event!]

Quality of Life Questionnaires*

- [Form already referred to in a previous event!]

BCG Instillation*

- [Form already referred to in a previous event!]

Immunological Substudy*

- [Form already referred to in a previous event!]

Maintenance Month 6 Week 2

General Information*

- [Form already referred to in a previous event!]

Treatment Modification*

- [Form already referred to in a previous event!]

In case of early stop of BCG instillations, side effects are to be evaluated and questionnaires are to be completed.

BCG Discontinuation Assessments*

- [Form already referred to in a previous event!]

BCG Instillation*

- [Form already referred to in a previous event!]

Immunological Substudy*

- [Form already referred to in a previous event!]

Side Effects*

- [Form already referred to in a previous event!]

Female LUTS Questionnaires*

- [Form already referred to in a previous event!]

Male LUTS Questionnaires*

- [Form already referred to in a previous event!]

Quality of Life Questionnaires*

- [Form already referred to in a previous event!]

Maintenance Month 6 Week 3

General Information*

- [Form already referred to in a previous event!]

Side Effects*

- [Form already referred to in a previous event!]

Treatment Modification*

- [Form already referred to in a previous event!]

Female LUTS Questionnaires*

- [Form already referred to in a previous event!]

Male LUTS Questionnaires*

- [Form already referred to in a previous event!]

Quality of Life Questionnaires*

- [Form already referred to in a previous event!]

BCG Instillation*

- [Form already referred to in a previous event!]

Immunological Substudy*

- [Form already referred to in a previous event!]

Observational Month 9

Cytology/Cystoscopy*

- [Form already referred to in a previous event!]

General Information*

- [Form already referred to in a previous event!]

In case of (early) study discontinuation at Month 9, side effects are to be evaluated and questionnaires are to be completed.

Study Discontinuation Assessments*

Study Discontinuation Assessments*

Did the patient discontinue the study?*	O Yes O No
Did the patient complete the ICIQ LUTS questionnaires?*	O Yes O No
Did the patient complete the QLQ-C30 questionnaires?*	O Yes O No

Side Effects*

- [Form already referred to in a previous event!]

Female LUTS Questionnaires*

- [Form already referred to in a previous event!]

Male LUTS Questionnaires*

- [Form already referred to in a previous event!]

Quality of Life Questionnaires*

- *[Form already referred to in a previous event!]*

Maintenance Month 12 Week 1

Cytology/Cystoscopy*

- [Form already referred to in a previous event!]

General Information*

- [Form already referred to in a previous event!]

Pregnancy Test*

- [Form already referred to in a previous event!]

Side Effects*

- [Form already referred to in a previous event!]

Treatment Modification*

- [Form already referred to in a previous event!]

Female LUTS Questionnaires*

- [Form already referred to in a previous event!]

Male LUTS Questionnaires*

- [Form already referred to in a previous event!]

Quality of Life Questionnaires*

- [Form already referred to in a previous event!]

BCG Instillation*

- [Form already referred to in a previous event!]

Immunological Substudy*

- [Form already referred to in a previous event!]

Maintenance Month 12 Week 2

General Information*

- [Form already referred to in a previous event!]

Treatment Modification*

- [Form already referred to in a previous event!]

In case of early stop of BCG instillations, side effects are to be evaluated and questionnaires are to be completed.

BCG Discontinuation Assessments*

- [Form already referred to in a previous event!]

BCG Instillation*

- [Form already referred to in a previous event!]

Immunological Substudy*

- [Form already referred to in a previous event!]

Side Effects*

- [Form already referred to in a previous event!]

Female LUTS Questionnaires*

- [Form already referred to in a previous event!]

Male LUTS Questionnaires*

- [Form already referred to in a previous event!]

Quality of Life Questionnaires*

- [Form already referred to in a previous event!]

Maintenance Month 12 Week 3 [End of Treatment]

General Information*
- *[Form already referred to in a previous event!]*

Side Effects*
- *[Form already referred to in a previous event!]*

Treatment Modification*
- *[Form already referred to in a previous event!]*

Female LUTS Questionnaires*
- *[Form already referred to in a previous event!]*

Male LUTS Questionnaires*
- *[Form already referred to in a previous event!]*

Quality of Life Questionnaires*
- *[Form already referred to in a previous event!]*

BCG Instillation*
- *[Form already referred to in a previous event!]*

Immunological Substudy*
- *[Form already referred to in a previous event!]*

Observational Month 15

General Information*

General information*

Has this Visit been done?*	O Yes O No
Date of visit*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Did the patient experience any Adverse Events since last visit/instillation?*	O Yes O No
Were there any changes to the Concomitant Treatment including antibiotics?*	O Yes O No

If Yes, please complete the Concomitant Medication form.

Pregnancy Test*

- [Form already referred to in a previous event!]

Cytology/Cystoscopy*

- [Form already referred to in a previous event!]

Observational Month 18

General Information*

General information*

Has this Visit been done?*	O Yes O No
Date of visit*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Did the patient experience any Serious Adverse Events related to study participation and/or treatment since last visit?*	O Yes O No

If Yes, please complete a Serious Adverse Event form.

Cytology/Cystoscopy*

- [Form already referred to in a previous event!]

Observational Month 21

General Information*

- [Form already referred to in a previous event!]

Cytology/Cystoscopy*

- [Form already referred to in a previous event!]

Observational Month 24

General Information*

- [Form already referred to in a previous event!]

Cytology/Cystoscopy*

- [Form already referred to in a previous event!]

Observational Month 30

General Information*

- [Form already referred to in a previous event!]

Cytology/Cystoscopy*

- [Form already referred to in a previous event!]

Observational Month 36

General Information*

- [Form already referred to in a previous event!]

Cytology/Cystoscopy*

- [Form already referred to in a previous event!]

Observational Month 42

General Information*

- [Form already referred to in a previous event!]

Cytology/Cystoscopy*

- [Form already referred to in a previous event!]

Observational Month 48

General Information*

- [Form already referred to in a previous event!]

Cytology/Cystoscopy*

- [Form already referred to in a previous event!]

Observational Month 54

General Information*

- [Form already referred to in a previous event!]

Cytology/Cystoscopy*

- [Form already referred to in a previous event!]

Observational Month 60

General Information*

- [Form already referred to in a previous event!]

Cytology/Cystoscopy*

- [Form already referred to in a previous event!]

Concomitant Medication

Concomitant Medication*

Concomitant Medication*

Did the patient take any medications at the start of the study and/or during the study?*	O Yes O No

Add as many Medications as needed by clicking on 'Add ItemGroup' [# _ _]*

Medication*	_ _
Route	∇ IV ∇ IH ∇ IM ∇ PR ∇ PV ∇ PO ∇ SC ∇ TO ∇ Other
Total Daily Dose	_ _ _ _ _ , _ _
Unit	∇ mg ∇ g ∇ µg ∇ L ∇ mL ∇ µL ∇ Other
Indication*	_ _
Started pre trial?*	O Yes O No
Start Date	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Ongoing at end of trial?	O Yes O No
Stop Date	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Adverse Events

{} [# _ _]*

Adverse Events*

Adverse Event*	_ _
Grade*	O Mild O Moderate O Severe O Life-threatening O Death
SAE?*	O Yes O No
Relationship to study treatment*	O No reasonable possibility O Reasonable possibility
Has the Study Treatment been modified due to this adverse event?*	O Yes O No
Start Date*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Outcome*	O Recovered/resolved O Recovering/resolving O Not recovered/not resolved O Recovered/resolved with sequalae O Fatal O Unknown O Ongoing at End of Study
Stop Date*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy

End of Study *

End of Study *

End of Study *

Date of study completion or discontinuation from the study *	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Did the patient discontinue the study prematurely? *	O Yes O No
Primary Reason for Discontinuation *	O Ineligible O Consent withdrawn O Adverse Event O Investigator decision O First recurrence which has been identified any time after the completion of Induction course of BCG O Occurrence of new CIS O Occurrence of urothelial carcinoma in the upper tract, or in the Prostatic Urethra O Occurrence of distant Metastases O Occurrence of a new malignancy requiring the use of systemic chemotherapy O Lost to follow up O Death O Other, specify
Other, specify *	_ _
Please specify: Date of Death *	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Related to bladder cancer? *	O Yes O No

Unscheduled Urine Examination

{ Unscheduled Urine Examination} [# _ _]*

Unscheduled Urine Examination number*
Unscheduled Urine Examination number* _ _

Nitrite test*
- *[Itemgroup already referred to in a previous form!]*

Urine culture*
- *[Itemgroup already referred to in a previous form!]*

Mycobacterium DNA PCR
- *[Itemgroup already referred to in a previous form!]*

Löwenstein cultures
- *[Itemgroup already referred to in a previous form!]*

Unscheduled Cytology/Cystoscopy

{ Unscheduled Cytology/Cystoscopy} [# _ _]*

Unscheduled Cytology*

Has a cytology been performed?*	O Yes O No
Date of cytology*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Material*	O Voided urine cytology O Wash-out cytology
Cytology result*	O Normal exfoliated cells O Cells showing inflammatory changes or dyscaryosis O Specimen with moderate dysplasia or papillary clusters (suspicious) O Specimen with severe dysplasia O Specimen with evidently malignant cells O Specimen could not be evaluated
	If abnormal and tumor-free cystoscopy, please complete the Unscheduled UUTI, Biopsies and Wash Cytology form

Unscheduled Cystoscopy*

Has a cystoscopy been performed?*	O Yes O No
Date of cystoscopy*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Kind of cystoscopy*	O Flexible O Rigid
Advanced imaging method used?*	O Yes O No
If Yes, please specify: Method:*	O Blue light cystoscopy O NBI O Other, specify
Other, specify*	_ _
Lesions with high suspicion for malignancy at cystoscopy*	O Yes O No
If Yes, please specify: Flat*	O Yes O No
Exophytic tumor*	O Yes O No
Aspect*	O Papillary O Solid O Both
Number*	O Single Tumor O Multiple Tumors
	In case of suspicious lesions, please complete the Unscheduled TUR form

Unscheduled TUR

{ Unscheduled TUR} [# _ _]*

Should be performed in the case of suspicious lesions or mucosal abnormalities

Unscheduled TUR*

Date of TUR* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Bladdermap

Indicate number and size (maximum diameter) of **pathologically confirmed papillary** tumors at each location

A: Trigone*

- *[Itemgroup already referred to in a previous form!]*

B: Right ureteral orifice*

- *[Itemgroup already referred to in a previous form!]*

C: Left ureteral orifice*

- *[Itemgroup already referred to in a previous form!]*

D: Right wall*

- *[Itemgroup already referred to in a previous form!]*

E: Left wall*

- *[Itemgroup already referred to in a previous form!]*

F: Anterior wall*

- *[Itemgroup already referred to in a previous form!]*

G: Posterior wall*

- *[Itemgroup already referred to in a previous form!]*

H: Dome=fundus*

- *[Itemgroup already referred to in a previous form!]*

I: Neck*

- *[Itemgroup already referred to in a previous form!]*

J: Prostatic urethra*

- *[Itemgroup already referred to in a previous form!]*

K: Prostatic substance*

- *[Itemgroup already referred to in a previous form!]*

*

Highest pT category of papillary tumor:* O T0 O Ta O T1 O Tis O ≥T2

*

O WHO 2004 O WHO 1973

Which WHO grading system would you like to use?*

Highest grade of papillary tumor (WHO 2004)* O Papilloma O PUNLMP O LG O HG O Not available

Highest grade of papillary tumor (WHO 1973)* O Papilloma O Grade 1 O Grade 2 O Grade 3 O Not available

In patients with Ta-T1 tumors, was associated CIS present?* O Yes O No

Was muscle present in the specimen?* O Yes O No

Was primary CIS present?* O Yes O No

If Yes, specify Location(s)* _

In case of recurrence or new CIS, please complete the End of Study form.

Unscheduled UUTI

{ Unscheduled Upper Urinary Tract Investigation} [# _ _]*

Should be performed in case of positive cytology and tumor free cystoscopy

Unscheduled Upper Urinary Tract Investigation*

Date of investigation*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Type of investigation*	O CT-Urography O IVU O Other
If other, specify*	_ _
Was investigation suspicious for upper urinary tract tumor?*	O Yes O No

Biopsies

{ Biopsies} [# _ _]*

Biopsies*

Date of biopsies*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Indicate histology of random/targeted biopsy performed in each of following locations:	
Right lateral bladder wall (cold cup)	O Cancer O No cancer O Not Done
Left lateral bladder wall (cold cup)	O Cancer O No cancer O Not Done
Posterior bladder wall (cold cup)	O Cancer O No cancer O Not Done
Anterior bladder wall (cold cup)	O Cancer O No cancer O Not Done
Bladder dome (cold cup)	O Cancer O No cancer O Not Done
Bladder base (cold cup)	O Cancer O No cancer O Not Done
Bladder trigone (cold cup)	O Cancer O No cancer O Not Done
Prostatic urethra biopsy (pre-colicular area) (resection biopsy)	O Cancer O No cancer O Not Done

In case of recurrence or new CIS, please complete the End of Study form.

Unscheduled Wash Cytology

{ Unscheduled Wash Cytology} [# _ _]*

Should be performed via ureteroscope whenever possible within 6 weeks in case of positive cytology and tumor-free cystoscopy+biopsies and negative upper urinary tract imaging

Unscheduled Wash Cytology*

Date of wash cytology*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Cytology result left site*	O Normal exfoliated cells O Cells showing inflammatory changes or dyscaryosis O Specimen with moderate dysplasia or papillary clusters (suspicious) O Specimen with severe dysplasia O Specimen with evidently malignant cells O Specimen could not be evaluated
Cytology result right site*	O Normal exfoliated cells O Cells showing inflammatory changes or dyscaryosis O Specimen with moderate dysplasia or papillary clusters (suspicious) O Specimen with severe dysplasia O Specimen with evidently malignant cells O Specimen could not be evaluated

In case of occurrence of urothelial carcinoma in the upper tract, please complete the End of Study form.

Protocol Deviation

{ Protocol Deviation} [# _ _]*

Protocol Deviation*

Date of Occurrence*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Initially reported by*	O Investigator O CRA
Visit*	O Eligibility and Randomisation O Screening O Induction cycle (month 1 and 2) O Maintenance cycle (month 3, 6, 9 and 12) O Observational phase
Type of Deviation*	O Inclusion / exclusion criteria O Randomisation Error O Non-compliance with protocol assessments O Non-compliance with study treatment O Use of prohibited medication(s) O Other, specify
Other, specify*	_ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _
Description of deviation*	_ _

To be completed by EAU RF

Protocol Deviation review by EAU RF*

Date review*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Deviation category*	O Minor O Major
Recommended action*	O None O Other, specify
Other, specify*	_ _

Unscheduled Pregnancy Test

Unscheduled Pregnancy Test [# _ _]*

Pregnancy Test*

- *[Itemgroup already referred to in a previous form!]*

Pregnancy Report Form

Pregnancy Report Form*

Dates of Report*

Initial (within 24 hours)* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Follow up* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Patient Description

Date of Birth* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Initials* _ _

Intravesical BCG Study Treatment*

Nr. of instillations* _ _

Total Dose* _

Start Date* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Stop Date* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Action Taken regarding investigational product (IP)* O Drug withdrawn O Dose reduced O Dose increased O Dose not changed O Unknown O Not applicable

Concomitant Medications [# _ _]*

Drug Name* _

Reason for Medication* _

Route* _

Total Daily Dose (including Units)* _

Start Date* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Stop Date* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Ongoing?* O Yes O No

Mother's relevant medical/family history*

Date of last menstrual period* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Date pregnancy confirmed* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Mother's relevant medical/family history*

Method of confirmation*

Estimated date of delivery* _ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Number of previous pregnancies Pre-term*

Number of previous pregnancies Full-term*

Normal births*

Stillbirths*

Children born with defects*

Spontaneous abortion*

Elective abortion*

Other*

Specify*

Additional factors impacting outcome of pregnancy* O Yes O No

Yes, specify*

Pregnancy Outcome*

Pregnancy Outcome* O Stillbirth O Foetal death O Normal birth O Spontaneous abortion O Elective abortion O Other

Mode of delivery*

Other, specify*

Foetal/Neonatal status* O Normal O Birth defect (i.e., structural/chromosomal disorder) (Complete the SAE form) O Other disorder (e.g., non-structural, premature birth, intrauterine death/stillbirth)

Pregnancy Outcome*

Specify*	_ _
Infant Information	
Date of birth / miscarriage / termination*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy
Gestation*	_ _ weeks
Gender*	∇ Male ∇ Female ∇ Unknown
Weight*	_ _ _ _ , _ _ g
Additional details*	_ _
Investigator's signature*	O Yes O No
Date of Signature*	_ _ /_ _ /_ _ _ _ dd/mmm/yyyy

Date:	Investigator name:	Investigator signature:
____________	____________________	____________________

Administrative Protocol: pa_centeradmin

*Center administration**

Center administration*

Randomization setup*

Randomization to be performed/documented via* ∇ minimization algorithm ∇ manual entry

Date: _____ Investigator name: _____ Investigator signature: _____

Appendix 6

Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations versus Reduced Number of Intravesical Instillations with Standard Dose of BCG

A European Association of Urology Research Foundation Randomised Phase III Clinical Trial

CONFIDENTIAL

Final Version 1.1: May 2nd, 2013

Sponsor and Central Study-Management:
EAU Research Foundation
Mr. E.N. van Kleffensstraat 5
NL 6842 CV Arnhem
PO Box 30016
6803 AA Arnhem
The Netherlands
Tel: + 31 26 3890677
Fax +31 26 389 0679
E-mail: researchfoundation@uroweb.org
www.uroweb.org

EAU RF number: 2008 - 01
Eudract Number: 2010-019181-91

Lead Investigators:
Levent N. Türkeri
Dept. of Urology, Marmara University Medical School
Tophanelioglu Street 13-15 Altunizade
34660 Istanbul, Turkey
Telephone: +90 0216 3275050 / +90 0216 3252052
Fax: +90 0216 325 85 79
Email: turkeri@marmara.edu.tr

Marko M. Babjuk
Dept. of Urology, Charles University
2nd Faculty of Medicine
Úvalu 84
15006 Praha 5, Czech Republic
Telephone : +420 22443801
Fax : +420 224434821
Email : Marek.Babjuk@fnmotol.cz

Protocol writing committee:
Marko Babjuk, Prague
Luis Martinez-Pineiro, Madrid
Joan Palou Redorta, Barcelona
Anup Patel, London
Levent N. Türkeri, Istanbul
Marc-Oliver Grimm, Jena
Wim P.J. Witjes, Arnhem

Table of Contents

List of abbreviations and relevant definitions

AE	Adverse Event: any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
ALT	Alanin-aminotransferase
AR	Adverse Reaction: all untoward and unintended responses to an investigational medicinal product related to any dose administered.
ASA	American Society of Anesthesiology
AST	Aspartate-aminotranferase
BCG	Bacillus Calmette-Guérin
BUN	Blood Ureum Nitrogen
CIS	Carcinoma In Situ
CRF	Case Report Form
CV	Curriculum Vitae
CFU	Colony Forming Units
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CUETO	Club Urológico Español de Tratamiento Oncológico
DNA PCR	DeoxyriboNucleic Acid Polymerase Chain Reaction
EAU RF	European Association of Urology Research Foundation
EC	medical Ethics Committee
eCRF	Electronic Case Report Form
EU	European Union
EORTC	European Organisation for Research and Treatment of Cancer
EudraCT	European drug regulatory affairs Clinical Trials
GCP	ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996. European Directives 2001/20/EC and 2005/28/EC
GP	General Practitioner
HIV	Human Immunodeficiency Virus
IC	Informed Consent
ICIQ	International Consultation on Incontinence Questionnaire
IDMC	Independent Data Monitoring Committee

IFN	Interferon
IL	Interleukine
IVU	IntraVenous Urogram
LUTS	Lower Urinary Tract Symptoms
NMIBC	Non Muscle Invasive Bladder Cancer
mRNA	messenger Ribo Nucleic Acid
PCR	Polymerase chain reaction
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
SAE	Serious Adverse Event: A serious adverse event is any untoward medical occurrence that at any dose: results in death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalization; results in persistent or significant disability or incapacity or is a congenital anomaly/birth defect.
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction: A serious adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. summary of product characteristics for an authorised product.
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SWOG	South West Oncology Group (US)
TUR	TransUrethral Resection
UTI	Urinary Tract Infection
WBC	White Blood Cells
WHO ISUP	World Health Organisation / International Society of Urological Pathology

Confidentiality Statement

These materials contain confidential information belonging to the EAU Research Foundation (EAU RF) except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and not to disclose it to others (except where required by applicable law) nor use it for unauthorized purposes. In the event of actual or suspected breach of this obligation, the EAU RF should be promptly notified.

1. STUDY SYNOPSIS

Study Title and number	Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAU RF number 2008-01, Final Version 1.1, May 2nd 2013.
Rationale	Intravesical instillation of BCG is a widely accepted strategy to prevent recurrence of non muscle invasive bladder cancer. The most accepted treatment schedule is induction of BCG: weeks 1 through 6 plus maintenance (weeks 1,2,3) at months 3,6 and 12, but it is unknown how many administrations are really necessary. Scientific evidence prones to the hypothesis that after an initial sensitization to BCG antigens has occurred the number of instillations can be reduced for a proper anamnestic immune response resulting in similar clinical efficacy and potentially less side-effects and costs.
Objectives	The primary objective of this study is to identify if reduced number of BCG instillations are not inferior to standard number and dose intravesical BCG treatment in patients with high grade NMIBC. The primary endpoint for inferiority analysis is time to first recurrence. The secondary objectives are to identify if number and grade of recurrent tumors, rate of progression to a higher stage (T2 or higher) of the disease and safety, specifically the presence of treatment related toxicity > grade 2 differ between the two study arms.
Study Design & Intervention	This is a multicentre prospective, randomized, parallel group, not blinded, trial to compare the efficacy and safety of two different adjuvant treatment schedules: 1) Induction cycle BCG-full dose; weeks 1 through 6 plus maintenance cycles at months 3, 6 and 12 (wks 1,2,3); total 15 full dose BCG instillations 2) Induction cycle BCG-full dose (reduced frequency); weeks 1,2, and 6 plus maintenance cycles at months 3, 6 and 12 (wks 1,3); total 9 full dose BCG instillations. BCG intravesical instillation therapy is registered as adjuvant treatment for the prevention of recurrence of NMIBC and can be considered as standard treatment for the type of patients requested in this trial. For each individual centre, one of the three locally available BCG strains in Europe will be used:

	BCG Tice, BCG Medac or BCG Connaught. After the first transurethral resection (TUR), patient undergoes re-TUR at weeks 4-6 after initial resection. Treatment with the randomised treatment schedule will start 2 weeks after and no later than 6 weeks after the last resection. The first maintenance therapy should be given 3 months after the last instillation of the induction BCG cycle (week 6) and hereafter at months 6 and 12 after the last instillation of the induction BCG cycle. Standard Dose Instillations will take place with 1 vial of BCG. Follow up cystoscopy and cytology will be done every 3 months the first 2 years; bi-annually until the fifth year and yearly thereafter.
Study Population	A total of 1000 patients with high grade Ta-T1 urothelial carcinoma of the bladder with or without CIS and who did not receive any BCG intravesical instillation therapy are to be recruited from urology departments in European hospitals participating in this study. **Inclusion Criteria:** 1. Presence of high grade (Ta-T1) urothelial carcinoma of the bladder with or without CIS 1.1. Tumors can be primary or recurrent 1.2. Tumors can be single or multiple 2. Re-TUR should be performed at weeks 4-6 after initial resection, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tisssue) of the initial tumor site(s) 3. All visible tumors must be completely resected 4. Random biopsies either at initial or re-TUR should be performed prior to any induction BCG course from specific areas of the bladder 5. Early postoperative (within 6 hours of resection) single dose chemotherapy is allowed after the first resection. However, it should not be given after re-TUR if the patient is considered eligible for this study 6. Prior multi-instillation intravesical chemotherapy is allowed, provided that the last instillation was completed 3 months before randomisation in this study. 7. Signed and dated informed consent form. **Exclusion Criteria:** 1. Any previous intravesical BCG therapy 2. Presence of primary CIS only. 3. Presence of histopathologically proven muscle invasive urothelial carcinoma of the bladder at first or re-TUR surgical specimens 4. Patients with incomplete resection of visible tumors 5. Absence of muscle tissue in the re-TUR specimen(s) 6. Presence of any upper urinary tract tumors at any time 7. Presence of any other histological type of resected tumor other than urothelial carcinoma on the first or second resection 8. Presence of another malignancy other than the basal cell carcinoma of the skin 9. Presence of pregnancy or lactation 10. Presence of active tuberculosis, any form of immunodeficiency (eg HIV + serology, transplant recipients) and/or any other contraindication of BCG therapy 11. Patients with a WHO performance score of > 2 or ASA grade 4-5 12. Patients who have received any systemic cytostatic agents within the last

	3 months 13. Patients older than 80 years of age 14. Patients with uncontrollable UTI 15. Patients with White Blood Count (WBC) below 3.0 x 10^9/l or platelet count below 100 x 10^9/l at baseline 16. Renal and hepatic function values exceeding two times the upper normal value of the local laboratory.
Main study Endpoints	Primary endpoint: - time to first recurrence Secondary endpoints: - number and grade of recurrent tumors - rate of progression to a higher stage (T2 or higher) - incidence and severity of side effects.
Nature and extent of the burden and risks associated with participation and risk-benefit	The burden and risks associated with participation in the study is considered minimal and acceptable. The number of visits and treatments is equal to or less compared what patients with these criteria is offered when they are treated on a standard way which is BCG intravesical instillation therapy. Extra in this study are the symptoms and quality of life questionnaires that need to be completed. A potential risk for patients in the reduced frequency arm is that the treatment is less effective with respect to the prevention of recurrence compared to the standard frequency arm. A potential benefit is that side effects, both in quantity and quality, are expected to be less in the reduced frequency arm compared to the standard frequency arm. The risks related to the expected treatment outcome, quality and quantity of side effects of the study medication can be considered as acceptable. Surgical procedures, laboratory and radiological evaluations are not considered extra and are performed according to standard practice or at the investigators discretion for monitoring eventual recurrence or progression of disease. Possible benefit for the patient is that the patient is followed according to the latest standards and guidelines of treatment of NMIBC.
Timing	The study includes a 2-year recruitment phase, followed by a 3-year observation phase. Protocol ready: November 2012 Start EC submission procedure: December 2012 Start Initiation of the centers: February / March 2013 Recruitment from February / March 2013 – February / March 2015 Last patient follow up: May 2018. Study Closure: September 2018.

2. INTRODUCTION

Intravesical BCG therapy is considered the most effective form of treatment in patients with high-risk non-muscle invasive urothelial carcinoma of the bladder (NMIBC). Many years after the initial landmark report by Morales et al. which demonstrated the efficacy of BCG (1), there has been little change in the empirical dose and schedule described originally. Additional maintenance therapy consisting of 3 weekly instillations every 3 to 6 months improved long-term results following an initial induction course of 6-weekly instillations (2).

Futhermore, the 2 meta-analyses performed so far indicated that some form of maintenance following an induction therapy is required if the risk of progression is to be reduced (3,4).
In the analysis of 20 trials where BCG maintenance was given, a reduction of 37% in the odds of progression was observed (3). However, this meta-analysis could not determine which one of the BCG maintenance schedules was the most effective. In their meta-analysis, Bohle et al. concluded that at least one year of maintenance BCG was required (4).
However, toxicity associated with repeated instillations of BCG remains a major problem and requires dose modifications in an attempt to curb the side effects. It is noteworthy that only 16% of the patients in the SWOG study could receive all scheduled maintenance treatments due to substantial toxicity associated with this regimen (2).
Therefore, different schedules of BCG instillations were investigated in order to decrease the severity and frequency of side effects while maintaining the efficacy. The most common approach to reduce BCG toxicity has been dose reduction and a number of authors have proposed one third and one quarter dose instillations of BCG.
In a randomised study which compared one third dose to full dose BCG in 500 patients, CUETO found no overall difference in efficacy (5). Although fewer patients reported toxicity on the reduced dose, the incidence of severe systemic toxicity was similar in the standard and reduced dose groups.

In spite of the ongoing research concerning the optimum dose and schedule for BCG therapy, this has not been established yet, largely due to the absence of a complete understanding of mechanisms by which BCG mediates antitumor activity.
The exact mechanism of action of BCG remains uncertain, however, it is generally accepted that BCG therapy is immune dependent. After intravesical BCG instillation, the live BCG organisms bind to the urothelium and initiate an immune response and, most likely, activation of a so-called Th1 immune response is required for clinical efficacy (6). The Th1 response results in the production of cytokines as interferon (IFN)-γ, interleukin (IL)-2 and IL-12 which favour the development of cellular immune responses (delayed-type hypersensitivity, cytolysis and macrophage activation (7). The Th2 response is characterized by the synthesis of cytokines such as IL-4, IL-5, IL-6 and IL-10, and favours the generation of humoral immunity (antibodies) (8).

In general, following exposure to an antigen, the secondary immune response occurs more rapidly and is more vigorous. In an animal model, re-treatment with BCG effectively reduced the growth of transplanted transitional cell carcinoma but only when sufficient time had lapsed for the immune stimulation of previous BCG treatment to wane (9).

Development of the cytokine response would depend on the time interval during sensitization and challenge. During a repeat BCG instillation the immune system was shown to react more quickly which was reflected by a rapid increase in urinary IL-2 levels and this pattern was not influenced by the level of response to initial BCG challenge (10). Furthermore, IL-2 production can be down-regulated by repeated instillations with a short interval, presumably as a result of expression of regulatory cytokines. In a recent animal study, de Boer et al. demonstrated similar levels of IFN-γ, IL-2 and IL-12 (Th1) mRNA induction after a schedule of only two BCG instillations administered in week 1 and 6 (1 + 6 schedule), compared to 6 weekly instillations (7). Significantly lower levels of the Th2 cytokines of IL-10 and IL-4 mRNA by 1+6 schedule were observed in this study. However, reduction of the BCG instillation volume by 50% resulted in impaired Th1 responses. One additional instillation in week 2 or in week 5 under these suboptimal circumstances restored the cytokine responses completely, notably, for both the Th1 and Th2 cytokines. The authors concluded that to raise a Th1 cytokine response in the bladder, which is thought to be important for antitumor activity, BCG instillations at weeks 2, 3, 4, and 5 can be omitted, provided that the BCG dose is sufficient. Noteworthy, only one additional BCG instillation (half-dose, in week 2) was sufficient for restoring the Th1 cytokine response, which however also enhanced the Th2 response. Consequently, implementation of low frequency BCG instillation schedules should principally be meant to reduce the BCG dose and related adverse effects.

In conclusion, while the schedule with instillations at a regular dose in week 1 and 6 induced a cytokine response in which the Th1 response predominated, one extra instillation in week 2 or 5 will further increase the Th2 cytokine response. Since reduced number of instillations could provide equivalent Th1 cytokine expression to standard regimen and BCG-induced Th1/Th2 cytokine ratio was demonstrated to be associated with effective anti-tumor activity (11), novel reduced number of instillations strategy may provide an alternative way of BCG dose reduction.

Thus, the proposed investigation schedule is based on the hypothesis that after an initial sensitization to BCG antigens has occurred (as in the vaccination for Tuberculosis), intermediate instillations can be reduced for a proper anamnestic immune response and may result in similar clinical efficacy as standard BCG therapy.

3. STUDY OBJECTIVES & END POINTS

The primary objective of this study is to identify if reduced number of BCG instillations are not inferior to standard number and dose intravesical BCG treatment in patients with high grade NMIBC. Primary endpoint will be time to first recurrence.

Secondary endpoints are: number and grade of recurrent tumors; rate of progression to a higher stage (T2 or higher) of the disease and the incidence and severity of side effects, specifically the presence of treatment related toxicity > grade 2. These endpoints will be compared between the two study arms.

4. DESIGN OF THE STUDY

This is an international multicentre prospective, randomized, parallel group, not blinded, trial to compare the efficacy and safety of two different adjuvant treatment schedules:

- Induction cycle BCG-full dose; weeks 1 through 6 plus maintenance cycles at months 3, 6 and 12 (wks 1,2,3) and
- Induction cycle BCG-full dose (reduced frequency); weeks 1, 2 and 6 plus maintenance cycles at months 3, 6 and 12 (wks 1,3).

The study includes a 2-year recruitment phase, followed by a 3-year observation phase (i.e. the first randomised patient will be observed for 5 years in total, the last randomised patient will be observed for 3 years). Each investigator will commit himself to a minimal number of patients to recruit within 2 years from the start of the study.

4.1 Treatment

BCG intravesical instillation therapy is registered as adjuvant treatment for the prevention of recurrence of NMIBC and can be considered as standard treatment for the type of patients requested in this trial. For each individual centre, one of the three locally available BCG strains in Europe will be used: BCG Tice, BCG Medac or BCG Connaught.
Specification of BCG types and the standard procedures for preparation of BCG intravesical solutions that are available in the participating countries can be obtained via webaddresses as indicated in Appendix 5.
After the first transurethral resection (TUR), patient undergoes re-TUR at weeks 4-6 after initial resection. Treatment with the randomised treatment schedule will start 2 weeks after and no later than 6 weeks after the last resection (re-TUR).
The first maintenance therapy should be given 3 months (12 weeks) after the last instillation of the induction BCG cycle (week 6) and hereafter at months 6 (24 weeks) and 12 (48 weeks) after the last instillation of the induction BCG cycle (Appendix 11: Checklists). Standard Dose Instillations will take place with 1 vial of BCG.

In case of side effects the instillation schedule can be modified. The rules for modification of the treatment in different side effects are mentioned in Appendix 6. Any deviation from the required dose or schedule as well as the reason for the deviation should be documented carefully in the eCRF by the investigator.

In case of cessation of BCG treatment, if possible, follow up cytology and cystoscopy should be continued according to protocol.

To evaluate if optimization of BCG instillation can help to influence side effects and efficacy of BCG instillations a substudy in a limited number of centres with interest to participate in this substudy will take place. Patients with fluid restriction will be compared with patients without fluid restriction and patients with rotation during the instillation procedure will be compared with patients without rotation with respect to side effects and efficacy. A limited number of extra questions in the CRF will be completed in case the investigator decides to participate in this substudy (Appendix 10).

4.2 Concomitant Therapy

During the study, other treatments or the administration of other drugs for the prevention/treatment of NMIBC is not permitted. Any other non-experimental drug(s) in treatment for other indications are permitted, provided they are recorded in the eCRF.

4.3 Pre-Treatment Tests

1. Voided urine cytology not older than 2 weeks before first TUR or wash-out cytology at the time of first TUR.
2. Second TUR at 4-6 weeks after initial resection should include deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s). Bladder wash cytology at the time of the second TUR is required.
3. Upper urinary tract tumors should be excluded according to local standards (e.g. IVU, CT-Urography).
4. Urine culture to exclude any active UTI before the start of BCG instillations.
5. BUN, creatinine, AST, ALT, leucocytes, platelets according to standard practice.
6. ICIQ LUTS male and female questionnaires (Appendix 1).
7. EORTC QLQ-30 questionnaire (Appendix 2).
8. WHO Performance Score & ASA Performance Scale (Appendix 9).

4.4 Study Procedures & Follow-Up

1. During the first 2 years, all patients will be followed-up by 3 monthly control cystoscopies and voided urine cytology not older than 2 weeks before follow-up cystoscopy or wash-out cytology at the time of follow-up cystoscopy. Procedure of bladder wash out cytology is as follows: After the introduction of rigid cystoscope, before draining the bladder, 3 times wash with ≥ 50 cc saline will be performed and collected for pathological examination. In case of the use of flexible cystoscope for control cystoscopy, 3 times wash with ≥ 20 ml saline will be performed through the working channel of the instrument and collected for examination. The first cystoscopy should be performed at 6-8 weeks after the completion of last instillation of induction BCG. Follow up cystoscopy and cytology will be done every 3 months the first 2 years; bi-annually until the fifth year and yearly thereafter.
2. Any visible tumors on follow-up cystoscopies will be resected completely with additional biopsies of the tumor bed to provide samples of muscle tissue for appropriate pathological examination.
3. No random biopsies are required during the control cystoscopies. However, any suspicious lesion(s) must be biopsied to rule out the presence of any type of tumor(s).
4. When a recurrence is suggested by positive cytology, a biopsy has to be performed because a recurrence can only be established on histological examination.
   If the cytology is positive in case of tumor-free cystoscopy, upper urinary tract imaging should be performed according to local standards (e.g. IVU, CT-Urography). If the results of these investigations are negative, the patient should have retrograde cytology from the upper urinary tract alongside with random-biopsies of the bladder and also prostatic urethra in males, within 4 to 6 weeks. If all are negative, the patient should continue the BCG instillations according to the assigned protocol arm during the first year. If the patient is beyond 2 years in the protocol, the next control cystoscopy should be performed after 3 months (not 6 months as in patients with completely normal findings) to ensure the absence of any tumor(s).
4. Patients with recurrent tumors which are identified any time after the completion of induction course of BCG will go-off study and will be treated at the discretion of the responsible physician.
5. Urine cultures will be performed before the first instillation of BCG induction therapy to ensure the absence of a UTI. For subsequent instillations urine cultures are not required unless the patient presents with persistent symptoms or gross hematuria (more than 48 h) in which case Löwenstein cultures and/or Mycobacterium DNA PCR should also be obtained.

Discontinuation of BCG therapy and anti-tuberculosis drug therapy is indicated for at least 3 months if Löwenstein culture or PCR is positive.

6. Instillation(s) of BCG must be postponed in case of hematuria after traumatic catheterization and/or in non-treated urinary tract infection until complete resolution.
7. Questionnaires are to be completed prior to the first and last instillation of every cycle (ICIQ-LUTS and "EORTC QLQ 30" questionnaires (Appendix 1 and 2)). Also side effect evaluations of known local and systemic side effects (WHO Grading of Toxicity; Appendix 6) are to be peformed prior to the first and last instillation of every cycle. This is for the induction cycle prior to the first instillation, and prior to the week 6 instillation at the end of the 6 weeks BCG induction cycle or earlier in case of early stop of instillations. For the maintenance cycles at months 3,6 and 12, this is prior to the first and the last instillations of the cycle (Wk1, 3) or earlier in case of stop of instillations. Other side effects or adverse events are to be reported according to the CTCAE criteria up to month 15 unless the AE is serious and either related to study participation or related to study treatment; these SAEs need to be reported throughout the study. (CTCAE; Appendix 4). See also 6.3.
8. Follow up of the upper urinary tract in the absence of positive cytology should be performed according to local standards.

5. PATIENT SELECTION & WITHDRAWAL CRITERIA

5.1 Study Population

A total of 1000 patients with high grade* Ta-T1 urothelial carcinoma of the bladder with or without CIS and who did not receive any BCG intravesical instillation therapy are to be recruited from urology departments in European hospitals participating in this study.

5.2 Inclusion Criteria

To be eligible for this study, patients need to meet <u>all of the following inclusion criteria</u>:

1. Presence of high grade* (Ta-T1) urothelial carcinoma of the bladder with or without CIS
   1.1. Tumors can be primary or recurrent
   1.2. Tumors can be single or multiple

* Pathological Grading will be done according to WHO/ISUP classification (12)

2. Re-TUR should be performed at weeks 4-6 after initial resection, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tisssue) of the initial tumor site(s)
3. All visible tumors must be completely resected
4. Random biopsies either at initial or re-TUR should be performed prior to any induction BCG course from the following areas of the bladder:
   4.1. Right lateral wall (cold cup)
   4.2. Left lateral wall (cold cup)
   4.3. Posterior wall (cold cup)
   4.4. Dome (cold cup)
   4.5. Base (cold cup)
   4.6. Trigone (cold cup)
   4.7. Prostatic urethra (TUR of the pre-collicular area)
5. Early postoperative (within 6 hours of resection) single dose chemotherapy (e.g. Mitomycin C) is allowed after the first resection, since it is recommended in the "Guidelines" and the pathological information is not yet available. However, it should not be given after re-TUR if the patient is considered eligible for this study
6. Prior multi-instillation intravesical chemotherapy is allowed, provided that the last instillation was completed 3 months prior to randomisation in this study.
7. Signed and dated informed consent form.

5.3 Exclusion Criteria

Patients with any of the following exclusion criteria will NOT be eligible for the study:

1. Any previous intravesical BCG therapy
2. Presence of primary CIS only
3. Presence of histopathologically proven muscle invasive urothelial carcinoma of the bladder at first or re-TUR surgical specimens
4. Patients with incomplete resection of visible tumors
5. Absence of muscle tissue in the re-TUR specimen(s)
6. Presence of any upper urinary tract tumors at any time
7. Presence of any other histological type of resected tumor other than urothelial carcinoma on the first or second resection
8. Presence of another malignancy other than the basal cell carcinoma of the skin

9. Presence of pregnancy or lactation
10. Presence of active tuberculosis, any form of immunodeficiency (eg HIV + serology, transplant recipients) and/or any other contraindication of BCG therapy
11. Patients with a WHO performance score of > 2 or ASA grade 4-5 (Appendix 9)
12. Patients who have received any systemic cytostatic agents within the last 3 months
13. Patients older than 80 years of age
14. Patients with uncontrollable UTI
15. Patients with White Blood Count (WBC) below 3.0 x 10^9/l or platelet count below 100 x 10^9/l at baseline
16. Renal and hepatic function values exceeding two times the upper normal value of the local laboratory.

5.4 Patient Withdrawal and Early Dropouts (off study)

In the patient informed consent form the patients will be informed that they have the right to withdraw from the study at any time without affecting their subsequent care and may be withdrawn at the investigator's discretion at any time. In the event that the patient drops out, the investigator will, if possible, indicate the reason for withdrawal. Reasonable effort will be made to contact any patient lost to follow up during the course of the study in order to complete assessments and retrieve any outstanding data. Patients withdrawn from the trial will not be replaced.

Off study criteria:

- When the investigator considers it in the best interest of the patient that he/she will be withdrawn
- First recurrence after completion of the 6 weeks induction course of BCG.
- Occurrence of new CIS
- Occurrence of urothelial carcinoma in the upper tract, or in the prostatic urethra
- Patient requests withdrawal of informed consent
- Lost to follow up
- Occurrence of distant metastases
- Occurence of a new malignancy requiring the use of sytemic chemotherapy.

6. STUDY METHODS

6.1 Randomisation procedure

Randomisation will be done via the EAU RF website. When a patient is eligible to participate in the study and written informed consent has been obtained (Appendix 8: Patient Information and Informed Consent Form), the patient can be randomised via the website. Treatment allocation will be communicated by e-mail. For treatment allocation the following information will be needed:

- Institutions name
- Name of investigator
- Patient identification / Patients date of birth
- Date of last TUR
- Number of tumors
- Type of BCG strain that will be used: BCG Tice, BCG Medac or BCG Connaught
- Pathology result (Tumor grade and stage, and whether muscle was present in the specimen).
- CIS present: Y/N.

In this study, there are 5 stratification factors in which the marginal treatment totals should be balanced. These stratification factors are: 1) Center 2) pathological Ta versus pathological T1 bladder tumor 3) bladder tumor with CIS versus without CIS and 4) type of BCG strain used: BCG Tice, BCG Connaught or BCG Medac. The validated randomisation program uses the minimisation method with a random element as described by Pockock for treatment assignment [15].
At randomisation, a number will be allocated to the patient (patient sequential identification number). This number identifies the patient and must be reported on all eCRF's and other relevant documents. This patient sequential identification number identifies the patient for the Sponsor. The local investigator and his personnel maintain a list which identifies the patients' sequential identification number with the patients source data. This list is safeguarded by the local investigator and his personnel.

6.2 Study Organisation & Management

For this multicentre study, an initiating investigators meeting at a central location will be held to standardise data management procedures and resolve questions regarding protocol conduct. At the initiation meeting, the investigator and eventual other site study personnel will be instructed how to conduct the study- and data management procedures. In addition, the sites will be able to download the required materials via the EAU RF website. EAU RF's representatives may conduct field data

review periodically. It is the responsibility of EAU RF's representatives to verify adherence to the protocol and the completeness, accuracy and consistency of the data. The investigator or a qualified employee will enter all relevant data into eCRF's, in accordance with the instructions provided. The investigator may be requested to provide a copy of the applicable pathology reports. These copies will be used as source verification. An explanation for the omission of any required data should appear on the appropriate e-page. The investigator must sign an agreement thereby stating that she/he takes responsibility for the accuracy of the data in the entire eCRF.

Original patient records (e.g., hospital charts, clinical records, laboratory printouts) should be available at each study site for source document review by EAU RF's representatives. Source document review is the cross checking of information recorded on eCRF's with that recorded in the original patient records. In this study, source document review of specific types of information will be conducted for a percentage of patients (for example, 10 % of the patients enrolled). EAU RF's representatives ensure the privacy of the patient data by only collecting the patient data without the patient details that could identify the individual patient. The investigator should give the monitor access to all relevant patient data.

Queries to be issued to the investigator will consist of questions to clarify for instance missing data, inconsistencies, illegible data, illegal values and items that are not clearly corrected.

When all patient and visit data are received at EAU RF, all data problems have been resolved, all data checks and quality control checks have been performed, the study database is considered to be clean and can be locked. This cleaning and locking process will be performed on a per patient and per visit basis. In addition, the study centre may be audited in depth for study quality assurance by EAU RF's representatives, and/or inspected by a national regulatory authority. This audit may include review of all source documents, drug records, original clinic case-notes, some or all of the facilities used in the trial, etc. Patient confidentiality will be maintained at all times and consent for this will be obtained prior to entry of the patient into the clinical trial.

6.3 Safety reporting

6.3.1 Adverse Events (AE's)

An adverse event is any undesirable clinical occurrence in a patient whether it is considered to be drug related or not. The observed or volunteered adverse events regardless of suspected causal relationship to the study treatment will be recorded on the adverse event page of the eCRF. An adverse event is classified by the investigator as mild (1), moderate (2), severe (3) life threatening (4) or death (5) according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE, Appendix 4).

Events involving adverse treatment reactions, illness with onset during the study, or exacerbations of pre-existing illness should be recorded. Objective test finding (e.g. laboratory results) that need treatment should also be recorded.

Note that the following examples of adverse events do not need to be recorded:

• Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE.

• Hospitalisation for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline.

• Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).

• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

• The disease/disorder being studied, or expected recurrence, progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.

An example of events which are to be recorded in the medical history section of the eCRF and not as an AE is eg. pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e. prior to the first study product administration).

The investigator should also provide information on the duration (start and stop date), relation to study treatment, start of concomitant therapy and outcome of the adverse event. Follow up of the adverse event after therapy discontinuation, is required if the adverse event or its sequelae persist. Follow up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator. Adverse event information will be collected from the first instillation up to the visit at month 15. The Sponsor shall consider all adverse events and, if required, shall report them to the appropriate authorities.

6.3.2 Serious Adverse Events (SAE's)

A serious adverse event is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalization (except for elective hospitalization for a pre-existing condition that did not worsen from baseline; See 6.3.1)
- results in persistent or significant disability / incapacity or
- is a congenital anomaly/birth defect.

If, as a result of an adverse event during a clinical investigation, a patient has to be hospitalised, or their hospitalisation is unduly prolonged because of potential disability or danger to life or because

an intervention has been necessitated or the event is terminal, the adverse event is regarded as serious. For example, if – according to the investigator - an adverse event causes foetal distress, foetal death or a congenital anomaly or malignancy results from the use of the drug during a clinical investigation, this would be processed as a serious adverse event.

All serious adverse events which occur from the first instillation up to the visit at month 15 whether or not considered related to the treatment, must be reported immediately (within one day of the investigator becoming aware of the adverse event) by sending a completed Serious Adverse Event Report Form by e-mail or fax to EAU RF. Serious adverse events **related to either study participation or related to study treatment** should be reported throughout the entire study period.

An event which is part of the natural course of the disease under study (i.e., disease recurrence or progression) is captured as an efficacy measure; therefore it does not need to be reported as a SAE. Progression/recurrence of the tumor will be recorded in the clinical assessments in the eCRF. Death due to a progressive disease is to be recorded on a specific form in the eCRF but not as a SAE. However, if recurrence or progression of the underlying disease is more severe than what would normally be expected for the patient, or if the investigator considers that there was a causal relationship between treatment with BCG or protocol design/procedures and the disease progression/recurrence, then this must be reported as a SAE. Any new cancer (non-related to the cancer under study) must be reported as an SAE.

The Sponsor will report SAE's to the EC that approved the protocol, according to the requirements of that EC.

Table: Timing of reporting obligations of (S)AEs

Study activity	Treatment phase		Follow-up	Follow-up
	First BCG instillation visit	Last BCG instillation visit	Visit Month 15	Up to end of study
Reporting of AEs	■	■	■	
Reporting of SAEs	■	■	■	
Reporting of SAEs related to study participation	■	■	■	■
Reporting of SAEs related to study treatment	■	■	■	■

6.3.3 Suspected Unexpected Serious Adverse Reactions (SUSAR's)

Suspected unexpected adverse reactions are SAE's considered to be related to study treatment, of which the nature, or severity, is not consistent with the summary of product characteristics of the

BCG strain used in this trial (See Appendix 5).

The Sponsor will report (expedited) all SUSARs to the investigators, competent authorities and EC's. The expedited reporting will occur within the per law defined time intervals which is currently not later than 15 days after the Sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term is currently a maximum of 7 days for a preliminary report, with another 8 days for completion of the report.

6.4 Premature Termination of the Study

For reasonable cause, the Sponsor, may terminate this study provided a written notice is submitted at a reasonable time in advance of intended termination.

7. STATISTICAL CONSIDERATIONS

7.1 Patient Accrual, Study Duration and Calculation of Patient Numbers

The assumptions for the power calculations are the following.

- Primary endpoint on which sample size is based is median time to first recurrence.
- The median time to first recurrence for the study population is 60 months
- Recruitment period is 2 years
- Follow up after recruitment is 3 years
- Nulhypothesis H0: "the experimental arm is inferior compared to the standard arm. Inferiority is defined as the true ratio of median time to first recurrence lower than 0.75 (e.g. < 45 / 60 months).
- Alternative hypothesis H1: "the experimental arm is not inferior compared to the standard arm. Non-inferiority is defined as the true ratio of median time to first recurrence higher than 0.75 (e.g. ≥ 45 / 60 months).
- Anticipated drop out percentage is 15 %

nQuery 7.0 was used for the initial power calculations (13).

In order to establish therapeutic equivalence, the true ratio of median time to first recurrence ($t_{experimental}/t_{standard}$) must not be lower than 0.75. Taking this ratio as the lower margin of the one-sided equivalence range and given the above mentioned assumptions and using a one-sided error rate alpha of 2.5%, the following power calculations were simulated with the in the table indicated number of patients per arm.

N per arm	Number of events needed	power *
373	298	70
419	335	75
474	379	80
542	434	85
634	508	90

* Power to obtain a statistical significant non-inferior result of the reduced frequency arm in comparison with the standard arm.

From this table, the sample size needed per arm is 500 patients per arm which gives the total number of patients to be randomized at 1000 patients at an acceptable power of between 80 and 85%.

Recruitment period will be 2 years and all patients will be followed for an additional 3 years or until recurrence or progression, if occurs before this period.

7.2 Final Statistical Analyses

Patient characteristics, demographics and baseline measurements will be summarized in order to provide a characterization of the patient population. Descriptive statistics, e.g. mean, standard deviation, median, range, frequency distributions as appropriate will be presented for each randomization group: Standard frequency versus reduced frequency BCG arms.

The initial safety analysis will be performed when all patients have finished the treatment phase (after 3 years which is 1 year after the last patient was randomized). The incidence and severity of all adverse events will be tabulated per treatment group. Treatment related toxicity > grade 2 will be compared between arms.

The description of the safety data will be performed, first globally then for each of the study arms.

The efficacy analysis will be performed when the last included patient has a follow up of 3 years. The intention to treat efficacy analysis will be performed including all patients who are randomized. Another per protocol efficacy analysis will be performed with all patients randomized and treated with at least one BCG instillation and who have a regulary end of the study. This could be a recurrence during the study as well as the completed instillation schedule and follow up in case the patient does not develop a recurrence.

Efficacy variables to be analyzed per treatment group are:

- time to first recurrence
- number and grade of recurrent tumors

- rate of progression to a higher stage (T2 or higher) of the disease.

Time to first recurrence is the time between the first transurethral resection of the tumor till the time of first recurrence. Time to first recurrence will be estimated by means of the Kaplan Meier method and comparison between treatment groups will be done by means of the log-rank test.
A Cox proportional hazards model will be applied to correct for treatment effects and to assess the influence of prognostic and confounding factors.
Observed sample percentages will be compared between treatment groups by means of a Chi square test.
The analyses of other outcome measurements will be analyzed in an exploratory way with methods appropriate for the type of the variable. Both the safety data and the efficacy data will be summarized by appropriate descriptive statistics.
For each patient entering the reason for discontinuation (e.g. patient decision, urologists decision, lack of efficacy, adverse events) should be clarified. The description of the reason for discontinuation will be performed.
The results of questionnaires will be analysed per treatment group and compared between groups of patients with similar reasons for discontinuation.
All tests of efficacy hypotheses based on between-treatment comparisons will be performed at the 2.5% level of significance and will be one-sided. Statistical tests based on within-treatment comparisons will be performed at the 5% level of significance and will be two-sided. No adjustments will be made to nominal significance levels to account for multiple comparisons made on the same data.
For the primary endpoint analyses time to first recurrence, missing follow up data will be censored at the last known follow up date. This is common practice but does rely on the assumption that censoring is independent from the probability of an event. For this reason we will ask patients for reasons for dropping out of the trial when this is possible.
For missing questionnaire data, the following procedures are planned for missing values. We will first inspect and evaluate the reasons for the missing values. In the (possibly unlikely) event that the missing data can be labeled as missing at random, we will suffice with ordinary multiple imputation for the analyses. When no valid reasoning for missing at random can be made, we will use the delta adjustment procedure of Van Buuren for scenarios that are congruent to the reasons for the missing data (14). For the sake of completeness we will also perform complete case analyses and use Last Observation Carried Forward for questionnaires that are administered more than once.

7.3 Interim Analysis

An interim analysis will be performed on the primary end-point at the time that 50% of the patients are recruited and observed for at least 6 months since their randomisation in the study.

The reason for performing the interim analysis is based on ethical safety considerations. In the presence of evidence of inferiority of the reduced frequency arm, the study will be stopped. In case this result will not be reached, the study will continue as planned.

The safety interim analysis will be performed using a significance level of 1% (one sided). Inferiority is defined as a true ratio of median time to first recurrence ($t_{experimental}/t_{standard}$) lower than 0.75. If there are doubts on the efficacy of the reduced frequency arm, further in depth analyses will be performed to investigate a possible imbalance in prognostic factors. The IDMC will consider to stop the study when the upper limit of the 95% CI is less than 0.75. No changes in the sample size are required because of the interim analysis.

The efficacy interim analysis on time to first recurrence will also be performed between the different BCG strains used. Statistical tests between BCG strains will be performed at the 5% level of significance and will be two-sided.

Results of the interim analysis will be evaluated by an Independent Data Monitoring Committee (IDMC). The decision of stopping the trial in case of significant results will be evaluated by the IDMC. In order to maintain data integrity, the Steering Committee will be blinded to the analysis results and will remain blinded if the IDMC will suggest to continue the study.

8. ETHICAL CONSIDERATIONS

8.1 Regulation Statement

This study will be conducted according to the principles of the Declaration of Helsinki (version, date, see for the most recent version: www.wma.net) and in accordance with the European and local regulations and applicable guidelines.

8.2 Recruitment / Consent and Ethical Review Procedure

Eligible patients will be fully informed by the local investigator and/or the local research coordinator and his research staff, whatever is applicable, about the study and asked to participate.

The patient will receive a patient information sheet (Appendix 8) and will have ample opportunity to ask any question he/she might have. He/she will have sufficient time to consider the study's implications before deciding to participate in the study. Patient's consent will be noted on an informed consent form (Appendix 8).

If during the study the patient for whatever reason no longer wishes to participate he/she can withdraw his/her consent at any time, without any further consequences regarding his/her treatment.

Prior to the start of the study, in some countries, the protocol has to be approved by one recognized medical ethics review committee for all participating institutions (the accredited review committee). The EC shall form a conclusion on the scientific and medical-ethical aspects of the protocol. If the EC requires further information to form its decision or believes the protocol needs to be adjusted, it shall inform the Sponsor immediately. On the basis of the additional information or the adjusted protocol, the EC shall reach its conclusion about whether or not the protocol is acceptable in terms of the research's scientific and medical-ethical aspects. Approval will be indicated in writing with reference to the final protocol number, version and date. The use of medication as described in this protocol must not under any circumstances deviate from the agreed protocol. In exceptional circumstances, for example when the health of the patient is at risk, the investigator can use his clinical judgement and alterations may be made. The event must then be documented in detail to EAU RF and, if applicable, the EC's and the other investigators should be notified.

If in the opinion of the local investigator or the Sponsor the clinical observations in the study suggest it may be unwise to continue, they will be able to terminate the study locally or entirely, respectively. If it becomes apparent that patient enrolment is unsatisfactory or the quantity or quality of the data received is inaccurate or incomplete on a chronic basis, the Sponsor has the right to terminate the study and remove all study equipment from the investigational site. If the study is stopped early the EC should be informed about the reasons.

8.3 Benefit and Risks Assessment

The burden and risks associated with participation in the study is considered minimal and acceptable. The number of visits and treatments is equal to or less compared what patients with these criteria is offered when they are treated on a standard way which is BCG intravesical instillation therapy. Extra in this study are the symptoms and quality of life questionnaires that need to be completed. A potential risk for patients in the reduced frequency arm is that the treatment is less effective with respect to the prevention of recurrence compared to the standard frequency arm. A potential benefit is that side effects, both in quantity and quality, are expected to be less in the reduced frequency arm compared to the standard frequency arm. The risks related to the expected treatment outcome, quality and quantity of side effects of the study medication (Appendix 5) can be

considered as acceptable. Surgical procedures, laboratory and radiological evaluations are not considered extra and are performed according to standard practice or at the investigators discretion for monitoring eventual recurrence or progression of disease. Possible benefit for the patient is that the patient is followed according to the latest standards and guidelines of treatment of NMIBC.

8.4 Compensation for Injury

If necessary, each participating site will arrange a liability insurance which is in accordance with the local legal requirements. The sponsor, EAU RF, will arrange a clinical trial insurance according to national and GCP requirements.

8.5 Incentives

There are no special incentives or financial compensations that patients will receive through participation in the study.

9. ADMINISTRATIVE ASPECTS AND PUBLICATION

9.1 Participating Local Investigator

The participating local investigator is authorised to randomise patients in this study as soon as EC approval has been obtained and, depending on local regulations, approval has been obtained from the managing board or the board of directors of the hospital. It is the responsibility of the investigator at the local site to verify adherence to the protocol, the protection of the rights of the patient, the completeness, accuracy and consistency of the data to be entered by eCRF and adherence to local regulations.

9.2 Sponsor

The Sponsor (EAU RF) is responsible for protocol writing and case report form design, patient registration and assigning patient sequential numbers, handling of SAE and SUSAR reports, performing consistency checks of the case report forms, issuing queries in case of inconsistencies, reviewing and confirming all objective tumor responses and the preparation of the manuscript for publication. Some of these responsibilities will be handled by third parties acting on behalf of the Sponsor.

9.3 Amendments

Amendments are changes made to the research protocol after a favourable opinion by the EC has been given. All amendments will be notified to the Managing Board of the participating centre that gave a favourable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the EC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree: the safety or physical or mental integrity of the patients of the trial; the scientific value of the trial; the conduct or management of the trial; or the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the EC that gave a favourable opinion.

Non-substantial amendments will not be notified to the EC, but will be recorded and filed by the sponsor. Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation.

Considering the long duration of this trial it is foreseen that participating sites may discontinue their participation, new sites will be added or that the coordinating investigator of individual sites changes. Any of these changes will not result in a substantial amendment if the reasons for these changes are of a logistic nature only and do not jeopardise the overall conduct of this study.

9.4 Annual Progress Report

The Sponsor will submit a summary of the progress of the trial to the EC once a year. Information will be provided on the date of inclusion of the first patient, numbers of patients included and numbers of patients that have completed the trial, serious adverse events / suspected unexpected serious adverse reactions, other problems, and amendments.

9.5 End of Study Report

The Sponsor / investigator will notify the EC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor/investigator will notify the EC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the EC.

9.7 Public Disclosure and Publication Policy

Any formal presentation or publication of data collected from this trial will be considered as a joint publication by the investigator(s). The Lead investigators and the protocol writing committee

members will be authors on presentations/publications. Every participating site should designate one member to be author on presentations/publications. Further authorship will be determined by the Sponsor according to the number of eligible patients enrolled and the quality of the patients' follow up at each participating site.

For multi-center studies, it is mandatory that the first publication is based on data from all centers, analysed as stipulated in the protocol by epidemiologists/statisticians in conjunction with the Sponsor, and not by the investigators themselves. Investigators participating in this multi-center study agree not to present data gathered from one center or a small group of centers before the full, initial publication, unless formally agreed to by the Sponsor.

The Sponsor must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). The Sponsor will review the communications for accuracy, verify that confidential information is not being inadvertently divulged and to provide any relevant supplementary information.

10. REFERENCES

1. Morales, A., Eidinger, D. and Bruce, A. W.: Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol, 116: 180, 1976.
2. Lamm, D. L., Blumenstein, B. A., Crissman, J. D., Montie, J. E., Gottesman, J. E., Lowe, B. A. et al: Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group study. J Urol, 163: 1124, 2000.
3. Sylvester RJ, van der Meijden APM, Lamm DL. Intravesical bacillus Calmette-Gue´rin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol, 168:1964–70, 2002.
4. Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guérin versus mitomycin C for superficial bladder cancer: a formal metaanalysis of comparative studies on recurrence and toxicity. J Urol,169:90–5, 2003.
5. Martinez-Pineiro JA, Flores N, Isorna S, Solsona E, Sebastian JL, Pertusa C, et al. Long-term follow-up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacille Calmette-Gue´rin with a reduced dose of 27 mg in superficial bladder cancer. BJU Int, 89:671–80, 2002.
6. Böhle A, Brandau S. Immune mechanisms in bacillus Calmette-Guerin immunotherapy for superficial bladder cancer J Urol, 170:964–9, 2003.

7. de Boer EC, Rooyakkers, S. J. Schamhart, D. H.et al. BCG dose reduction by decreasing the instillation frequency: effects on local Th1/Th2 cytokine responses in a mouse model. Eur Urol, 48:333-338, 2005.

8. DeBoer, E. C., De Jong, W. H., Steerenberg, P. A. et al: Induction of urinary interleukin-1 (IL-1), IL-2, IL-6, and tumour necrosis factor during intravesical immunotherapy with bacillus Calmette-Guerin in superficial bladder cancer. Cancer Immunol Immunother, 34: 306, 1992.

9. Reichert, D. F. and Lamm, D. L.: Long term protection in bladder cancer following intralesional immunotherapy. J Urol, 132:570, 1984.

10. de Reijke T M, de Boer E., Kurth KH et al. Urinary interleukin-2 monitoring during prolonged bacillus Calmette-Guerin treatment: can it predict the optimal number of instillations? J Urol, 161: 67-71, 1999.

11. Riemensberger J, Bohle A, Brandau S. IFN-gamma and IL-12 but not IL-10 are required for local tumour surveillance in a syngeneic model of orthotopic bladder cancer. Clin Exp Immunol, 127:20–6, 2002.

12. Epstein JI, Amin MB, Reuter VR, Mostofi FK. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Am J Surg Pathol, 22:1435-1448, 1998.

13. Janet D. Elashoff (2007) nQuery Advisor Version 7.0 User's Guide.

14. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med. 1999 Mar 30;18(6):681-94.

15. Pocock SJ: Clinical Trials: a practical approach. John Wiley & Sons Ltd. ISBN 0 471 90155 5, © 1983, reprint 1993.

16. Abrams P, Avery K, Gardener N, Donovan J. The International Consultation on Incontinence Modular Questionnaire: www.iciq.net. J Urol. 2006;175:1063-1066; discussion 1066.

17. Donovan JL, Abrams P, Peters TJ, et al. The ICS-'BPH' Study: the psychometric validity and reliability of the ICSmale questionnaire. Br J Urol. 1996;77:554-562.

18. Groenwold M, Klee MC, Sprangers MA, Aaronson NK: Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. J Clin Epidemiol 50 (4): 441-450, 1997.

19. Rischmann P, Desgrandchamps F, Malavaud B, Chopin DK. BCG intravesical instillations: recommendations for side-effects management. Eur Urol 2000; 37 (Suppl 1):33–6.

20. Witjes JA, Palou J, Soloway M, Lamm D, Brausi M, Spermon JR, Persad R, Buckley R, Akaza H, Colombel M, Böhle A: Clinical Practice Recommendations for the Prevention and Management of Intravesical Therapy Associated Adverse Events European Urology Supplements October 2008 (Vol. 7, Issue 10, Pages 667-674).

21. Oken MM, Creech RH, Tormey DC, et al (1982). "Toxicity and response criteria of the Eastern Cooperative Oncology Group". Am. J. Clin. Oncol. 5 (6): 649–55.

22. Little JP. Consistency of ASA grading. Anaesthesia 1995; 59: 658-659.

23. Au JL, Badalament RA, Wientjes MG, et al: International Mitomycin C Consortium. Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase II trial. J Natl Cancer Inst 2001; 93(8): 597-604.

24. Babjuk M, Oosterlinck W, Sylvester R et al.: EAU Guidelines on Non-Muscle-Invasive Urothelial Carcinoma of the Bladder – 2011 Update. Eur Urol 2011; 59: 997-1008.

Appendix 1 ICIQ LUTS female and male questionnaires

Initial number **CONFIDENTIAL** DAY MONTH YEAR
Today's date

ICIQ-FLUTS 08/04

Female LUTS Questionnaire (Ref. 16,17)

Urinary symptoms

Many people experience urinary symptoms some of the time. We are trying to find out how many people experience urinary symptoms, and how much they bother them. We would be graeful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1. Please write in your date of birth:

DAY MONTH YEAR

2a. During the night, how many times do you have to get up to urinate, on average?

none	0
one	1
two	2
three	3
four or more	4

2b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all a great deal

3a. Do you have a sudden need to rush to the toilet to urinate?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

3b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all a great deal

4a. Do you have pain in your bladder?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

4b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

5a. How often do you pass urine during the day?

every four hours or more	☐	0
every three hours	☐	1
every two hours	☐	2
hourly	☐	3

5b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

F score: sum scores 2a-5a ☐☐

6a. Is there a delay before you can start to urinate?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

6b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

7a. Do you have to strain to urinate?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

7b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

8a. Do you stop and start more than once while you urinate?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

8b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

V score: sum scores 6a+7a+8a ☐☐

9a. Does urine leak before you can get to the toilet?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

9b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

10a. How often do you leak urine?

never	0
once or less per week	1
two to three times per week	2
once per day	3
several times per day	4

10b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all — a great deal

11a. Does urine leak when you are physically active, exert yourself, cough or sneeze?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

11b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all — a great deal

12a. Do you ever leak urine for no obvious reason and without feeling that you want to go?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

12b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all — a great deal

13a. Do you leak urine when you are asleep?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

13b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all a great deal

I score: sum scores9a-13a ☐☐

© BFLUTS-SF

Thank you very much for answering these questions.

Copyright © "ICIQ Group" : the ICIQ-FLUTS is based on the BFLUTS SF

Initial number

CONFIDENTIAL

DAY MONTH YEAR
Today's date

ICIQ-MLUTS 01/06

Male LUTS Questionnaire (Ref. 16,17)

Urinary symptoms

Many people experience urinary symptoms some of the time. We are trying to find out how many people experience urinary symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1. Please write in your date of birth:

DAY MONTH YEAR

2a. Is there a delay before you can start to urinate?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

2b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

3a. Do you have to strain to <u>continue</u> urinating?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

3b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

4a. Would you say that the strength of your urinary stream is…

normal	☐	0
occasionally reduced	☐	1
sometimes reduced	☐	2
reduced most of the time	☐	3
reduced all of the time	☐	4

4b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

5a. Do you stop and start more than once while you urinate?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

5b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

6a. How often do you feel that your bladder has not emptied properly after you have urinated?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

6b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

VS: sum scores 2-6 ☐☐

7a. Do you have a sudden need to rush to the toilet to urinate?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

7b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

8a. Does urine leak before you can get to the toilet?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

8b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

9a. Does urine leak when you cough or sneeze?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

9b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

10a. Do you ever leak for no obvious reason and without feeling that you want to go?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

10b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

11a. Do you leak urine when you are asleep?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

11b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

12a. How often have you had a slight wetting of your pants a few minutes after you had finished urinating and had dressed yourself?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

12b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

IS: sum scores 7-12

13a. How often do you pass urine during the day?

1 to 6 times ☐	0
7 to 8 times ☐	1
9 to 10 times ☐	2
11 to 12 times ☐	3
13 or more times ☐	4

13b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all a great deal

14a. During the night, how many times do you have to get up to urinate, on average?

none ☐	0
one ☐	1
two ☐	2
three ☐	3
four or more ☐	4

14b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all a great deal

© ICS*male*SF

Thank you very much for answering these questions.

Copyright © "ICIQ Group" : the ICIQ-MLUTS is based on the ICSmaleSF

Appendix 2 QLQ-C30

THE QLQ-C30 VERSION 3.0 (Ref. 18)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are not « right » or « wrong » answers. The information that you provide will remain strictly confidential.

Please fill in your initials :
Your birthday (Day, Month, Year) :
Today's date (Day, Month, Year) :

		Not at all	A little	Quite a Bit	Very much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase ?	1	2	3	4
2.	Do you have any trouble taking a long walk ?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house ?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day ?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet ?	1	2	3	4
During the past week :		Not at all	A little	Quite a Bit	Very much
6.	Were you limited in doing either your work or other daily activities ?	1	2	3	4
7.	Were are you limited in pursuing your hobbies or other leisure time activities ?	1	2	3	4
8.	Were you short of breath ?	1	2	3	4
9.	Have you had pain ?	1	2	3	4
10.	Did you need to rest ?	1	2	3	4
11.	Have you had trouble sleeping ?	1	2	3	4
12.	Have you felt weak ?	1	2	3	4
13.	Have you lacked appetite ?	1	2	3	4
14.	Have you felt nauseated ?	1	2	3	4
15.	Have you vomited ?	1	2	3	4

During the past week :		Not at all	A little	Quite a Bit	Very much
16.	Have you been constipated ?	1	2	3	4
17.	Have you had diarrhea ?	1	2	3	4
18.	Were you tired ?	1	2	3	4
19.	Did pain interfere with your daily activities ?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television ?	1	2	3	4
21.	Did you feel tense ?	1	2	3	4
22.	Did you worry ?	1	2	3	4
23.	Did you feel irritable ?	1	2	3	4
24.	Did you feel depressed ?	1	2	3	4
25.	Have you had difficulty remembering things ?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities ?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties ?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week ?

1 2 3 4 5 6 7

Very poort Excellent

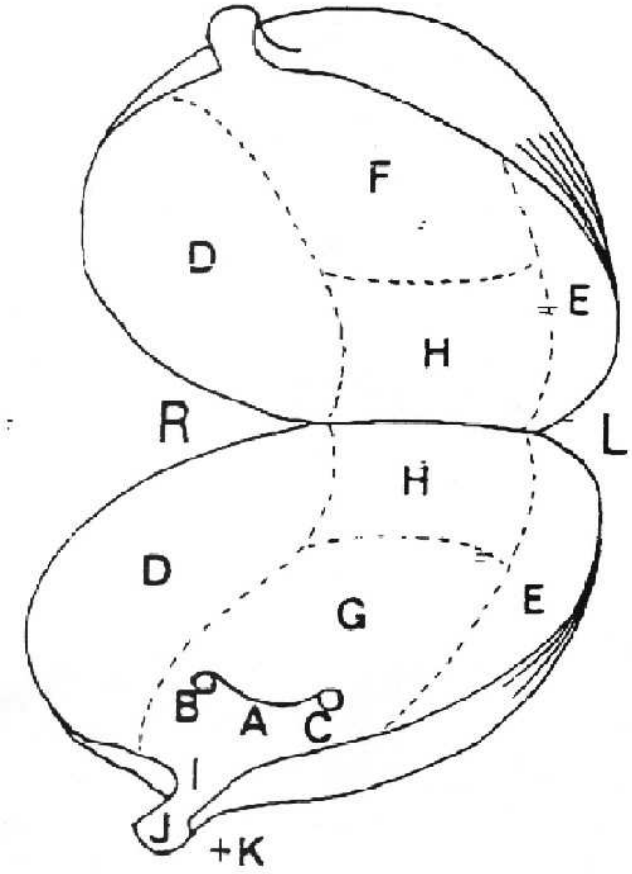
30. How would you rate your overall quality of life during the past week ?

1 2 3 4 5 6 7

Very poort Excellent

Appendix 3 Bladder Map

Bladder Map



A: Trigone:
B: Right ureteral orifice
C: Left ureteral orifice
D: Right wall
E: Left wall
F: Anterior wall
G: Posterior wall
H: Dome=fundus
I: Neck
J: Prostatic urethra
K: Prostatic substance

Appendix 4 Common Terminology Criteria for Adverse Events v 3.0 (CTCAE)

The Common Terminology Criteria for Adverse Events can be used via the internet:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

This is a handy search engine in which the adverse event can be searched and graded easily.

On request, EAU RF will provide the participating sites with the CTCAE 72 pages pdf file or a paper version, if needed.

Appendix 5 Product Information BCG Strains

Product Information obtained via website:

BCG Tice:

http://www.spfiles.com/piticebcglive.pdf

BCG Connaught:

http://www.vaccineshoppecanada.com/secure/pdfs/ca/immucyst_e.pdf and
http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=7779

BCG Medac (other name: BCG RIVM):

http://db.cbg-meb.nl/Bijsluiters/h26876.pdf
http://www.pharmazie.com/graphic/A/20/1-24620.pdf

Appendix 6 Definition and Management of Side Effects of BCG Treament

Grading of Toxicity:

World Health Organization grading of toxic drug effects, will be used as a guide for determining when intravesical therapy may be contraindicated (Ref. 19):

Grade 1: Moderate and <48 h (usually requires no modification of intravesical therapy)
Grade 2: Severe and/or >48 h (usually requires suspension of instillations until resolution of symptoms)
Grade 3: Local, regional, systemic, and immunoallergic (resumption of instillations must be evaluated in the light of the benefit-risk ratio with dose reduction)
Grade 4: Systemic BCG reactions (cessation of BCG therapy is required).

Table: International Bladder Cancer Group recommendations for the management of intravesical therapy–related local and systemic adverse events (© with permission of the authors (Ref. 20))

Side effect	Grade	Management options
Local side effects common to intravesical chemotherapy and BCG		
Non-bacterial or chemical cystitis	1	Oxybutynin, phenazopyridine, propantheline bromide, or anti-inflammatory agents (NSAIDs)
	2	Oxybutynin, phenazopyridine, propantheline bromide, or NSAIDs Consider postponement of intravesical therapy and subsequent dose reductions if cystitis persists beyond 48 h For prolonged BCG cystitis, consider use of a quinolone antibiotic
Gross hematuria	1–2	Perform urine culture to exclude hemorrhagic cystitis Suspend instillations until urine clears Catheterisation and bladder irrigation for clots may be required
Contracted bladder	≥2	Suspend instillations until resolution of symptoms Hydrodistention Cystectomy may be required in some instances
Ureteral obstruction	≥2	Usually temporary and self-limited Exclude presence of CIS or muscle-invasive (T2) bladder cancer Percutaneous drainage or stenting of the kidney may be required
Local side effects associated with BCG		
Symptomatic granulomatous prostatitis	>2	High-dose fluoroquinolones Isoniazid and rifampicin for 3 mo, plus quinolones and steroids Suspension of intravesical therapy
Epididymo-orchitis	>2	High-dose fluoroquinolones Isoniazid and rifampicin for 3 mo Suspension of intravesical therapy Orchidectomy if severe and persistent
Local side effects associated with intravesical chemotherapy		
Contact dermatitis	≥2	Prevention • Careful cleansing of hands after drug handling • Cleansing of genitals and perineum after voiding Cessation of therapy Topical steroids for relief of symptoms
Systemic side effects associated with BCG		
General malaise, fever	1	Generally resolve within 48 h with or without antipyretics
Persistent high-grade fever (>38.5 °C for >48 h)	≥2	Permanent discontinuation of BCG instillations Immediate evaluation Prompt treatment with two or more antimicrobial agents (eg, fluoroquinolones, isoniazid, rifampicin) while diagnostic evaluation, including cultures, is conducted Consultation with an infectious diseases specialist
Systemic BCG reactions	4	Prevention • Initiate BCG at least 2 wk post TURBT (if no signs and symptoms of hematuria) Cessation of BCG For severe infection • High-dose fluoroquinolones • Isoniazid, rifampicin, and ethambutol daily for 6 mo • Early, high-dose corticosteroids as long as symptoms persist • Consider an empirical non-specific antibiotic to treat Gram-negative bacteria and/or *Enterococcus*
Allergic reactions	1–2	Antihistamines and NSAIDs Consider suspension of BCG instillations
	3–4	Discontinue BCG instillations Consider isoniazid and rifampicin plus corticosteroids for persistent symptoms

Appendix 7 Protocol Signature Sheet

Investigator Signature:

I have read and agree to the **'Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAR RF number 2008-01 Final Version, May 2nd, 2013'.**

I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

NAME:
TITLE: INVESTIGATOR: SIGNATURE: _____

DATE: _____

PLACE:

Full investigational site contact details, including telephone numbers, will be documented in the Trial Master File.

Principal Investigators:

NAME: Prof. Levent N. Türkeri
SIGNATURE: _____

DATE: _____

PLACE: ISTANBUL

NAME: Prof. Marko M. Babjuk
SIGNATURE: _____

DATE: _____

PLACE: PRAGUE

Appendix 8 Patient Information and Informed Consent Form

EAU RF nr 2008-01 Version 1.3, 25 October 2012

The European Association of Urology Research Foundation (EAU RF) is conducting a study on patients who have a disease similar to yours. The study will be conducted at the European level under the supervision of physicians recognized as experts in this area of expertise. In Germany, the study will be coordinated by Prof. Dr. M.-O. Grimm, Director of the department of urology, University Clinic, Jena. We would like to invite you to participate in this project after you have been given full information about this study.

In order to be able to take a knowledge-based decision whether or not you should participate in this study, you should be informed about its possible risks and benefits. This process is known as informed consent. This patient information form gives detailed information about the research study which your physician will discuss with you. Once you understand the study, you will be asked to sign the informed consent form if you wish to participate. When you have signed the form, you will receive a copy to keep as a record.

The research study being proposed to you is entitled:
"Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG.
A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAU RF number 2008-01 (AUO-Studie AB37/10)".

Introduction:
Your doctor has discovered that you have a high grade non-muscle invasive bladder tumor(s). This means that the tumor is not yet invading the urinary bladder muscle. The tumor is limited to the superficial part of the urinary bladder inside wall. The standard treatment consists of an operation through the urethra, the canal through which urine is discharged from the bladder (TUR-Bladder) where the tumor(s) are removed completely. A separate information folder supplied by employees of the department of urology will be used to inform you about the risks of this operation.
However, there is chance of over 50% that the disease may recur in the near future. It could also become more malignant. In order to avoid recurrence, an adjuvant treatment after the operation is necessary. This therapy consists of repeated bladder instillations through the urethra with a drug called Bacillus Calmette Guèrin (BCG). This drug was originally developed as a vaccine against lung tuberculosis. Independent from this indication, BCG has been found one of the best drugs to prevent recurrence of non-muscle invasive bladder cancer. Other known drugs that are used for instillation are chemotherapeutic drugs like Mitomycin, Doxorubicin and Epirubicin. However, these chemotherapeutic drugs are not used as standard of care to prevent recurrence of high grade non-muscle invasive bladder tumor(s). Unfortunately, it is unknown how many bladder instillations with BCG are necessary. Scientific evidence prones to the fact that the standard number of instillations can be reduced for a proper immune response resulting in similar clinical efficacy and potentially less side-effects and costs. In this study, we investigate the efficacy of BCG standard number versus BCG reduced number of bladder instillations. Moreover, we look carefully at the symptoms and side effects that may be caused by the drug or by the instillation procedure. A total of 1000 patients will be asked to participate and the study duration will be approximately 5 years. The incidence and severity of side effects may bother you and affect your quality of life during the treatment period. The symptoms and quality of life aspects have to be filled in by you in simple questionnaires. If this is difficult for you, ask us, we can help or advise you.

What do we expect from you ?
1. You will be examined clinically and undergo blood tests and urine examinations as usual. These tests do not differ from patients who do not participate in this study.
2. Specific care is taken that all tumors are completely resected. Four to six weeks after the first surgical resection a control cystoscopy is performed where the site of the initial tumor will again be biopsied.
3. Randomization will decide which treatment will be given to you (standard number of instillations or the reduced number of instillations. The randomization is made by a computer after you have been registered onto the trial. Neither you nor your physician can anticipate which treatment you will receive. If you are randomized for the standard number of instillations, you will start with 6 weekly instillations with BCG

(cycle 1) followed by 3 weekly instillations at months 3, 6 and 12 (cycles 2,3 and 4) after the operation – in total 15 instillations.
If you are randomized for the reduced frequency arm you will receive instillations at weeks 1, 2 and 6 (cycle 1) followed by instillations on week 1 and 3 at months 3, 6 and 12 (cycles 2,3 and 4) after the operation – in total 9 instillations.
Questionnaires are to be completed before the first and last instillation of each cycle which is in total 2 times in each of the four cycles – in total 8 times.
4. You will receive no payment for your participation. All medical examinations and analyses are standard and reimbursable by the health insurance as they are part of the normal routine.

After entering the study, you will be followed at fixed time periods: every three months the first 2 years, bi-annually the 3rd year and annually thereafter, when your physician will do a control cystoscopy. If your physician diagnoses a recurrence of your bladder tumor(s), the tumor will again be removed and further treatment will be decided at the discretion of you and your physician. Your study participation will end after a maximum of 5 years of follow up or earlier, when a recurrence is observed.
Your participation is entirely voluntary. You may decline from participating or withdraw your consent at any time. This will not affect your further treatment.

Are there risks, side-effects or discomforts when you decide to participate ?
The burden and risks associated with participation in the study is considered minimal and acceptable. The number of visits to the clinic and treatments is equal to or less compared with what patients with these criteria is offered when they are treated on a standard way which is BCG intravesical instillation therapy. Extra in this study are the lower urinary tract symptoms questionnaires (13 questions for females and 14 for males) and quality of life questions (30 questions) that need to be completed. This will take you an additional 15-20 minutes to complete.

A potential risk for patients in the reduced frequency arm is that the treatment is less effective with respect to the prevention of recurrence compared to the standard frequency arm. A potential benefit is that side effects, both in quantity and quality, are expected to be less in the reduced frequency arm compared to the standard frequency arm. The risks related to the expected treatment outcome and quality and quantity of side effects of the BCG treatment can be considered as low and acceptable.

Side effects that are common when using BCG instillations in the bladder are: fever, chills, malaise, flu-like symptoms, increased fatigue or an increase in urinary symptoms, (such as burning or pain on urination). You are advised to notify your physician if any of these symptoms last more than 48 hours or increase in severity. You should also notify your physician immediately if you experience any of the following less frequent occurring symptoms: joint pain, eye complaints (such as pain, irritation or redness), an increase in urinary symptoms (such as urgency, frequency of urination, blood in urine), cough, skin rash, jaundice, nausea or vomiting.

BCG contains live mycobacterium, that may be excreted with the urine. Therefore, you are advised to follow appropriate hygienic procedures to protect family and close contacts from infection. When you live with or in close quarters to persons who are immune-compromised (on chemotherapy, etc.), you should exercise special caution to avoid inadvertently transmitting BCG infection to such susceptible persons. After the instillation, BCG is retained in the bladder for as long as possible (up to 2 hours) and then voided. To avoid transmission of BCG to others, for 6 hours after treatment you should void while seated to avoid splashing of urine. Urine voided during this time should be disinfected with an equal volume of household bleach for 15 minutes before flushing or disposal. Unless medically contraindicated, you should increase fluid intake to "flush" the bladder for several hours following treatment with intravesical BCG. You may experience pain or burning with the first void after treatment. During the first week after BCG treatment a condom should be used during sexual intercourse.

Additional laboratory and radiological evaluations are not foreseen in the study and are performed at the investigators discretion for monitoring eventual recurrence or progression of disease.

Possible benefit for the patient is that the patient is treated according to the latest standards and guidelines of the treatment of non-muscle invasive bladder tumor(s).

For all patients participating in this study an insurance policy covers any damage that may occur during the course of this study.
Name of the insurer:
Policy number:
Contact person:
Telephone number contact person:

Together with this information sheet, you will receive a copy of the insurance details for your attention and consideration. See the attachment.

Privacy statement
For this study, the data related to your disease and your date of birth will be, dependent on the reason for collection, processed anonymously and only for the purpose of the study. This means that your full name and date of birth are only recognizable in the informed consent form that will be archived only in the hospital where you are treated for possible required verification of your willingness to participate in the study. For every patient that participates in the study the central research office will attribute a patient number that will consequently be used to identify the patient for processing the study data. This patient number cannot lead to the identification of the participant outside the hospital where you are treated. Anonymity of participants is strictly observed. When the study results are published, the anonymity of participants will be maintained.

If you do not have any further questions and you want to participate in this study, you are kindly invited to sign the informed consent form that is attached. You will receive a copy of this patient information as well as a copy of the informed consent for your records.

Thank you for your attention and your willingness to participate.

The studyleader:

*Prof. Dr. med. M.-O. Grimm**
Chair dept. of Urology
University Hospital Jena

This clarification was prepared by:

- *Prof. Dr. med. M.-O. Grimm**
- *Dr. F.H. Hartmann*
- *Dr. M. Horstmann*
- *Frau Dr. S. Foller*
- *Frau Dr. M. Hartmann*

_____	_____
Place, Date	Signature Participant
_____	_____
Place, Date	Signature Physician
_____	_____
Place, Date (only applicable if the participant cannot read)	Signature Witness

** Italic part is hospital specific and has to be adapted for each of the participating centres.*

Patient Consent Form Standard Version 1.3 date October 25th, 2012: **Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAU RF number 2008-01.**

- I have read and understand the patient information form related to this research study and my physician has answered all my questions regarding the registry.
- I had sufficient time to consider my participation in this research study and I am aware that participation is completely voluntary.
- I realize that I may decide to withdraw my participation at any time without affecting the quality of my health care.
- I understand and agree that personal data will be collected from my medical records in a anonymised manner, used and processed by the EAU RF or any other designated third party that is involved in the registry (e.g. hospital, physician, regulatory bodies and medical ethics committees).
- I authorize and instruct my physician(s) and institution to release the necessary personal - anonymised - data to the EAU RF and any other designated third party involved in the registry.
- The EAU RF and all other designated third parties involved in the registry shall maintain the confidentiality of all data provided compliant with all applicable data protection and privacy laws and shall not use my name or other identifying characteristics in publications.
- I have received a copy of the Patient Information and Consent Form and I hereby agree to participate in this registry.
- I hereby consent to my personal and confidential data being:
  1. processed by the EAU RF for the purposes as described above;
  2. disclosed by the EAU RF to third parties as indicated in point 4 of this page for the purposes as described above.

type/print name

_____	_____	_____
(Patient)	Signature	Date

I hereby declare that I have fully informed the patient about this research study and explained to him its nature, aim, procedures and duration in full detail. I also declare that I have provided the patient with the information sheet and a dated and signed copy of the informed consent form.

type/print name

_____	_____	_____
(Physician) (has to sign always)	Signature	Date

type/print name

_____	_____	_____
(Name of presenter, if applicable) (who presented/explained the document)	Signature	Date

Appendix 9 WHO Performance Score & ASA Performance Scale

WHO Performance Score

The WHO score (published by Oken *et al* in 1982 (Ref. 21), also called the ECOG or Zubrod score (after C. Gordon Zubrod), runs from 0 to 5, with 0 denoting perfect health and 5 death:

0. Asymptomatic
1. Symptomatic but completely ambulatory
2. Symptomatic, <50% in bed during the day
3. Symptomatic, >50% in bed, but not bedbound
4. Bedbound
5. Death

ASA Performance Scale

ASA stands for American Society of Anesthesiologists. In 1963 the ASA adopted a five category physical status classification system for assessing a patient before surgery. A sixth category was later added (Ref. 22). These are:

1. A normal healthy patient.
2. A patient with mild systemic disease.
3. A patient with severe systemic disease.
4. A patient with severe systemic disease that is a constant threat to life.
5. A moribund patient who is not expected to survive without the operation.
6. A declared brain-dead patient whose organs are being removed for donor purposes.

Appendix 10 Substudy: "Prospective evaluation of the influence of fluid restrictions before BCG instillation and technique of BCG instillation on side-effects and efficacy of treatment"

The intravesical instillation of BCG is effective treatment of selected patients with NMIBC. The technique of instillation and measures used before and during instillation are not standardized. The role of optimization of instillation was shown after intravesical chemotherapy but has never been confirmed after BCG instillation (23,24).
There are measures that are recommended by some experts, like fluid restriction before instillation and patient rotation during instillation. Their impact on treatment efficacy and side-effects is not known.

The objective of the sub-study is to evaluate if optimization of BCG instillation can help to influence side effects and efficacy of BCG instillations. For this sub study a limited number of centres with interest to participate will be asked to participate. Patients with fluid restriction will be compared with patients without fluid restriction and patients with rotation during the instillation procedure will be compared with patients without rotation with respect to side effects and efficacy. Appropriate statistics will be used.

Design of the Sub-study:

Part A: Prospective, parallel evaluation of influence of fluid restriction.

Before the BCG instillation patients will be instructed according to standard practice:

1. Patients with fluid restriction: To drink only small cup of water (no tea or coffee) during breakfast (at least 4 hours before the scheduled instillation). Until the instillation and during instillation patient will not drink or eat food with large amounts of water (fruit, vegetables etc.)
2. Patients without fluid restriction: Patient will have usual fluid intake until one hour before instillation. Patient will not drink immediately before instillation and during the instillation.

The following parameters will be evaluated and compared before, during and after the instillation procedure:

- Whether the patient received fluid restriction: Yes or No.
- The urine volume drained from the bladder immediately pre-instillation.
- Whether patient achieved full length of retention of BCG (2 hours). The full length of retention will be registered in all patients, also in those patients who did not reach the full length of retention.
- The amount of urine in the bladder after two hours of instillation (either by opening the catheter and measuring the amount of urine in catheterized patients or voiding in patients in whom the catheter has been removed or by ultrasound in patients without catheter during instillation).

Part B: Prospective, controlled evaluation of influence of patient rotation during instillation.

Before the BCG instillation patients will be instructed according to standard practice:

1. Patients with rotation: The position of the patient during instillation will be changed each 30 minutes – supine position, left side, right side, prone position, vertical position.

2. The position of the patient during instillation will be random, it will not be actively influenced.

The following will be evaluated and compared after the instillation procedure:

- Whether the patient was rotated: Yes or No.

#

Appendix 11 Checklists

Randomisation

Checklist Standard Frequency Arm

Date:	Pretreat-ment …../…../…..	TUR ..../..../....	Re-TUR or biopsy ..../..../....	month 1 wk1 .../..../...	month 1 wk2 .../…./...	month 1 wk3 .../..../...	month 1 wk4 .../…./...	month 2 wk5 .../..../...	month 2 wk6 .../..../...	mth 3 .../..../... mth 6 .../..../...	mth 9 .../..../...	mth 12 .../..../...	mth 15 etc. [3]
Informed consent	X												
In and Exclusion criteria	X	X	X										
Medical History	X												
Concomitant Medication	X		X	X	X	X	X	X	X	X	X	X	X[3]
Physical Examination including WHO/ASA score	X												
Laboratory Examination[1]	X	(X)	(X)										
Radiologic Examination[2]	X	(X)	(X)									X[2]	
Urine Culture prior to start of BCG instillations	X	(X)	(X)										
TUR		X	(X)										
Cystoscopy		X	X							X[3]	X	X	X[3]
Bladder Wash Cytology	X[4]	X[4]	X							X[4]	X[4]	X[4]	X[3,4]
Instillations				X	X	X	X	X	X	X[5]		X[5]	
ICIQ LUTS and QLQ-30[6]	X[6]	(X)	(X)	X[6]					X[6]	X[6]		X[6]	
Adverse Events (CTCAE)[7]	(X)	(X)	(X)	X	X	X	X	X	X	X	X	X	X

[1] Laboratory examination should be done prior to start of BCG instillations according to local practice: BUN, creatinine, AST, ALT, leucocytes, platelets.
[2] Radiologic Examination according to local practice: eg. chest X-ray (only at baseline) and CT abdomen at baseline and annually with and without IV contrast material (CT-Urography) to exclude upper urinary tract tumors. IVU is also acceptable where CT is not available.
[3] Follow up cystoscopies, cytology, concomitant medication recording to be continued at 3 monthly intervals the first 2 years, bi-annually the 3rd year and annually thereafter. First follow-up cystoscopy should be performed 6-8 weeks after the last instillation of induction BCG.
[4] Voided urine cytology not older than 2 weeks before or wash-out cytology at the time of first TUR and at the time of follow up cystoscopies.
[5] First maintenance therapy should be given 3 months after the last instillation of the induction BCG cycle and consists of two instillations at week 1 and week 3 within this month.
[6] At baseline prior to the first instillation, and prior to the 6th instillation at the end of the induction course or earlier in case of early stop of instillations. Also, at months 3,6 and 12 also prior to the first and the last instillations (Wk1,3) or earlier in case of stop of instillations.
[7] WHO toxicity grading of known local and systemic side effects (Appendix 6) are to be peformed at baseline prior to the first instillation, and prior to the 6th instillation at the end of the induction course or earlier in case of early stop of instillations. Also, at months 3,6 and 12 also prior to the first and the last instillations (Wk1,3) or earlier in case of stop of instillations. Other Adverse Events are to be reported according CTCAE up to month 15 unless the AE is serious and either related to study participation or related to study treatment; these SAEs need to be reported throughout the study.

Randomisation

Checklist Reduced Frequency Arm

Date:	Pretreat-ment …../…../…..	TUR ..../..../....	Re-TUR or biopsy ..../..../....	month 1 wk1 .../..../...	month 1 wk2 .../…./...	mth 2 wk 6 .../..../...	mth 3 wk 18 .../..../...	mth 6 .../..../...	mth 9 .../..../...	mth 12 .../..../...	mth 15 etc. [3]
Informed consent	X										
In and Exclusion criteria	X	X	X								
Medical History	X										
Concomitant Medication	X		X	X	X	X	X	X	X	X	X[3]
Physical Examination including WHO/ASA score	X										
Laboratory Examination[1]	X	(X)	(X)								
Radiologic Examination[2]	X	(X)	(X)							X[2]	
Urine Culture prior to start of BCG instillations	X	(X)	(X)								
TUR		X	(X)								
Cystoscopy		X	X				X[3]	X	X	X	X[3]
Bladder Wash Cytology	X[4]	X[4]	X				X[4]	X[4]	X[4]	X[4]	X[3,4]
Instillations				X	X	X	X[5]	X[5]		X[5]	
ICIQ LUTS and QLQ-30[6]				X[6]		X[6]	X[6]	X[6]		X[6]	
Adverse Events (NCI CTC)[7]	(X)	(X)	(X)	X	X	X	X	X	X	X	X

[1] Laboratory examination should be done prior to start of BCG instillations according to local practice: BUN, creatinine, AST, ALT, leucocytes, platelets.
[2] Radiologic Examination according to local practice: eg. chest X-ray (only at baseline) and CT abdomen at baseline and annually with and without IV contrast material (CT-Urography) to exclude upper urinary tract tumors. IVU is also acceptable where CT is not available.
[3] Follow up cystoscopies, cytology, concomitant medication recording to be continued at 3 monthly intervals the first 2 years, bi-annually the 3rd year and annually thereafter. First follow-up cystoscopy should be performed 6-8 weeks after the last instillation of induction BCG.
[4] Voided urine cytology not older than 2 weeks before or wash-out cytology at the time of first TUR and at the time of follow up cystoscopies.
[5] First maintenance therapy should be given 3 months after the last instillation of the induction BCG cycle and consists of two instillations at week 1 and week 3 within this month.
[6] At baseline prior to the first instillation, and prior to the 6th instillation at the end of the induction course or earlier in case of early stop of instillations. Also, at months 3,6 and 12 also prior to the first and the last instillations (Wk1,3) or earlier in case of stop of instillations.
[7] WHO toxicity grading of known local and systemic side effects (Appendix 6) are to be peformed at baseline prior to the first instillation, and prior to the 6th instillation at the end of the induction course or earlier in case of early stop of instillations. Also, at months 3,6 and 12 also prior to the first and the last instillations (Wk1,3) or earlier in case of stop of instillations. Other Adverse Events are to be reported according CTCAE up to month 15 unless the AE is serious and either related to study participation or related to study treatment; these SAEs need to be reported throughout the study.

Appendix 7

CLINICAL TRIAL PROTOCOL AMENDMENT

Amendment Version, Date:	Amendment Final 01, May 27th, 2014
Scope of applicability:	**All participating sites**
Protocol Title:	**Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations versus Reduced Number of Intravesical Instillations with Standard Dose of BCG** **A European Association of Urology Research Foundation Randomised Phase III Clinical Trial**
Acronym:	NIMBUS
Protocol-Code-Number:	EAU-RF 2008-01
Protocol Version, Date:	Amended final version 2, May 19th 2014
EudraCT-Number:	2010-019181-91
Sponsors Name and Address:	EAU Research Foundation Wim P.J. Witjes Mr. E.N. van Kleffensstraat 5 NL 6842 CV Arnhem PO Box 30016 6803 AA Arnhem The Netherlands Tel: + 31 26 389 0677 Fax +31 26 389 0679 E-mail: w.witjes@uroweb.org

Coordinating Investigator:

Levent N. Türkeri
Dept. of Urology, Marmara University Medical School
Tophanelioglu Street 13-15 Altunizade
34660 Istanbul, Turkey
Telephone: +90 0216 3275050 / +90 0216 3252052
Fax: +90 0216 325 85 79
Email: turkeri@marmara.edu.tr

Marko M. Babjuk
Dept. of Urology, Charles University
2nd Faculty of Medicine
Úvalu 84
5006 Praha 5, Czech Republic
Telephone : +420 22443801
Fax : +420 224434821
Email : Marek.Babjuk@fnmotol.cz

Trial Epidemiologist:

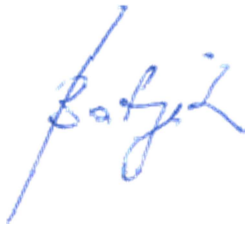
Wim P.J. Witjes

The information contained in this document is the property of the sponsor of this trial. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the sponsor.

Signatures

The undersigned confirm that they agree to the clinical trial protocol amendment.

Levent N. Türkeri	27 May 2014	
Name:	**Date**	**Signature**
Principal Investigator		



Marko M. Babjuk	27 May 2014	
Name:	**Date**	**Signature**
Principal Investigator		

Wim P.J. Witjes	27 May 2014	
Name:	**Date**	**Signature**
Trial Epidemiologist &		
Representation of Sponsor		

Table of contents

Changes of clinical trial protocol

The following amendment describes the changes of the clinical trial protocol after approval of the PEI on May 24th 2013.

The table describes the changes in detail. The left column gives the headline or chapter where the change has to be made. The right column describes the change.

Headline/Chapter	**original text for revision, ~~deleted~~, *added new text***
Titel Page • **Protocol Version, Date**	~~Final Version 1.1, May 2nd 2013,~~ *Amended final version 2, May 19th, 2014*
Header	~~Final Version 1.1, May 2nd 2013,~~ *Amended final version 2, May 19th, 2014*
List of abbreviations and relevant definitions	*UUTI- Upper UrinaryTract Investigation*
Study Synopsis p.6 • **Study Design & Intervention**	After the first transurethral resection (TUR), patient undergoes re-TUR ~~at~~ *6* weeks *(between* 4-~~6~~*8 weeks)* after *the complete resection. Patients with histological detection of high-grade NMBIC in the re-TUR who undergo a second re-TUR are eligible for the study if they fulfil all selection criteria i.e. patients should be macroscopically tumorfree. If so, first re-TUR is considered as TUR as defined by the protocol.* ~~The first maintenance therapy should be given 3 months after the last instillation of the induction BCG cycle (week 6) and hereafter at months 6 and 12 after the last instillation of the induction BCG cycle. Standard Dose Instillations will take place with 1 vial of BCG.~~ *The first maintenance therapy should be given 3 months (12 weeks) after the last instillation of the induction BCG cycle (week 6) and hereafter at months 6 (24 weeks) and 12 (48 weeks) after the last instillation of the induction BCG cycle (Appendix 13: Checklists). Standard Dose Instillations will take place with 1 vial of BCG. The weekly BCG instillations during induction and maintenance cycles have to be conducted within 7 ± 2 days.*
Reason:	Re-TUR is scheduled at week 6 ± 2 weeks after TUR with complete resection and to add a more precise definition of the timing of BCG instillations. Follow up cystoscopy and cytology will be done every 3 months the first 2 years; bi-annually until the fifth year ~~and yearly thereafter~~
Reason:	Patients are participating for a maximum of 5 years in the study.
Study Synopsis p.7 • **Study Population**	2. Re-TUR should be performed at weeks 4-~~6~~ *8* after initial resection, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tisssue) of the initial tumor site(s) 4. ~~Random biopsies either at initial or re-TUR should be performed prior to any induction BCG course from specific areas of the bladder.~~

Study Synopsis **p.7** • **Timing** **Reason:**	 Protocol ready: November 2012 Start EC submission procedure: December 2012 Start Initiation of the centers: ~~February / March 2013~~*November 2013* Recruitment from ~~February / March 2013 – February / March 2015~~ *December 2013 – December 2015* Last patient follow up: ~~May 2018~~, *December 2018* Study Closure: ~~September 2018,~~ *June 2019* Actual timelines are based on delayed start of the study.
3. Study Objectives & End points **Reason:**	*The objectives of a cytokines substudy and a DNA substudy that will take place in selected centres only are, to evaluate the impact of therapy on cytokines and to evaluate the results of DNA analysis as a prognostic factor, respectively (Appendices 11,12).* Two substudies for selected centres only are added in Appendix 11 and 12.
4.1 Treatment **p. 10** **Reason:** **<u>Reason:</u>**	After the first transurethral resection (TUR), patient undergoes re-TUR ~~at weeks 4-6 after initial resection.~~*6 weeks (between 4-8 weeks) after the complete resection. Patients with histological detection of high-grade NMBIC in the re-TUR who undergo a second re-TUR are eligible for the study if they fulfil all inclusion criteria i.e. patients should be macroscopically tumorfree. If so, first re-TUR is considered as TUR as defined by the protocol.* The urologist may need additional TURs for complete removal of the bladder tumor. Re-TUR is scheduled at week 6 ± 2 weeks after TUR with complete resection. The first maintenance therapy should be given 3 months (12 weeks) after the last instillation of the induction BCG cycle (week 6) and hereafter at months 6 (24 weeks) and 12 (48 weeks) after the last instillation of the induction BCG cycle (Appendix ~~11~~ *13*: Checklists). Standard Dose Instillations will take place with 1 vial of BCG. *The weekly BCG instillations during induction and maintenance cycles have to be conducted within 7 ± 2 days.* To add a more precise definition of the timing of BCG instillations.
4.2 Concomitant medication **Reason:**	4.2 Concomitant ~~Therapy~~ Medication *Concomitant medication has to be documented up to the visit at month 15 (last BCG instillation of the maintenance cycle = end of treatment).* More precise definition of the documentation period of concomitant medication.
4.3 Pre-Treatment Tests **p.12** **Reason:**	. ~~1. Voided urine cytology not older than 2 weeks before first TUR or wash-out cytology at the time of first TUR.~~ 2. ~~Second TUR at 4-6 weeks~~ *Re-TUR at 6 ± 2 weeks* after initial resection should include deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s). Bladder wash cytology at the time of the second re*-TUR or voided urine cytology not older than 2 weeks before re*-TUR is required. One bladder wash or voided urine cytology at the time of re-TUR at 6 ± 2 weeks (after complete TUR) is sufficient.

4.4 Study Procedures & Follow-Up **p. 12**	1. The first cystoscopy should be performed at 6-8 weeks after the completion of last instillation of induction BCG. Follow up cystoscopy and cytology will be done every 3 months the first 2 years *and bi-*annually until the fifth year ~~and yearly thereafter~~.
Reason:	The study duration is 5 years.
5.2 Inclusion Criteria **p. 14**	2. Re-TUR should be performed at weeks 4-~~6~~ *8* after initial resection, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tisssue) of the initial tumor site(s)
Reason:	Change in timing Re-TUR from weeks 4-6 to weeks 4-8.
	~~4. Random biopsies either at initial or re-TUR should be performed prior to any induction BCG- course from the following areas of the bladder:~~ ~~4.1. Right lateral wall (cold cup)~~ ~~4.2. Left lateral wall (cold cup)~~ ~~4.3. Posterior wall (cold cup)~~ ~~4.4. Dome (cold cup)~~ ~~4.5. Base (cold cup)~~ ~~4.6. Trigone (cold cup)~~ ~~4.7. Prostatic urethra (TUR of the pre-collicular area)~~
Reason:	According to the updated EAU bladder cancer guidelines 2014, random biopsies are not required. Obtaining specimens by biopsies are performed at the discretion of the investigator.
6.1 Randomisation procedure **p. 16**	In this study, there are 5 stratification factors in which the marginal treatment totals should be balanced. These stratification factors are: 1) Center 2) pathological Ta versus pathological T1 bladder tumor 3) bladder tumor with CIS versus without CIS, ~~and~~ 4) type of BCG strain used: BCG Tice, BCG Connaught or BCG Medac *and 5) single or multiple tumours.*
Reason:	To amend the 5th stratification factor
6.3.2. Serious Adverse Events (SAE's) **p. 18**	The Sponsor will report SAE's to the EC that approved the protocol ~~according to the requirements of that EC~~ *and to the regulatory authority via the annual development safety update reports (DSUR) (see chapter 9.4)*
Reason:	To describe the process of reporting more detailed.
9.4 Annual Progress Report **p. 26**	**9.4 Annual ~~Progress~~ *Development Safety Update Report*** The Sponsor will submit a summary of the progress of the trial *and safety* to the EC *and the regulatory authorities* once a year. Information will be provided on the date of inclusion of the first patient, numbers of patients included, *medication exposure* and numbers of patients that have completed the trial, serious adverse events / suspected unexpected serious adverse reactions, other problems, *changes in safety information of BCG strains* and amendments.
Reason:	Change reflects changed obligations re. safety reporting procedures.

Appendix 7: Protocol Signature **p. 47**	I have read and agree to the 'Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAR RF number 2008-01~~ Final Version, May 2nd, 2013~~'. *Final Version 2, May 19th, 2014*'
Appendix 8: Patient Information and Informed Consent Form **p. 48**	EAU RF nr 2008-01 Version ~~1.3, 25 October 2012,~~ *2, May 19th, 2014.* What do we expect from you? 2. Specific care is taken that all tumors are completely resected. Four to ~~six~~ *eight* weeks after the first surgical resection a control cystoscopy is performed where the site of the initial tumor will again be biopsied. After entering the study, you will be followed at fixed time periods: every three months the first 2 years *and* bi-annually ~~the 3rd year and annually thereafter~~ *until the 5th year*, when your physician will do a control cystoscopy. *For selected centres which participate in the immunological substudy, the following should be added:* *As part of the study you are invited to take part in optional research to better understand the immunological response to the BCG instillation. Therefore, we ask you to collect urine samples prior to and 4 and 8 hours after each instillation during the entire instillation process of the study. Collected samples will be transferred to the EAU RF or other laboratories working with the EAU RF where these urine samples are used to measure immunological important substances in the urine. The EAU RF will require anyone who works with your sample to hold the information and any results in confidence. These urine samples are extra and should not take place in case you should decide not to participate in this optional research. You will not have any individual benefit of the collection of urine samples.* *For selected centres which participate in the DNA substudy, the following should be added:* *As part of the study you are invited to take part in optional research to better understand why some patients react favourably to BCG instillations and others experience a recurrence. Therefore, we ask you 10 ml of your blood in order to be able to investigate your DNA specifics. Collected samples will be transferred to the EAU RF or other laboratories working with the EAU RF where these blood samples are used to measure Bladder Cancer related DNA specifics. The EAU RF will require anyone who works with your sample to hold the information and any results in confidence. This blood sample is extra and should not take place in case you should decide not to participate in this optional research. You will not have any individual benefit of the collection of your blood sample.*

	~~This clarification was prepared by:~~ ~~o Prof. Dr. med. M.-O. Grimm*~~ ~~o Dr. F.H. Hartmann~~ ~~o Dr. M. Horstmann~~ ~~o Frau Dr. S. Foller~~ ~~o Frau Dr. M. Hartmann~~
Reason:	New substudies for selected centres were added. Qualified physicians can change during the study. Therefore we implement free text that can be filled in with the investigator's name. The informed consent remains unaffected. Patient Consent Form Standard Version ~~1.3~~ *2* ~~date October 25th, 2012~~, *May 19th, 2014* **F*or selected centres which participate in the immunological substudy, the following should be added:*** • *I have been given time and opportunity to consider taking part in optional immunological research.* *By ticking the appropriate bullet in the next question, I freely give my consent to take part in this optional immunological research, as follows, and understand that if I select 'No' to such testing, it will not affect my participation in the clinical study.* • *I agree that my urine samples will be used by the EAU RF or laboratories working with the EAU RF for "optional immunological research".* *Yes* *No* *Tick as appropriate* ***For selected centres which participate in the DNA substudy, the following should be added:*** • *I have been given time and opportunity to consider taking part in optional DNA research.* *By ticking the appropriate bullet in the next question, I freely give my consent to take part in this optional DNA research, as follows, and understand that if I select 'No' to such testing, it will not affect my participation in the clinical study.* • *I agree that my blood samples will be used by the EAU RF or laboratories working with the EAU RF for "optional immunological research".* *Yes* *No* *Tick as appropriate*
Reason:	New Substudies for selected centres were added.

Appendix 11: Checklists **p. 56**	Appendix 11 ~~Checklists~~ *Substudy: "Prospective evaluation of cytokines following BCG instillations"* *For details c.f.protocol*
Appendix 12 **p. 58**	*Substudy: "Validation of predictive genetic markers for BCG response"* *For details c.f.protocol*
Appendix 13: **Checklists** **p. 61-62**	Schedule has to be adapted following the changes in the protocol: main points are • latest date of written Informed Consent (IC) • Follow up cystoscopy and cytology will be done every 3 months the first 2 years; ~~bi-annually the 3rd year~~ bi-annually until the fifth year ~~and yearly thereafter~~ • Bladder wash cytology *or voided urine cytology*. • ~~Radiologic Examination~~ *Upper urinary tract investigation* according to local practice: eg. chest X-ray (only at baseline) and CT abdomen at baseline and annually with and without IV contrast material (CT-Urography) to exclude upper urinary tract tumors. IVU is also acceptable where CT is not available. • *Bladder map* (Cystoscopy) For details see the updated checklist

Reason for changes

After first experience with the protocol from the German investigators, the protocol is finetuned in a way that studytimelines are adapted according to daily urological practices. Also the safety reporting process has been updated according to the newest obligations. Two scientific interesting substudies for selected centres only have been added and the patient information sheet and informed consent form have been updated accordingly.

Possible consequences and risks:

None compared with the previous version.

The changes in the trial protocol will have no consequences for the trial subjects and there are no apparent risks.

Documents affected by the amendment

The changes affect the Patient Information, Informed Consent and the electronic Case Report Form. Appropriate changes are or will be made in these documents.

Consequences on subjects treated in the trial before implementation of the amendment.

The changes have no implications on subjects treated in the trial before implementation of the amendment.

Appendix 8

CLINICAL TRIAL PROTOCOL AMENDMENT

Amendment Version, Date:	Amendment final version 3, July 9th, 2015
Scope of applicability:	**All participating sites**
Protocol Title:	**Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations versus Reduced Number of Intravesical Instillations with Standard Dose of BCG** **A European Association of Urology Research Foundation Randomised Phase III Clinical Trial**
Acronym:	NIMBUS
Protocol-Code-Number:	EAU-RF 2008-01
Protocol Version, Date:	Amended final version 2, May 19th 2014
EudraCT-Number:	2010-019181-91
Sponsors Name and Address:	EAU Research Foundation Wim P.J. Witjes Mr. E.N. van Kleffensstraat 5 NL 6842 CV Arnhem PO Box 30016 6803 AA Arnhem The Netherlands Tel: + 31 26 389 0677 Fax +31 26 389 0679 E-mail: w.witjes@uroweb.org

Coordinating Investigator:

Levent N. Türkeri
Dept. of Urology, Marmara University Medical School
Tophanelioglu Street 13-15 Altunizade
34660 Istanbul, Turkey
Telephone: +90 0216 3275050 / +90 0216 3252052
Fax: +90 0216 325 85 79
Email: turkeri@marmara.edu.tr

Marko M. Babjuk
Dept. of Urology, Charles University
2nd Faculty of Medicine
Úvalu 84
5006 Praha 5, Czech Republic
Telephone : +420 22443801
Fax : +420 224434821
Email : Marek.Babjuk@fnmotol.cz

Trial Epidemiologist:

Wim P.J. Witjes

The information contained in this document is the property of the sponsor of this trial. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the sponsor.

Signatures

Levent N. Türkeri	2015 6 Jul	
Name:	**Date**	**Signature**
Principal Investigator		

Marko M. Babjuk	2015 5 Jul	
Name:	**Date**	**Signature**
Principal Investigator		

Wim P.J. Witjes	2015	
Name:	**Date**	**Signature**
Trial Epidemiologist &		
Representation of Sponsor	9-Juli	

Table of contents

Reason for changes

After first experience of the Dutch investigators with the protocol, the protocol is fine-tuned in a way that study timelines and study procedures are adapted according to daily urological practices.
These include:

- Widening period between induction cycle and maintenance cycle (maintenance cycle can be 6-12 weeks after last induction installation)
- No restriction of time period between cytology and BCG installation
- Instead of two urine samples at 4 and 8 hours, one sample will be collected between 4-8 hours after each installation.

The worldwide shortage of BCG has hampered accrual of the NIMBUS trial. Therefore, the recruitment period was extended from 2 to 3 years.

Tables of Checklists were adapted to more clarify the timing of study procedures.

Possible consequences and risks

None compared with the previous version.
The changes in the trial protocol will have no consequences for the trial subjects and there are no apparent risks.

Documents affected by the amendment

The changes affect the Study Protocol, the electronic Case Report and the patient information for one of the substudies. Appropriate changes are or will be made in these documents. Patient Information and Informed Consent are not affected.

Consequences on subjects treated in the trial before implementation of the amendment.

The changes have no implications on subjects treated in the trial before implementation of the amendment.

Changes of clinical trial protocol

The following table describes the changes in detail. The left column gives the headline or chapter where the change has to be made. The right column describes the change.

Headline/Chapter	**original text for revision, ~~deleted~~, *added new text***
Title Page • **Protocol Version, Date**	~~Amended final version 2, May 19th 2014,~~ *Amended final version 3, July 9th, 2015*
Header	~~Amended final version 2, May 19th 2014,~~ *Amended final version 3, July 9th, 2015*
Study Synopsis p.5	~~Amended final version 2, May 19th 2014,~~ *Amended final version 3, July 9th, 2015*
Study Synopsis p.6 • **Study Design & Intervention** **Reason:**	The first maintenance therapy should be given ~~3 months (12 weeks)~~ *at month 3 that is defined as 6-12 weeks* after the last instillation of the induction BCG cycle (week 6) and hereafter at months 6 (~~24~~*18-24* weeks) and 12 (~~48~~*42-48* weeks) after the last instillation of the induction BCG cycle (Appendix 13: Checklists). In the Netherlands, it is routine urological practice to give the first maintenance therapy 6 weeks after the last instillation of the induction BCG cycle (week 6). Therefore, the time frame between induction cycle and maintenance cycle has been widened (maintenance cycle can be 6-12 weeks after last induction installation). The time frames of month 6 and month 12 are adapted accordingly.
Study Synopsis p.7 • **Timing** **Reason:**	The study includes a ~~2~~*3*-year recruitment phase, followed by a 3-year observation phase Protocol ready: November 2012 Start EC submission procedure: December 2012 Start Initiation of the centres: November 2013 Recruitment from December 2013 – December ~~2015~~*2016* Last patient follow up: December ~~2018~~*2019* Study Closure: June ~~2019~~*2020* Actual timelines are based on delayed accrual study because of shortages of BCG (recruitment period is extended from 2 to 3 years).
4. DESIGN OF THE STUDY **Reason:**	The study includes a ~~2~~*3*-year recruitment phase, followed by a 3-year observation phase (i.e. the first randomised patient will be observed for ~~5~~*6* years in total, the last randomised patient will be observed for 3 years). Each investigator will commit himself to a minimal number of patients to recruit within ~~2~~*3* years from the start of the study. The worldwide shortage of BCG has hampered accrual of the NIMBUS trial. Therefore, the recruitment period is extended from 2 to 3 years.

4.1 Treatment **p. 11**	The first maintenance therapy should be given ~~3 months (12 weeks)~~ *at month 3 that is defined as 6-12 weeks* after the last instillation of the induction BCG cycle (week 6) and hereafter at months 6 (~~24~~*18-24* weeks) and 12 (~~48~~*42-48* weeks after the last instillation of the induction BCG cycle (Appendix 13: Checklists).
Reason:	In the Netherlands, it is routine urological practice to give the first maintenance therapy 6 weeks (instead of 12 weeks) after the last instillation of the induction BCG cycle (week 6). Therefore, the time frame between induction cycle and maintenance cycle has been widened (maintenance cycle can be 6-12 weeks after last induction installation).
4.3 Pre-Treatment Tests **p.12**	1. Re-TUR at 6 -/+ 2 weeks after initial resection should include deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumour site(s). Bladder wash cytology at the time of re-TUR or voided urine cytology ~~not older than 2 weeks~~ *preferably* before re-TUR is required*.*
Reason:	The time frame between cytology and re-TUR can vary depending on local practice. Therefore, the time restriction has been omitted.
4.4 Study Procedures & Follow-Up **p. 12**	1. During the first 2 years, all patients will be followed-up by 3 monthly control cystoscopies and voided urine cytology ~~not older than 2 weeks~~ before follow-up cystoscopy or wash-out cytology at the time of follow-up cystoscopy.
Reason:	The time frame between cytology and re-TUR can vary depending on local practice. Therefore, the time restriction has been omitted.
6.3 Safety reporting **6.3.1 Adverse Events (AE's)** **p.18**	Note that the following examples of adverse events do not need to be recorded *and, in case that one of the following examples fulfil the definition of an SAE, also do not need to be reported:*
Reason:	Further explanation of which SAEs also do not need to be reported

<table>
<tr>
<td>7.1 Patient Accrual, Study Duration and Calculation of Patient Numbers
p. 20

p.21</td>
<td>The assumptions for the power calculations are the following.

Primary endpoint on which sample size is based is median time to first recurrence.
The median time to first recurrence for the study population is 60 months
Recruitment period is <s>2</s>3 years

<table>
<tr><th>N per arm</th><th>Number of events needed</th><th>power *</th></tr>
<tr><td><s>373</s>346</td><td>298</td><td>70</td></tr>
<tr><td><s>419</s>388</td><td>335</td><td>75</td></tr>
<tr><td><s>474</s>439</td><td>379</td><td>80</td></tr>
<tr><td><s>542</s>502</td><td>434</td><td>85</td></tr>
<tr><td><s>634</s>588</td><td>508</td><td>90</td></tr>
</table>
From this table, the sample size needed per arm is 500 patients per arm which gives the total number of patients to be randomized at 1000 patients at an acceptable power of <s>between 80 and</s> 85%.
Recruitment period will be <s>2</s>3 years and all patients will be followed for an additional 3 years or until recurrence or progression, if occurs before this period.</td>
</tr>
<tr>
<td>Reason:</td>
<td>The worldwide shortage of BCG has hampered accrual of the NIMBUS trial. Therefore, the recruitment period is extended from 2 to 3 years. N per arm and % power are adjusted accordingly.</td>
</tr>
<tr>
<td>Appendix 7: Protocol Signature
p. 47</td>
<td>I have read and agree to the ‘Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAR RF number 2008-01. <s>Final Version 2, May 19th, 2014</s>’ Amended final version 3, July 9th, 2015</td>
</tr>
</table>

Appendix 8: Patient Information and Informed Consent Form **p. 48**	EAU RF nr 2008-01 Version ~~2, May 19th, 2014.~~ *Amended final version 3, July 9th, 2015* The European Association of Urology Research Foundation (EAU RF) is conducting a study on patients who have a disease similar to yours. The study will be conducted at the European level under the supervision of physicians recognized as experts in this area of expertise. In Germany, the study will be coordinated by Prof. Dr. M.-O. Grimm, Director of the department of urology, University Clinic, Jena. *In the Netherlands, the study will be coordinated by Dr. T van der Heijden, Department of Urology, Radboud UMC, Nijmegen.* We would like to invite you to participate in this project after you have been given full information about this study.
Reason:	In November 2014, the trial has started in The Netherlands. Dr. T van der Heijden of the Radboud UMC in Nijmegen is the national coordinator.
p.49	….Moreover, we look carefully at the symptoms and side effects that may be caused by the drug or by the instillation procedure. A total of 1000 patients will be asked to participate and the study duration will be in total approximately ~~5~~*6* years…… After entering the study, you will be followed at fixed time periods: every three months the first 2 years and bi-annually until *maximal* the ~~5~~*6*th year, when your physician will do a control cystoscopy.
Reason:	The worldwide shortage of BCG has hampered accrual of the NIMBUS trial. Therefore, the recruitment period is extended from 2 to 3 years and total duration of the project from 5 to 6 years
p.50	As part of the study you are invited to take part in optional research to better understand the immunological response to the BCG instillation. Therefore, we ask you to collect *one* urine sample~~s~~ prior to *each installation* and *one urine sample between* 4 and 8 hours after each~~t~~ instillation during the entire instillation process of the study.
Reason:	According to local urological practice it is difficult to obtain two urine samples at 4 and 8 hours after each installation. Therefore, one sample will be collected between 4-8 hours after each installation.
p.51	Patient Consent Form Standard Version ~~2~~*3* ~~May 19th 2014,~~ date July 9th, 2015: **Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG.** **A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAU RF number 2008-01.**

Appendix 11 Substudy: "Prospective evaluation of cytokines following BCG instillations" **METHODS** **p.56** **Reason:**	*One* ~~S~~spot urine sample~~s~~ will be collected from each patient prior to *each installation* and *one spot urine sample between* 4 and 8 hr after each instillation both during the induction and maintenance period. According to local urological practice it is difficult to obtain two urine samples at 4 and 8 hours after each installation. Therefore, one sample will be collected between 4-8 hours after each installation.
Appendix 13: **Checklists** **p. 61-62** **Reason:**	The tables has been replaced with the tables depicted below (see page 9 and 10) **Appendix 13 Checklists** — *Checklist Standard Frequency Arm* **Checklist Reduced Frequency Arm** Tables of Checklists were adapted to more clarify the timing of study procedures.

Appendix 13 Checklists

Checklist Standard Frequency Arm

				Induction cycle						Maintenance cycle										Follow-up	
	Screening*	Re-TUR	Randomisation	month 1				month 2		mth 3			mth 6			mth 9	mth 12			mth 15	mth 18-21-24-30-36-42-48
				wk1	wk2	wk3	wk4	wk5	wk6	wk1	wk2	wk3	wk1	wk2	wk3		wk1	wk2	wk3		
BCG Instillation				X	X	X	X	X	X	X	X	X	X	X	X		X	X	X		
Bladder Wash / voided urine Cytology (1)		X								X			X			X	X			X	X
Cystoscopy (Bladder map)		X								X			X			X	X			X	X
ICIQ LUTS and QLQ-30 (2)				X					X	X		X	X		X		X		X		
Laboratory Examination (3)	X																				
Upper Urinary Tract Investigation (4)	X																				
Informed consent			X																		
Medical History			X																		
In and Exclusion criteria			X																		
Physical Examination including WHO/ASA score			X																		
Concomitant Medication			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine Culture prior to start of BCG instillations (5)			X																		
(Serious) Adverse Events (CTCAE) (6)				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SAE's related to study participation/treatment (CTCAE) (6)				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* standard procedures according to local practice, retrospective documentation after written informed consent.

[1] Voided urine cytology before or wash-out cytology at the time of re-TUR and at the time of follow up cystoscopies

[2] Prior to the first instillation and prior to the 6th instillation at the end of the induction course or earlier in case of early stop of instillations. Also, at months 3, 6 and 12 also prior to the first and the last instillations (Wk1,3) or earlier in case of stop of instillations.

[3] Laboratory examination should be done prior to re-TUR according to local practice: BUN, creatinine, AST, ALT, leucocytes, platelets

[4] Upper Urinary Tract Investigation (UUTI) according to local practice: e.g. chest X-ray (only at baseline) and CT abdomen at baseline and annually with and without IV contrast material (CT-Urography) to exclude upper urinary tract tumors. IVU is also acceptable where CT is not available. UUTI should be done within 8 weeks prior to re-TUR.

[5] Urine culture between re-TUR and prior to 1st BCG-instillation.

[6] WHO toxicity grading of known local and systemic side effects (Appendix 6) are to be performed prior to the first instillation, and prior to the 6th instillation at the end of the induction course or earlier in case of early stop of instillations. Also, at months 3,6 and 12 also prior to the first and the last instillations (Wk1,3) or earlier in case of stop of instillations. All Adverse Events are to be reported according CTCAE up to month 15 unless the AE is serious and either related to study participation or related to study treatment; these SAEs need to be reported throughout the study.

Checklist Reduced Frequency Arm

				Induction cycle						Maintenance cycle										Follow-up	
	Screening*	Re-TUR	Randomisation	month 1				month 2		mth 3			mth 6			mth 9	mth 12			mth 15	mth 18-21-24-30-36-42-48
				wk1	wk2	wk3	wk4	wk5	wk6	wk1	wk2	wk3	wk1	wk2	wk3		wk1	wk2	wk3		
BCG Instillation				X	X				X	X		X	X		X		X		X		
Bladder Wash / voided urine Cytology (1)		X								X			X			X	X			X	X
Cystoscopy (Bladder map)		X								X			X			X	X			X	X
ICIQ LUTS and QLQ-30 (2)				X					X	X		X	X		X		X		X		
Laboratory Examination (3)	X																				
Upper Urinary Tract Investigation (4)	X																				
Informed consent			X																		
Medical History			X																		
In and Exclusion criteria			X																		
Physical Examination including WHO/ASA score			X																		
Concomitant Medication			X	X	X				X	X		X	X		X	X	X		X	X	
Urine Culture prior to start of BCG instillations (5)			X																		
(Serious) Adverse Events (CTCAE) (6)				X	X				X	X		X	X		X	X	X		X	X	
SAE's related to study participation/treatment (CTCAE) (6)				X	X				X	X		X	X		X	X	X		X	X	X

* standard procedures according to local practice, retrospective documentation after written informed consent.

[1] Voided urine cytology before or wash-out cytology at the time of re-TUR and at the time of follow up cystoscopies

[2] Prior to the first instillation and prior to the 6th instillation at the end of the induction course or earlier in case of early stop of instillations. Also, at months 3, 6 and 12 also prior to the first and the last instillations (Wk1,3) or earlier in case of stop of instillations.

[3] Laboratory examination should be done prior to re-TUR according to local practice: BUN, creatinine, AST, ALT, leucocytes, platelets

[4] Upper Urinary Tract Investigation (UUTI) according to local practice: e.g. chest X-ray (only at baseline) and CT abdomen at baseline and annually with and without IV contrast material (CT-Urography) to exclude upper urinary tract tumors. IVU is also acceptable where CT is not available. UUTI should be done within 8 weeks prior to re-TUR.

[5] Urine culture between re-TUR and prior to 1st BCG-instillation.

[6] WHO toxicity grading of known local and systemic side effects (Appendix 6) are to be performed prior to the first instillation, and prior to the 6th instillation at the end of the induction course or earlier in case of early stop of instillations. Also, at months 3,6 and 12 also prior to the first and the last instillations (Wk1,3) or earlier in case of stop of instillations. All Adverse Events are to be reported according CTCAE up to month 15 unless the AE is serious and either related to study participation or related to study treatment; these SAEs need to be reported throughout the study.

CLINICAL TRIAL PROTOCOL AMENDMENT

Amendment Version, Date:	Amendment final version 4, May 2nd, 2016
Scope of applicability:	**All participating sites**
Protocol Title:	**Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations versus Reduced Number of Intravesical Instillations with Standard Dose of BCG** **A European Association of Urology Research Foundation Randomised Phase III Clinical Trial**
Acronym:	NIMBUS
Protocol-Code-Number:	EAU-RF 2008-01
Protocol Version, Date:	Amended final version 3, July 9th 2015
EudraCT-Number:	2010-019181-91
Sponsors Name and Address:	EAU Research Foundation Wim P.J. Witjes Mr. E.N. van Kleffensstraat 5 NL 6842 CV Arnhem PO Box 30016 6803 AA Arnhem The Netherlands Tel: + 31 26 389 0677 Fax +31 26 389 0679 E-mail: w.witjes@uroweb.org

Coordinating Investigator:

Levent N. Türkeri
Dept. of Urology, Marmara University Medical School
Tophanelioglu Street 13-15 Altunizade
34660 Istanbul, Turkey
Telephone: +90 0216 3275050 / +90 0216 3252052
Fax: +90 0216 325 85 79
Email: turkeri@marmara.edu.tr

Marko M. Babjuk
Dept. of Urology, Charles University
2nd Faculty of Medicine
Úvalu 84
5006 Praha 5, Czech Republic
Telephone : +420 22443801
Fax : +420 224434821
Email : Marek.Babjuk@fnmotol.cz

Trial Epidemiologist:

Wim P.J. Witjes

The information contained in this document is the property of the sponsor of this trial. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the sponsor.

Signatures

The undersigned confirm that they agree to the clinical trial protocol amendment.

Levent N. Türkeri	25 May 2016	
Name:	**Date**	**Signature**
Principal Investigator		

Marko M. Babjuk	25.05.2016	
Name:	**Date**	**Signature**
Principal Investigator		

Wim P.J. Witjes	26-05-2016	
Name:	**Date**	**Signature**
Trial Epidemiologist &		
Representation of Sponsor		

Table of contents

Reason for changes

After the first period of experience of the investigators with the protocol, the protocol is fine-tuned in a way that study timelines and study procedures are adapted according to daily urological practices and availability of BCG.

Amendment protocol:

- to include patients with abnormal laboratory values (White Blood Count, platelet count, renal and hepatic function) indicated to be Not Clinically Significant by investigator
- to have no maximum age for inclusion
- to include patients with incidental PCa in active surveillance (without PCa treatment).

The worldwide shortage of BCG of the last two years has hampered the start-up of new sites/countries and accrual of the NIMBUS trial. Therefore, the recruitment period was extended from 3 to 4 years. The total number of patients is adapted accordingly.

Text has been adapted in some sections of the protocol to more clarify the study procedures.

Possible consequences and risks

None compared with the previous version.

The changes in the trial protocol will have no consequences for the trial subjects and there are no apparent risks.

Documents affected by the amendment

The changes affect the Study Protocol and the electronic Case Report. Appropriate changes are or will be made in these documents. Patient Information and Informed Consent are not affected.

Consequences on subjects treated in the trial before implementation of the amendment.

The changes have no implications on subjects treated in the trial before implementation of the amendment.

Changes of clinical trial protocol

The following table describes the changes in detail. The left column gives the headline or chapter where the change has to be made. The right column describes the change.

Headline/Chapter	**original text for revision, ~~deleted,~~ *added new text***
Title Page • **Protocol Version, Date**	~~Amended final version 3, July 9th 2015,~~ *Amended final version 4, May 2nd, 2016*
Header	~~Amended final version 3, July 9th 2015,~~ *Amended final version 4, May 2nd, 2016*
Study Synopsis p.5 • **Study Title and number**	~~Amended final version 3, July 9th 2015,~~ *Amended final version 4, May 2nd, 2016*
Study Synopsis p.5 • **Study Design and & Intervention**	After the first transurethral resection (TUR), patient undergoes re-TUR 6 weeks (between 4-8 weeks) after the *macroscopic* complete resection. • *Patients without tumor in the re-TUR specimen are eligible for the study.* • Patients with histological detection of high-grade *papillary* NMIBC in the re-TUR ~~who~~should undergo a second re-TUR *and* are eligible for the study if they fulfil all selection criteria i.e. patients should be, macroscopically *and histologically confirmed*, ~~tumor~~free *of high-grade papillary tumors in the re-re-TUR specimen*. If so, first re-TUR is considered as TUR as defined by the protocol. • *In case of patients having low grade tumor in the re-TUR (e.g. a tumor not seen at initial TUR), patients can be included in the study if according to the investigator, the low grade papillary tumor has been totally removed or patients undergo a second re-TUR (re-re-TUR) at the discretion of the investigator. If, in these patients, a re-re-TUR is conducted, first re-TUR is considered as TUR as defined by the protocol and patients can be included provided that all requirements are met.*
Study Synopsis p.7 • **Study Population** **Reason:**	A total of ~~1000~~ *824* patients with high grade Ta-T1 urothelial *papillary* carcinoma of the bladder with or without CIS and who did not receive any BCG intravesical instillation therapy are to be recruited from urology departments in European hospitals participating in this study The recruitment period is changed from 3 to 4 years. The total number of patients is adapted accordingly. See also 7.1 for recalculated N per arm and % power.

Study Synopsis p.7 • **Study Population** **Reason:**	**Inclusion Criteria:** 1. Presence of high grade (Ta-T1) urothelial *papillary* carcinoma of the bladder with or without CIS *3. Re-re-TUR should be performed in case of histological detection of high grade papillary NMBIC in the re-TUR, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s).* *4. Histopathologically confirmed absence of high-grade papillary NMIBC in the re-TUR specimen and/or re-re-TUR specimen* 5. All visible *papillary* tumors must be completely resected It is important that patients are macroscopically and histologically free of high-grade papillary tumors before they start the study treatment. Therefore, a second re-TUR should be performed in case of histological detection of high grade papillary NMIBC in the re-TUR.
Study Synopsis p.7 • **Study Population** **Reason:**	**Exclusion Criteria:** 8. Presence of another malignancy other than the basal cell carcinoma of the skin *or localised prostate cancer in active surveillance.* Untreated localised prostate cancer will not have any clinically significant effect on the course of the disease under study.
Study Synopsis p.7 • **Study Population** **Reason:**	**Exclusion Criteria:** The following exclusion criteria are deleted: 11. Patients with a WHO performance score of > 2 or ASA grade 4-5 13. Patients older than 80 years of age 15. Patients with White Blood Count (WBC) below 3.0 x 10^9/l or platelet count below 100 x 10^9/l at baseline) 16. Renal and hepatic function values exceeding two times the upper normal value of the local laboratory. To the **Inclusion Criteria** is added: *9. Patients is clinically fit enough to receive BCG treatment.* These exclusion criteria may not be of clinical significance. If the treating physician decides that the patient is clinically fit enough to receive BCG treatment, the patient is eligible for study participation.
Study Synopsis p.7 • **Timing** **Reason:**	The study includes a ~~*34*~~ year recruitment phase, followed by a 3-year observation phase Protocol ready: November 2012 Start EC submission procedure: December 2012 Start Initiation of the centres: November 2013 Recruitment from December 2013 – December ~~2016~~ *2017* Last patient follow up: December ~~2019~~*2020* Study Closure: June ~~2020~~*2021* Actual timelines are based on delayed accrual study because of shortages of BCG (recruitment period is extended from 3 to 4 years).
4. DESIGN OF THE STUDY **Reason:**	The study includes a ~~*34*~~-year recruitment phase, followed by a 3-year observation phase (i.e. the first randomised patient will be observed for ~~6~~*7* years in total, the last randomised patient will be observed for 3 years). Each investigator will commit himself to a minimal number of patients to recruit within ~~3~~4 years from the start of the study. The worldwide shortage of BCG has hampered accrual of the NIMBUS trial. Therefore, the recruitment period is extended from 3 to 4 years.

4.1 Treatment	After the first transurethral resection (TUR), patient undergoes re-TUR 6 weeks (between 4-8 weeks) after the *macroscopic* complete resection. • *Patients without tumor in the re-TUR specimen are eligible for the study.* • Patients with histological detection of high-grade *papillary* NMIBC in the re-TUR ~~who~~should undergo a second re-TUR *and* are eligible for the study if they fulfil all selection criteria i.e. patients should be, macroscopically *and histologically confirmed*, ~~tumor~~free *of high-grade papillary tumors in the re-re-TUR specimen*. If so, first re-TUR is considered as TUR as defined by the protocol. • *In case of patients having low grade tumor in the re-TUR (e.g. a tumor not seen at initial TUR), patients can be included in the study if according to the investigator, the low grade papillary tumor has been totally removed or patients undergo a second re-TUR (re-re-TUR) at the discretion of the investigator. If, in these patients, a re-re-TUR is conducted, first re-TUR is considered as TUR as defined by the protocol and patients can be included provided that all requirements are met.*
4.3 Pre-Treatment Tests p.12 **Reason:**	Re-TUR *(*~~at~~ 6 + 2 weeks after initial resection*) or re-re-TUR (in case of high grade papillary NMIBC in re-TUR)* should include deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s). A second re-TUR should be performed in case of histological detection of high grade papillary NMIBC in the re-TUR which must contain muscle tissue to exclude MIBC.
5.1 Study Population p.14 **Reason:**	A total of ~~1000~~ *824* patients with high grade* Ta-T1 urothelial papillary carcinoma of the bladder with or without CIS and who did not receive any BCG intravesical instillation therapy are to be recruited from urology departments in European hospitals participating in this study. The recruitment period is changed from 3 to 4 years. The total number of patients is adapted accordingly. See also 7.1 for recalculated N per arm and % power.
5.2 Inclusion Criteria p.14 **Reason:**	1. Presence of high grade (Ta-T1) urothelial *papillary* carcinoma of the bladder with or without CIS *3. Re-re-TUR should be performed in case of histological detection of high grade papillary NMIBC in the re-TUR, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s)* *3. Re-re-TUR should be performed in case of histological detection of high grade papillary NMBIC in the re-TUR, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s)* *4. Histopathologically confirmed absence of high-grade papillary NMIBC in the re-TUR specimen and/or re-re-TUR specimen* 5. All visible *papillary* tumors must be completely resected It is important that patients are macroscopically and histologically free of high-grade papillary tumors before they start the study treatment. Therefore, a second re-TUR should be performed in case of histological detection of high grade papillary NMBIC in the re-TUR.
5.3 Exclusion Criteria p. 14 **Reason:**	*8. Presence of another malignancy other than the basal cell carcinoma of the skin or localised prostate cancer in active surveillance.* Untreated localised prostate cancer will not have any clinically significant effect on the course of the disease under study.

<table>
<tr><td>5.3 Exclusion Criteria
p. 15, Inclusion criteria
p.14

Reason:</td><td>Exclusion Criteria:
The following exclusion criteria are deleted:
11. Patients with a WHO performance score of > 2 or ASA grade 4-5
13. Patients older than 80 years of age
15. Patients with White Blood Count (WBC) below 3.0 x 10^9/l or platelet count below 100 x 10^9/l at baseline)
16. Renal and hepatic function values exceeding two times the upper normal value of the local laboratory.

To the Inclusion Criteria is added: 9. Patients is clinically fit enough to receive BCG treatment.

These exclusion criteria may not be of clinical significance. If the treating physician decides that the patient is fit to receive BCG treatment, the patient is eligible for study participation.</td></tr>
<tr><td>7.1 Patient Accrual, …..
p. 20

Reason:</td><td>- Recruitment period is ~~3~~4 years

The recruitment period is changed from 3 to 4 years. The total number of patients is adapted accordingly. See also 7.1 for recalculated N per arm and % power.</td></tr>
<tr><td>7.1 Patient Accrual, Study Duration and Calculation of Patient Numbers
p.21

Reason:</td><td>The assumptions for the power calculations are the following.
- Primary endpoint on which sample size is based is median time to first recurrence.
- The median time to first recurrence for the study population is 60 months
- Recruitment period is ~~3~~4 years
<table><tr><td>N per arm</td><td>Number of events needed</td><td>power *</td></tr><tr><td>~~346~~324</td><td>298</td><td>70</td></tr><tr><td>~~388~~365</td><td>335</td><td>75</td></tr><tr><td>~~439~~412</td><td>379</td><td>80</td></tr><tr><td>~~502~~472</td><td>434</td><td>85</td></tr><tr><td>~~588~~552</td><td>508</td><td>90</td></tr></table>From this table, the sample size needed per arm is ~~500~~412 patients per arm which gives the total number of patients to be randomized at ~~1000~~ 824 patients at an acceptable power of 80%.
Recruitment period will be ~~3~~4 years and all patients will be followed for an additional 3 years or until recurrence or progression, if occurs before this period.

The worldwide shortage of BCG has hampered accrual of the NIMBUS trial. Therefore, the recruitment period is extended from 3 to 4 years. N per arm and % power are adjusted accordingly.</td></tr>
<tr><td>Appendix 7: Protocol Signature
p. 46</td><td>I have read and agree to the ‘Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAR RF number 2008-01. F~~inal version 3, July 9th, 2015~~ Final Version 4, May 2nd, 2016.</td></tr>
</table>

Appendix 10

CLINICAL TRIAL PROTOCOL AMENDMENT

Amendment Version, Date:	Amendment final version 5, May 15th, 2017
Scope of applicability:	**All participating sites**
Protocol Title:	**Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations versus Reduced Number of Intravesical Instillations with Standard Dose of BCG** **A European Association of Urology Research Foundation Randomised Phase III Clinical Trial**
Acronym:	NIMBUS
Protocol-Code-Number:	EAU-RF 2008-01
Protocol Version, Date:	Amended final version 4, May 2nd 2016
EudraCT-Number:	2010-019181-91
Sponsors Name and Address:	EAU Research Foundation Wim P.J. Witjes Mr. E.N. van Kleffensstraat 5 NL 6842 CV Arnhem PO Box 30016 6803 AA Arnhem The Netherlands Tel: +31 26 389 0677 Fax +31 26 389 0679 E-mail: w.witjes@uroweb.org

Coordinating Investigator:

Levent N. Türkeri
Dept. of Urology, Marmara University Medical School
Tophanelioglu Street 13-15 Altunizade
34660 Istanbul, Turkey
Telephone: +90 0216 3275050 / +90 0216 3252052
Fax: +90 0216 325 85 79
Email: turkeri@marmara.edu.tr

Marko M. Babjuk
Dept. of Urology, Charles University
2nd Faculty of Medicine
Úvalu 84
5006 Praha 5, Czech Republic
Telephone : +420 22443801
Fax : +420 224434821
Email : Marek.Babjuk@fnmotol.cz

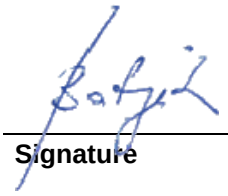
Trial Epidemiologist:

Wim P.J. Witjes

The information contained in this document is the property of the sponsor of this trial. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the sponsor.

Signatures

The undersigned confirm that they agree to the clinical trial protocol amendment.

Levent N. Türkeri	21 June 2017	
Name:	**Date**	**Signature**
Principal Investigator		

Marko M. Babjuk	21 June 2017	
Name:	**Date**	**Signature**
Principal Investigator		

Wim P.J. Witjes		
Name:	**Date**	**Signature**
Trial Epidemiologist &		
Representation of Sponsor	21 June 2017	

Table of contents

Reason for changes

The recommendations to perform a second Transurethral Resection (TUR) of the bladder in the diagnosis of bladder cancer are changed in the 2017 EAU guidelines. It is now recommended to perform a second TUR in case of a T1 tumor in the initial resection and not for all HG/G3 tumors as was recommended in the EAU guidelines of 2016. In the amended protocol it is left at the investigator discretion to perform a Re-TUR (or-Re-Re-TUR) in case of a pTa HG tumor in the initial resection (or Re-TUR), provided muscle was present and reported in the specimen and there was a complete macroscopic resection of all of the papillary tumor(s) at the initial resection (or Re-TUR).
The aftermath of the worldwide BCG shortage (from 2014 to 2016) and delays in obtaining approvals of national and/or local regulatory authorities has hampered the start-up of new countries/sites and accrual of the NIMBUS trial. Therefore, the recruitment period was extended from 4 to 6 years.

The presence of pregnancy is an exclusion criterion in the current protocol. It is not clearly described in the current version of the protocol how to practice adequate contraception and to continue such precautions during the study treatment period. Text has been adapted in some sections of the protocol and in the patient information to more clarify the study procedures for female patients of childbearing potential.

Text has been adapted in some sections of the protocol to more clarify the study procedures.

Possible consequences and risks

None compared with the previous version.
The changes in the trial protocol will have no consequences for the trial subjects and there are no apparent risks.

Documents affected by the amendment

The changes affect the Study Protocol, the Patient Information and the electronic Case Report. Appropriate changes are or will be made in these documents. The Informed Consent Form is not affected.

Consequences on subjects treated in the trial before implementation of the amendment.

The changes have no implications on subjects treated in the trial before implementation of the amendment.

Changes of clinical trial protocol

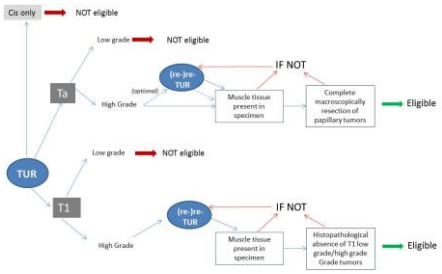
The following table describes the changes in detail. The left column gives the headline or chapter where the change has to be made. The right column describes the change. The page numbers are based on the track-change version of the study protocol.

Headline/Chapter	**original text for revision, ~~deleted,~~ *added new text***
Title Page • **Protocol Version, Date**	~~Amended final version 4, May 2nd, 2016,~~ *Amended final version 5, May 15th, 2017*
Header	~~Amended final version 4, May 2nd, 2016,~~ *Amended final version 5, May 15th, 2017*
Study Synopsis p.5 • **Study Title and number**	~~Amended final version 3, July 9th 2015,~~ *Amended final version 5, May 15th, 2017*

Study Synopsis p.6 • **Study Design and & Intervention**	~~After the first transurethral resection (TUR), patient undergoes re-TUR 6 weeks (between 4-8 weeks) after the macroscopic complete resection.~~ ~~• Patients without tumor in the re-TUR specimen are eligible for the study.~~ ~~• Patients with histological detection of high-grade papillary NMIBC in the re-TUR should undergo a second re-TUR and are eligible for the study if they fulfil all selection criteria i.e. patients should be, macroscopically and histologically confirmed, free of high-grade papillary tumors in the re-re-TUR specimen. If so, first re-TUR is considered as TUR as defined by the protocol.~~ ~~• In case of patients having low grade tumor in the re-TUR (e.g. a tumor not seen at initial TUR), patients can be included in the study if according to the investigator, the low grade papillary tumor has been totally removed or patients undergo a second re-TUR (re-re-TUR) at the discretion of the investigator. If, in these patients, a re-re-TUR is conducted, first re-TUR is considered as TUR as defined by the protocol and patients can be included provided that all requirements are met.~~ *• In case of patients having Ta high grade tumor in the initial resection; a) patients can be included in the study provided muscle was present and reported in the specimen and the Ta high grade tumor has been totally removed, or b) patients undergo a re-TUR at the discretion of the investigator.* *• Patients having T1 high grade tumor in the initial resection, should undergo a re-TUR. Patients with histological detection of T1 tumor in the re-TUR should undergo a second re-TUR. These patients are eligible for the study provided muscle is present and reported in the specimen and if the patients are, macroscopically and histologically confirmed, free of T1 tumors in the (re-)re-TUR specimen.* *A re-TUR (or re-reTUR) should be performed within 4-8 weeks after initial resection (or re-TUR).* Treatment with the randomised treatment schedule will start 2 weeks after and no later than 6 weeks after the last resection (*initial resection, re-TUR or re-re-TUR).* .
Reason:	The 2017 EAU guidelines recommend to perform a second TUR in case of a T1 tumor in the initial resection and not for all HG/G3 tumors. It is left at the investigator discretion to perform a Re-TUR (or-Re-Re-TUR) in case of a TaHG tumor in the initial resection (or Re-TUR), provided muscle was present and reported in the specimen and there was a complete (macroscopically) resection of all the papillary tumor(s).

Study Synopsis p.7 • **Study Population**	**Inclusion Criteria:** *2a. In case of a Ta high grade tumor in the initial resection, a re-TUR can be performed at the discretion of the investigator. Initial resection or re-TUR must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the (initial) tumor site(s)* 2*b. In case of a T1 high grade tumor in the initial resection*, a re-TUR should be performed at weeks 4-8 after initial resection, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s) 3. Re-re-TUR should be performed *at weeks 4-8 after re-TUR* in case of histological detection of *T1 low/high grade tumor* ~~high-grade papillary NMIBC~~ in the re-TUR, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s) 4. Histopathologically confirmed absence of *T1 low/high grade tumor(s)* ~~high-grade papillary NMIBC~~ in the re-TUR specimen and/or re-re-TUR specimen.
Reason:	The 2017 EAU guidelines recommend to perform a second TUR in case of a T1 tumor in the initial resection and not for all HG/G3 tumors. It is left at the investigator discretion to perform a Re-TUR (or-Re-Re-TUR) in case of a TaHG tumor in the initial resection (or Re-TUR), provided muscle was present and reported in the specimen and there was a complete (macroscopically) resection of all the papillary tumor(s).
Study Synopsis p.7/p.8 • **Study Population**	**Inclusion Criteria:** ~~*6. Early postoperative (within 6 hours of resection) single dose chemotherapy is allowed after the first resection. However, it should not be given after re-TUR if the patient is considered eligible for this study*~~ ~~*7. Prior multi-instillation intravesical chemotherapy is allowed, provided that the last instillation was completed 3 months before randomisation in this study*~~ **Exclusion Criteria:** ~~11~~9. Patients who have received any systemic cytostatic agents *or multi-instillation intravesical chemotherapy* ~~with~~in the ~~last~~ 3 months *prior to randomisation.* *Early postoperative (within 6 hours of resection) single dose chemotherapy is allowed after the first resection. However, it should not be given after (re-)re-TUR if the patient is considered eligible for this study.* ~~Prior multi-instillation intravesical chemotherapy is allowed, provided that the last instillation was completed 3 months before randomisation in this study~~
Reason:	To allow early postoperative single dose chemotherapy and prior multi-instillation intravesical chemotherapy are not inclusion criteria *per se* and therefore added to exclusion criterion 9.
Study Synopsis p.7 • **Study Population**	**Inclusion Criteria:** *6. If the patient is male, he must use a condom during sexual intercourse during the first week after BCG treatment. …..*
Reason:	Text has been added to clarify the need for males to take hygienic measures to protect close contacts from infections.

Study Synopsis **p.7** • **Study Population** **Reason:**	**Inclusion Criteria:** *6…….. If the patient is female, and of childbearing potential, she must practice adequate contraception for 30 days prior to administration of study treatment, have a negative pregnancy test and continue such precautions during all study treatment period and for 3 months after the last BCG treatment.* Text has been added to more clarify the study procedures for female patients of childbearing potential.
Study Synopsis **p.7** • **Study Population** **Reason:**	**Exclusion Criteria:** ~~5. Absence of muscle tissue in the (re)-re-TUR specimen(s)~~ This exclusion criterion can be deleted as inclusion criteria 2-4 describe the requirement of presence muscle tissue in the (re)-re-TUR specimen.
Study Synopsis **p.7** • **Study Population** **Reason:**	**Exclusion Criteria:** 6. Presence of another malignancy *in the 5 years prior to randomisation, except for* ~~other than~~ the basal cell carcinoma of the skin or localised prostate cancer in active surveillance The time frame in which presence of another malignancy is not allowed has now been specified (within 5 years).
Study Synopsis **p.8** • **Timing** **Reason:**	The study includes a ~~4~~*6* year recruitment phase, followed by a 3-year observation phase Recruitment *period Germany*:~~from~~ December 2013 – *November ~~2017~~2019* *Recruitment period The Netherlands: November 2014-November 2019* *Recruitment period France: July 2017-November 2019* *Recruitment period Spain: October 2017-November 2019* Last patient follow up: ~~December 2020~~ *November 2022* Study Closure: ~~2021~~*2023*. Actual timelines are based on delayed accrual because of worldwide shortage of BCG in 2014-2016 and delays in obtaining approvals of national and/or local regulatory authorities (recruitment period is extended from 4 to 6 years).
4. DESIGN OF THE STUDY **p.11** **Reason:**	The study includes a ~~4~~*6* year recruitment phase, followed by a 3-year observation phase (i.e. the first randomised patient will be observed for ~~7~~*9* years in total, the last randomised patient will be observed for 3 years). Each investigator will commit himself to a minimal number of patients to recruit within ~~4~~*5* years from the start of the study. Worldwide shortage of BCG in 2014-2016 and delays in obtaining approvals of national and/or local regulatory authorities has hampered accrual of the NIMBUS trial. Therefore, the recruitment period is extended from 4 to 6 years.

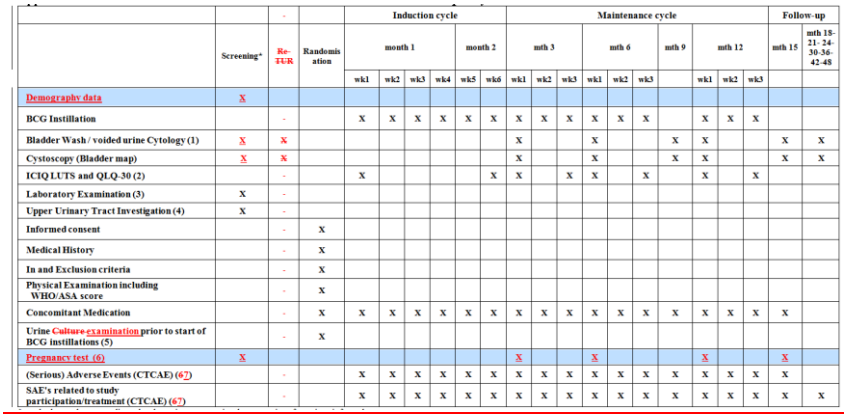
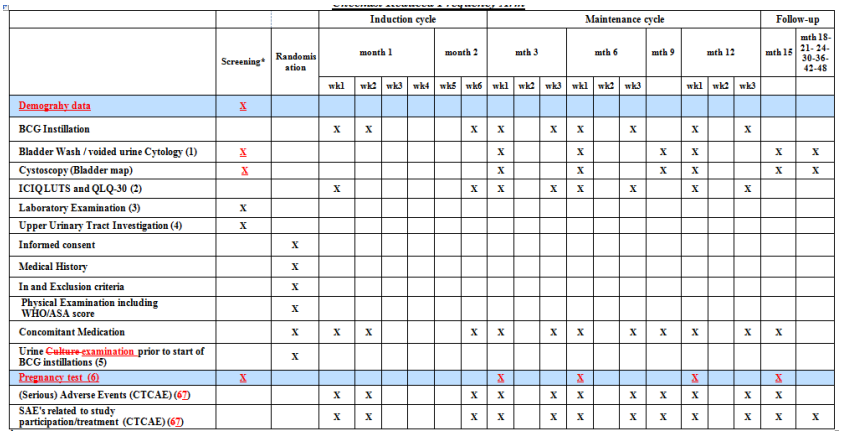
4.1 Treatment **p.11**	*BCG will be prescribed by the investigator according to usual daily practice.*
Reason:	As concluded by the Ethical Committee of the CMO Radboud (Nov 20, 2014, LR/CMO 747) patients to be included in NIMBUS would normally receive BCG treatment and therefore there is no need for EAU Research Foundation acting as the sponsor of NIMBUS to provide the drug in the standard or reduced frequency arm for free. BCG can be prescribed on the usual way where it will be reimbursed by the Dutch health care system.
4.1 Treatment **P12/13**	~~After the first transurethral resection (TUR), patient undergoes re-TUR 6 weeks (between 4-8 weeks) after the macroscopic complete resection.~~ • ~~Patients without tumor in the re-TUR specimen are eligible for the study.~~ • ~~Patients with histological detection of high-grade papillary NMIBC in the re-TUR should undergo a second re-TUR and are eligible for the study if they fulfil all selection criteria i.e. patients should be, macroscopically and histologically confirmed, free of high-grade papillary tumors in the re-re-TUR specimen. If so, first re-TUR is considered as TUR as defined by the protocol.~~ • ~~In case of patients having low grade tumor in the re-TUR (e.g. a tumor not seen at initial TUR), patients can be included in the study if according to the investigator, the low grade papillary tumor has been totally removed or patients undergo a second re-TUR (re-re-TUR) at the discretion of the investigator. If, in these patients, a re-re-TUR is conducted, first re-TUR is considered as TUR as defined by the protocol and patients can be included provided that all requirements are met.~~ • *In case of patients having Ta high grade tumor in the initial resection; a) patients can be included in the study provided muscle is present and reported in the specimen and the Ta high grade tumor has been totally removed, or b) patients undergo a re-TUR at the discretion of the investigator.* • *Patients having T1 high grade tumor in the initial resection, should undergo a re-TUR. Patients with histological detection of T1 tumor in the re-TUR should undergo a second re-TUR. These patients are eligible for the study if muscle is present in the specimen and if the patients are, macroscopically and histologically confirmed, free of T1 tumors in the (re-)re-TUR specimen.*  *Flow chart for eligibility patients with CIS only, Ta and T1 tumors in TUR* *A re-TUR (or re-reTUR) should be performed within 4-8 weeks after initial resection (or re-TUR).* Treatment with the randomised treatment schedule will start 2 weeks after and no later than 6 weeks after the last resection *(initial resection, re-TUR or re-re-TUR).*
Reason:	The 2017 EAU guidelines recommend to perform a second TUR in case of a T1 tumor in the initial resection and not for all HG/G3 tumors. It is left at the investigator discretion to perform a Re-TUR (or-Re-Re-TUR) in case of a TaHG tumor in the initial resection (or Re-TUR), provided muscle was present and reported in the specimen and there was a complete (macroscopically) resection of all the papillary tumor(s).

4.3 Pre-Treatment Tests p.14	**4.3 Pre-Treatment ~~Tests~~ *Assessments*** *1. Demography data: gender, childbearing potential, race, height and weight*.
Reason:	These data will be collected in the eCRF and should also be mentioned in the Study Protocol.
4.3 Pre-Treatment Assessments p.14	*2a. In case of patients having Ta high grade tumor in the initial resection, a Re-TUR can be performed at the discretion of the investigator. Initial resection or Re-TUR should include deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the (initial) tumor site(s).* ~~1~~*2b. In case of T1 high grade tumor in initial resection a* Re-TUR (~~6 +~~ *24-8* weeks after initial resection) or re-re-TUR (in case of ~~high-grade papillary NMIBC~~ T1 low grade/high grade tumor in re-TUR) *should be performed and* should include deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s).
Reason:	The 2017 EAU guidelines recommend to perform a second TUR in case of a T1 tumor in the initial resection and not for all HG/G3 tumors. It is left at the investigator discretion to perform a Re-TUR (or-Re-Re-TUR) in case of a TaHG tumor in the initial resection (or Re-TUR), provided muscle is present and reported in the specimen and there was a complete (macroscopically) resection of all the papillary tumor(s).
4.3 Pre-Treatment Assessments p.14	Bladder wash cytology at the time of *last resection (initial resection, re-TUR or re-*re-TUR) or voided urine cytology preferably before *last resection ~~(re-TUR)~~* is required *.4. Cystoscopy before or at the time of initial resection.* ~~2~~*5.* Upper urinary tract *(UUT)* tumors *should be excluded*. *UUT investigations can be performed* according to local standards (e.g., IVU, CT-Urography). ~~3~~*6*. *Any active urinary tract infection (UTI) should be excluded* ~~Urine culture to exclude any active UTI~~ before the start of BCG instillations. *UTI examination can be performed according to local practice (e.g., urine culture, urine strip test)*
Reason:	Text has been adapted to more clarify the study procedures.
4.3 Pre-Treatment Assessments p.14	*8. For females of childbearing potential, a pregnancy test must be performed within 7 days before start BCG treatment.*
Reason:	Text has been adapted more clarify the study procedures for female patients of childbearing potential
4.4 Study Procedures & Follow-Up p.15	*5. Urine examination (e.g.,* ~~U~~urine cultures*, urine strip test)* will be performed before the first instillation of BCG induction therapy to ensure the absence of a *urinary tract infection (*UTI*). For* subsequent instillations *UTI examinations* ~~urine cultures~~ are not required unless the patient presents with persistent symptoms or gross hematuria (more than 48 h) in which case Löwenstein cultures and/or Mycobacterium DNA PCR should also be obtained*.*
Reason:	Text has been adapted in to more clarify the study procedure.

4.4 Study Procedures & Follow-Up **p.16**	*9. During the treatment period, a pregnancy test will be done at months 3,6,12 and 3 months after last BCG treatment, and should be performed at any time during the study for all women of childbearing potential if the investigator or patient suspects that pregnancy has occurred while the subject was being treated on protocol therapy.* *Patients who become pregnant during the study treatment phase must not receive additional BCG instillations but may continue other study procedures at the discretion of the investigator (see also section 6.4).*
Reason:	Text has been added to clarify the study procedures for female patients of childbearing potential.
5.2 Inclusion Criteria **p.17**	**See changes in Study Synopsis (p.7)**
5.3 Exclusion Criteria **p.18**	**See changes in Study Synopsis (p.7)**
6.1 Randomisation procedure **p.19**	Randomisation will be done via a *web-based data management system* ~~the EAU RF website~~. When a patient is eligible to participate in the study and written informed consent has been obtained (Appendix 8: Patient Information and Informed Consent Form), the patient can be randomised via the website. Treatment allocation will be ~~communicated by e-mail~~ displayed immediately on the screen after entry of ~~. For treatment allocation~~ the following information ~~will be needed~~: • Institutions name • Name of investigator • Patient identification / Patients date of birth • Date of *informed consent* ~~last TUR~~ • Number of tumors • Type of BCG strain that will be used: BCG Tice, BCG Medac or BCG Connaught • Pathology result (Tumor ~~grade and~~ stage~~, and whether muscle was present in the specimen~~).
Reason:	Information on randomisation procedure was updated.

6.4 Pregnancy **p.23**	*6.4 Pregnancy* *Patients who become pregnant during the study treatment phase must not receive additional doses of study treatment but may continue other study procedures at the discretion of the investigator.* *The investigator, or his/her designee, will collect pregnancy information on any patient who becomes pregnant while participating in this study i.e. from signature of first informed consent till the concluding visit , or till recurrence/death if occurring before the concluding visit . The investigator, or his/her designee, will record pregnancy information on the Pregnancy Report Form and submit it to the Sponsor within 24 hours of learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether that be full-term or prematurely, information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.* *While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded and followed as an AE or a SAE, as described in Section 6.3.1 and 6.3,2.* *A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 6.3.2. Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered reasonably related in time to receipt of the investigational product by the investigator, will be reported to the Sponsor as described in Section 6.3.3. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.*
Reason:	This section has been added to clarify the study procedures for female patients of childbearing potential
7. STATISTICAL CONSIDERATIONS **7.1 Patient Accrual, Study Duration and Calculation of Patient Numbers** **p.24/P25**	- Recruitment period is ~~4~~6 years *with an average recruitment period of 4 years per country* - Recruitment period will be *on average* 4 years and all patients will be followed for an additional 3 years or until recurrence or progression, if occurs before this period
Reason	Text has been changed according to the adapted timelines
Appendix 1 ICIQ LUTS female and male questionnaires **p. 35**	**5a. How often do you pass urine during the day?** ~~*every four hours or more 0*~~ ~~*every three hours 1*~~ ~~*every two hours 2*~~ ~~*hourly 3*~~ *1 to 6 times 0* *7 to 8 times 1* *9 to 10 times 2* *11 to 12 times 3* *13 or more times 4*
Reason:	The text has been adapted according to the latest version of ICIQ FLUTS Questionnaire.

Appendix 7: Protocol Signature **p. 51**	I have read and agree to the 'Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAR RF number 2008-01. ~~Final Version 4, May 2nd, 2016~~. *Final Version 5, May 15th, 2017.*
Appendix 8: **Patient Information and Informed Consent Form** **p.52**	EAU RF nr 2008-01 Version ~~3~~4, ~~July~~ May ~~9~~15th, ~~2015~~ 2017.
Appendix 8: **Patient Information and Informed Consent Form** **p.52** **Reason:**	…. *In France, the study will be coordinated by Prof. M. Colombel, Hôpital Edouard Herriot, Lyon, France. In Spain, the study will be coordinated by Prof. Luis Martínez-Piñeiro, El Hospital Universitario La Paz, Madrid.* France and Spain are participating in this study
Appendix 8: **Patient Information and Informed Consent Form** **p.52** **Reason**	A total of ~~1000~~ *824* patients will be asked to participate and the study duration will be in total ~~6~~ *9* years. Text has been changed according to the adapted number of patients and time lines.
Appendix 8: **Patient Information and Informed Consent Form** **p.53/54** **Reason:**	…… *The possible risks of BCG treatment to a pregnant woman and foetus are not known. Female patients capable of childbearing will be asked to take appropriate precautions to avoid pregnancy during the whole period of treatment administration (at least 30 days prior to the first treatment and up to three months after the last administration). Pregnant women may not participate at any time in the study, and, if applicable, pregnancy tests will be done to make sure that you are not pregnant at study entry and during the study.* This section has been added to clarify the study procedures for female patients of childbearing potential
Appendix 8: **Patient Information and Informed Consent Form** **p. 54** **Reason:**	Collected samples will be transferred to the EAU RF or other laboratories working with the EAU RF where these blood samples are used to measure ~~Bladder Cancer~~ related DNA specifics. DNA specifics not related to Bladder cancer may also be important in the immune response to BCG treatment
Appendix 11: Substudy: "Prospective evaluation of cytokines following BCG instillations" **p. 60** **Reason:**	Levels of ~~IL-2, IL-4, IL10~~ *cytokines* and IFN-ɣ will be determined in urine with commercially available, highly specific and reproducible enzyme-linked immunosorbent assays. Other cytokines may also be important in the immune response to BCG treatment

Appendix 12 Substudy: "Validation of predictive genetic markers for BCG response" **p.62** **Reason:**	Single-SNP Centaurus assays (or a ~~custom made~~ *genome-wide* chip) will be used to genotype genetic polymorphisms ~~(at independent loci) that were found to be associated with recurrence and/or progression among the BCG treated discovery series at P<1x10-5~~ Genome-wide chips will be used to genotype polymorphisms gaining more broadened information.
Appendix 13 Checklists **P.64/66**	  [3] Voided urine cytology preferably before *last resection (initial resection*, re-TUR *or re-reTUR*) and follow up cystoscopies or wash-out cytology at the time of last resection and at the time of follow up cystoscopies [4] Upper Urinary Tract Investigation (UUTI) according to local practice (e.g., *CT-Urography, IVU*) ~~abdomen with and without IV contrast material (CT-Urography)~~ to exclude upper urinary tract tumors. ~~IVU is also acceptable where CT is not available. UUTI should be done within 8 weeks prior to re-TUR.~~ [5] Urine *examination*~~culture~~ between ~~re-TUR~~ *last resection* and prior to 1st BCG-instillation. *[6] For females of childbearing potential, a pregnancy test must be performed within 7 days before start BCG treatment. During the treatment period, a pregnancy test will be done at months 3,6,12 and, and should be performed at any time during the study for all women of childbearing potential if the investigator or patient suspects that pregnancy has occurred while the subject was being treated on protocol therapy.* **Reasons** The checklists have been updated according to the changes in the study procedures.

Appendix 11

CLINICAL TRIAL PROTOCOL AMENDMENT

Amendment Version, Date:	Amendment final version 6, January 7th, 2019
Scope of applicability:	**All participating sites**
Protocol Title:	**Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations versus Reduced Number of Intravesical Instillations with Standard Dose of BCG** **A European Association of Urology Research Foundation Randomised Phase III Clinical Trial**
Acronym:	NIMBUS
Protocol-Code-Number:	EAU-RF 2008-01
Protocol Version, Date:	Amended final version 5, May 15th, 2017
EudraCT-Number:	2010-019181-91
Sponsors Name and Address:	EAU Research Foundation Wim P.J. Witjes Mr. E.N. van Kleffensstraat 5 NL 6842 CV Arnhem PO Box 30016 6803 AA Arnhem The Netherlands Tel: +31 26 389 0677 Fax +31 26 389 0679 E-mail: w.witjes@uroweb.org

Coordinating Investigator:

Levent N. Türkeri
Dept. of Urology, Marmara University Medical School
Tophanelioglu Street 13-15 Altunizade
34660 Istanbul, Turkey
Telephone: +90 0216 3275050 / +90 0216 3252052
Fax: +90 0216 325 85 79
Email: turkeri@marmara.edu.tr

Marko M. Babjuk
Dept. of Urology, Charles University
2nd Faculty of Medicine
Úvalu 84
5006 Praha 5, Czech Republic
Telephone: +420 22443801
Fax: +420 224434821
Email: Marek.Babjuk@fnmotol.cz

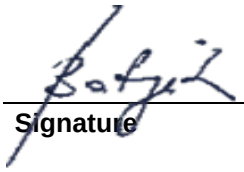
Trial Epidemiologist:

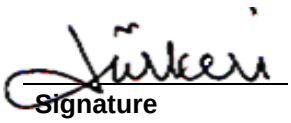
Wim P.J. Witjes

The information contained in this document is the property of the sponsor of this trial. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from the sponsor.

Signatures

The undersigned confirm that they agree to the clinical trial protocol amendment.

Levent N. Türkeri	23-01-2019	
Name:	**Date**	**Signature**
Principal Investigator		

Marko M. Babjuk	18-01-2019	
Name:	**Date**	**Signature**
Principal Investigator		

Wim P.J. Witjes	15-01-2019	
Name:	**Date**	**Signature**
Trial Epidemiologist &		
Representation of Sponsor		

Table of contents

Reason for changes

The IDMC has reviewed the data (based on data present in the eCRF on October 1th 2018) and requested some adaptation of the data analysis as described in *Paragraph 7.3 Interim Analysis* of the study protocol. Because the median time to first recurrence may not be reached (life table risk of recurrence remains below 50%), the IDMC proposes to change this criterion into a HR of 0.75. Because the requirement of a 1% one sided significance level is extremely restrictive, the IDMC proposes to test at a 2.5% one sided significance level which is in agreement with the upper limit of the 95% CI around the HR being less than 0.75.

In recent years, continued supply availability of BCG has been a main challenge in many countries including the countries that participate in the NIMBUS study. As a result, NIMBUS sites are forced to (temporary) switch to another BCG (sub)strain.
All the BCG vaccines currently in use derive from the original strain of BCG produced by Albert Calmette and Camille Guérin in 1924 at the Pasteur Institute. In addition to BCG Medac, BCG TICE and BCG Connaught, substrains used for vaccine production are Brazilian (Moreau/Rio de Janeiro), Danish (Copenhagen–1331), Japanese (Tokyo–172-1), Russian (Moscow–368) and Bulgarian (Sofia–SL222). Different strains tend to be used interchangeably, with no conclusive evidence existing to discriminate for efficacy and safety. The choice of the strains used in the different countries is therefore the result of historical use, production, logistics or other factors. (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5777639/)
In case of BCG shortage we will therefore allow the temporary use of locally approved BCG (sub)strains other than the three strains mentioned in the protocol, i.e. BCG Medac, BCG TICE and BCG Connaught.

Recruitment periods and national coordinators of the different countries vary and should not be listed in the protocol or Patient Information.

Some text was changed/added to update information or more clarify study procedures.

Possible consequences and risks

None compared with the previous version. The changes in the trial protocol will have no consequences for the trial subjects and there are no apparent risks.

Documents affected by the amendment

The changes affect the Study Protocol.
The Patient Information, the Informed Consent Form and electronic Case Report are not affected.

Consequences on subjects treated in the trial before implementation of the amendment.

The changes have no implications on subjects treated in the trial before implementation of the amendment.
There is no need to ask the subjects to re-sign the Informed Consent form.

Changes of clinical trial protocol

The following table describes the changes in detail. The left column gives the headline or chapter where the change has to be made. The right column describes the change. The page numbers are based on the track-change version of the study protocol.

Headline/Chapter	**original text for revision, ~~deleted~~, *added new text***
Title Page • **Protocol Version, Date**	~~*Amended final version 5, May 15th, 2017*~~ *Amended final version 6, January7th, 2019*
Header	~~*Amended final version 5, May 15th, 2017*~~ *Amended final version 6, January7th, 2019*
1.Study Synopsis p.5 • **Study Title and number**	~~*Amended final version 5, May 15th, 2017*~~ *Amended final version 6, January7th, 2019*
1.Study Synopsis p.6 • **Study Design & Intervention** **Reason:**	For each individual centre, one of the three locally available BCG strains in Europe will be used: BCG Tice, BCG Medac or BCG Connaught. *In case of a BCG shortage of one of these three strains, it is allowed to use another locally approved BCG strain, e.g., Moreau/Rio de Janeiro, Copenhagen -1331, Tokyo–172-1, Moscow–368, Sofia–SL222.* As a result of discontinued supply availability of BCG, sites are forced to (temporary) switch to another BCG (sub)strain. In case of BCG shortage we will therefore allow the use of locally approved BCG (sub)strains other than the three strains mentioned in the protocol, i.e. BCG Medac, BCG TICE and BCG Connaught.
1.Study Synopsis p.8 • **Timing** **Reason:**	The study includes a 6-year recruitment phase, followed by a 3-year observation phase. Protocol ready: November 2012 Start EC submission procedure: December 2012 Start Initiation of the centers: November 2013 ~~Recruitment period Germany: December 2013-November 2019~~ ~~Recruitment period The Netherlands: November 2014-November 2019~~ ~~Recruitment period France: July 2017-November 2019~~ ~~Recruitment period Belgium: June 2018-November 2019~~ ~~Recruitment period Spain: December 2018-November 2019~~ ~~Last patient follow up: November 2022~~ Study Closure: 2023 Recruitment periods of the different countries vary and should not be listed in the protocol. Recruitment period of a particular country/site will be described in applications to regulatory authorities and/or in clinical trial agreements.

4. DESIGN OF THE STUDY **p.10** **Reason:**	The study includes a 6-year recruitment phase, followed by a 3-year observation phase ~~(i.e. the first randomised patient will be observed for 9 years in total, the last randomised patient will be observed for 3 years)~~. Irrespective of the recruitment period patients will be observed for a maximum of 5 year.
4.1 Treatment **p. 11** **Reason:**	For each individual centre, one of the three locally available BCG strains in Europe will be used: BCG Tice, BCG Medac or BCG Connaught*. In case of a BCG shortage of one of these three strains, it is allowed to use another locally approved BCG strain, e.g., Moreau/Rio de Janeiro, Copenhagen–1331, Tokyo–172-1, Moscow–368, Sofia–SL222. Preferably, one type of strain should be used within one patient.* As a result of discontinued supply availability of BCG, sites are forced to (temporary) switch to another BCG (sub) strain. In case of BCG shortage we will therefore allow the use of locally approved BCG (sub)strains other than the three strains mentioned in the protocol, i.e. BCG Medac, BCG TICE and BCG Connaught.
4.4 Study Procedures & Follow-Up **p.15**	5. Patients with recurrent tumors ~~which are identified any time after the completion of induction course of BCG~~ will go-off study and will be treated at the discretion of the responsible physician.
5.4 Patient Withdrawal and Early Dropouts (off study) **p.18**	Off study criteria: • First recurrence ~~after completion of the 6 weeks induction course of BCG~~
6. STUDY METHODS **6.1 Randomisation procedure** **p.19**	• Type of BCG strain that will be used: BCG Tice, BCG Medac, ~~or~~ BCG Connaught, *or other* These stratification factors are: 1) Center 2) pathological Ta versus pathological T1 bladder tumor 3) bladder tumor with CIS versus without CIS 4) type of BCG strain used: BCG Tice, BCG Connaught, ~~or~~ BCG Medac *or other* and 5) single or multiple tumors

7. STATISTICAL CONSIDERATIONS	
7.1 Patient Accrual, Study Duration and Calculation of Patient Numbers p.23	The assumptions for the power calculations are the following. - Primary endpoint on which sample size is based is ~~median~~ time to first recurrence. - The ~~median~~ time to first recurrence for the study population is 60 months - Recruitment period is 6 years with an average recruitment period of 4 years per country - Follow up after recruitment is 3 years - Nulhypothesis H0: "the experimental arm is inferior compared to the standard arm. Inferiority is defined as the true *hazard* ratio ~~of median time to~~ *for* first recurrence is lower than 0.75 (e.g. < 45 / 60 months). - Alternative hypothesis H1: "the experimental arm is not inferior compared to the standard arm. Non-inferiority is defined as the true ratio ~~of median time to~~ *for* first recurrence *is* higher than or equal to 0.75 (e.g. ≥ 45 / 60 months). - Anticipated drop out percentage is 15 % nQuery 7.0 was used for the initial power calculations (13). In order to establish therapeutic equivalence, the true *hazard* ratio of ~~median time to~~ *for* first recurrence (texperimental/tstandard) must not be lower than 0.75.
7.3 Interim Analysis p.26	The ~~safety~~ interim analysis will be performed using a significance level of ~~1~~ *2,5 %* (one sided). Inferiority is defined as a true *hazard* ratio of ~~median time to~~ *for* first recurrence (~~t~~*hazard*$_{experimental}$/~~t~~*hazard*$_{standard}$) lower than 0.75. If there are doubts on the efficacy of the reduced frequency arm, further in depth analyses will be performed to investigate a possible imbalance in prognostic factors. The IDMC will ~~consider~~ advise to stop the study when the upper limit of the 95% CI is less than 0.75. No changes in the sample size are required because of the interim analysis. The efficacy interim analysis on *the hazard ratio* for ~~time to~~ first recurrence will also be performed between the different BCG strains used. Statistical tests between BCG strains will be performed at the 5% level of significance and will be two-sided. Results of the interim analysis will be evaluated by an Independent Data Monitoring Committee (IDMC). *After evaluation of the data, the IDMC will communicate an advice to the Steering Committee members to continue or stop the trial*. ~~The decision of stopping the trial in case of significant results will be evaluated by the IDMC.~~
Reason:	As the median time to first recurrence may not be reached (life table risk of recurrence remains below 50%), the IDMC proposes to change this criterion into a HR of 0.75. Because the requirement of a 1% one sided significance level is extremely restrictive, the IDMC proposes to test at a 2.5% one sided significance level which is in agreement with the upper limit of the 95% CI around the HR being less than 0.75.The IDMC proposes to test at a 2.5% one sided significance level which is in agreement with the upper limit of the 95% CI around the HR being less than 0.75.

<table>
<tr><td>Appendix 5 Product Information BCG Strains
p. 47</td><td>Product Information obtained via website:

BCG Tice:

https://www.medicines.org.uk/emc/product/1049/smpchttp://www.spfiles.com/piticebcglive.pdf ~~http://www.spfiles.com/piticebcglive.pdf~~

BCG Connaught:

http://www.vaccineshoppecanada.com/secure/pdfs/ca/immucyst_e.pdf ~~and~~
~~http://emc.medicines.org.uk/emc/assets/c/html/displaydoc.asp?documentid=7779~~

BCG Medac (other name: BCG RIVM):

https://www.hpra.ie/HOMEPAGE/medicines/medicines-information/find-a-medicine/results/item?change=5741581&pano=PA0623/004/001&t=BCG-MEDAC

Information on other BCG substrains
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5777639/
http://www.bcg.gr.jp/english/menu1.html</td></tr>
<tr><td>Appendix 7 Protocol Signature
p. 50</td><td>I have read and agree to the ‘Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAR RF number 2008-01. ~~Final Version 5, May 15th, 2017~~. Amended final version 6, January 7th, 2019</td></tr>
<tr><td>Appendix 13 Checklists

p. 63,64</td><td><table>
<tr><td></td><td colspan="2">Follow-up</td></tr>
<tr><td>2</td><td>mth 15</td><td>mth 18-21-24-30-36-42-48-54-60</td></tr>
<tr><td>wk3</td><td></td><td></td></tr>
<tr><td></td><td></td><td></td></tr>
</table>.</td></tr>
<tr><td></td><td></td></tr>
</table>

Appendix 12

Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations versus Reduced Number of Intravesical Instillations with Standard Dose of BCG

A European Association of Urology Research Foundation Randomised Phase III Clinical Trial

CONFIDENTIAL

Amended final version ~~67~~:	~~January~~ November 7th, 2019
Sponsor and Central Study-Management:	EAU Research Foundation Mr. E.N. van Kleffensstraat 5 NL 6842 CV Arnhem PO Box 30016 6803 AA Arnhem The Netherlands Tel: +31 26 389 0677 Fax: +31 26 389 0679 E-mail: researchfoundation@uroweb.org www.uroweb.org
EAU RF number:	2008 - 01
Eudract Number:	2010-019181-91
Lead Investigators:	Levent N. Türkeri Dept. of Urology, Marmara University Medical School Tophanelioglu Street 13-15 Altunizade 34660 Istanbul, Turkey Telephone: +90 0216 327 50 50 / +90 0216 325 20 52 Fax: +90 0216 325 85 79 Email: turkeri@marmara.edu.tr Marko M. Babjuk Dept. of Urology, Charles University 2nd Faculty of Medicine Úvalu 84 15006 Praha 5, Czech Republic Telephone: +420 22443801 Fax: +420 224434821 Email: Marek.Babjuk@fnmotol.cz
Protocol writing committee:	Marko Babjuk, Prague Luis Martinez-Pineiro, Madrid Joan Palou Redorta, Barcelona Anup Patel, London Levent N. Türkeri, Istanbul Marc-Oliver Grimm, Jena Wim P.J. Witjes, Arnhem

Table of Contents

List of abbreviations and relevant definitions

AE	Adverse Event: any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.
ALT	Alanin-aminotransferase
AR	Adverse Reaction: all untoward and unintended responses to an investigational medicinal product related to any dose administered.
ASA	American Society of Anesthesiology
AST	Aspartate-aminotranferase
BCG	Bacillus Calmette-Guérin
BUN	Blood Ureum Nitrogen
CIS	Carcinoma In Situ
CRF	Case Report Form
CV	Curriculum Vitae
CFU	Colony Forming Units
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CUETO	Club Urológico Español de Tratamiento Oncológico
DNA PCR	DeoxyriboNucleic Acid Polymerase Chain Reaction
EAU RF	European Association of Urology Research Foundation
EC	medical Ethics Committee
eCRF	Electronic Case Report Form
EU	European Union
EORTC	European Organisation for Research and Treatment of Cancer
EudraCT	European drug regulatory affairs Clinical Trials
GCP	ICH Harmonised Tripartite Guideline E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) Step 5, adopted by CPMP July 1996. European Directives 2001/20/EC and 2005/28/EC
GP	General Practitioner

HIV	Human Immunodeficiency Virus
IC	Informed Consent
ICIQ	International Consultation on Incontinence Questionnaire
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IL	Interleukine
IVU	IntraVenous Urogram
LUTS	Lower Urinary Tract Symptoms
NMIBC	Non Muscle Invasive Bladder Cancer
mRNA	messenger Ribo Nucleic Acid
PCR	Polymerase chain reaction
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
SAE	Serious Adverse Event: A serious adverse event is any untoward medical occurrence that at any dose: results in death; is life-threatening; requires inpatient hospitalisation or prolongation of existing hospitalization; results in persistent or significant disability or incapacity or is a congenital anomaly/birth defect.
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction: A serious adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. summary of product characteristics for an authorised product.
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SWOG	South West Oncology Group (US)
TUR	TransUrethral Resection
UTI	Urinary Tract Infection
UUTI	Upper Urinary Tract Investigation
WBC	White Blood Cells
WHO ISUP	World Health Organisation / International Society of Urological Pathology

Confidentiality Statement

These materials contain confidential information belonging to the EAU Research Foundation (EAU RF) except as may be otherwise agreed to in writing, by accepting or reviewing these materials, you agree to hold such information in confidence and not to disclose it to others (except where required by applicable law) nor use it for unauthorized purposes. In the event of actual or suspected breach of this obligation, the EAU RF should be promptly notified.

1. STUDY SYNOPSIS

Study Title and number	Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAU RF number 2008-01, Amended final version 6, January 7th, 2019
Rationale	Intravesical instillation of BCG is a widely accepted strategy to prevent recurrence of non muscle invasive bladder cancer. The most accepted treatment schedule is induction of BCG: weeks 1 through 6 plus maintenance (weeks 1,2,3) at months 3,6 and 12, but it is unknown how many administrations are really necessary. Scientific evidence prones to the hypothesis that after an initial sensitization to BCG antigens has occurred the number of instillations can be reduced for a proper anamnestic immune response resulting in similar clinical efficacy and potentially less side-effects and costs.
Objectives	The primary objective of this study is to identify if reduced number of BCG instillations are not inferior to standard number and dose intravesical BCG treatment in patients with high grade NMIBC. The primary endpoint for inferiority analysis is time to first recurrence. The secondary objectives are to identify if number and grade of recurrent tumors, rate of progression to a higher stage (T2 or higher) of the disease and safety, specifically the presence of treatment related toxicity > grade 2 differ between the two study arms. As of Protocol Amendment 7, the primary and secondary objectives of the NIMBUS study will not be assessed as planned (see added section Study Synopsis below and Section 2.2).
Study Design & Intervention	This is a multicentre prospective, randomized, parallel group, not blinded, trial to compare the efficacy and safety of two different adjuvant treatment schedules: 1) Induction cycle BCG-full dose; weeks 1 through 6 plus maintenance cycles at months 3, 6 and 12 (wks 1,2,3); total 15 full dose BCG instillations 2) Induction cycle BCG-full dose (reduced frequency); weeks 1,2, and 6 plus maintenance cycles at months 3, 6 and 12 (wks 1,3); total 9 full dose BCG instillations. BCG intravesical instillation therapy is registered as adjuvant treatment for the

	prevention of recurrence of NMIBC and can be considered as standard treatment for the type of patients requested in this trial. For each individual centre, one of the three locally available BCG strains in Europe will be used: BCG Tice, BCG Medac or BCG Connaught. In case of a BCG shortage of one of these three strains, it is allowed to use another locally approved BCG strain, e.g., Moreau/Rio de Janeiro, Copenhagen -1331, Tokyo–172-1, Moscow–368, Sofia–SL222. • In case of patients having Ta high grade tumor in the initial resection; a) patients ~~can be~~were included in the study provided muscle ~~is~~ was present and reported in the specimen and the Ta high grade tumor ~~has~~ had been totally removed, or b) patients ~~undergo~~ underwent a re-TUR at the discretion of the investigator. • Patients having T1 high grade tumor in the initial resection, should have undergone a re-TUR. Patients with histological detection of T1 tumor in the re-TUR should have undergone a second re-TUR. These patients ~~are~~ were eligible for the study provided muscle ~~is~~ was present and reported in the specimen and the patients ~~are~~were, macroscopically and histologically confirmed, free of T1 tumors in the (re-re-TUR specimen. A re-TUR (or re-reTUR) should ~~be~~ have been performed within 4-8 weeks after initial resection (or re-TUR). Treatment with the randomised treatment schedule ~~will start~~should have been started 2 weeks after and no later than 6 weeks after the last resection (initial resection, re-TUR or re-re-TUR). The first maintenance therapy should ~~be~~ have been given at month 3 that ~~is~~ was defined as 6-12 weeks after the last instillation of the induction BCG cycle (week 6) and hereafter at months 6 (18-24 weeks) and 12 (42-48 weeks) after the last instillation of the induction BCG cycle (Appendix ~~13~~14: Checklists). Standard Dose Instillations ~~will take~~took place with 1 vial of BCG. The weekly BCG instillations during induction and maintenance cycles ~~have to be~~should have been conducted within 7 ± 2 days. Follow up cystoscopy and cytology ~~will be done~~should have been done every 3 months the first 2 years and bi-annually until the fifth year. As of Protocol Amendment 7, the follow-up period has been shortened (see added section Study Synopsis below and Section 2.2).
Study Population	~~A total of 824 p~~Patients with high grade Ta-T1 urothelial papillary carcinoma of the bladder with or without CIS and who did not receive any BCG intravesical instillation therapy ~~are~~ were ~~to be~~ recruited from urology departments in European hospitals participating in this study. **Inclusion Criteria:** 1. Presence of high grade (Ta-T1) urothelial papillary carcinoma of the bladder with or without CIS 1.1. Tumors can be primary or recurrent 1.2. Tumors can be single or multiple 2a. In case of a Ta high grade tumor in the initial resection, a re-TUR can be performed at the discretion of the investigator. Initial resection or re-TUR must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the (initial) tumor site(s) 2b. In case of a T1 high grade tumor in the initial resection, a re-TUR should

	be performed at weeks 4-8 after initial resection, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s) 3. Re-re-TUR should be performed at weeks 4-8 after re-TUR in case of histological detection of T1 low/high grade tumor in the re-TUR, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s) 4. Histopathologically confirmed absence of T1 low/high grade tumor(s) in the re-TUR specimen and/or re-re-TUR specimen 5. All visible papillary tumors must be completely resected 6. If the patient is male, he must use a condom during sexual intercourse during the first week after BCG treatment. If the patient is female, and of childbearing potential, she must practice adequate contraception for 30 days prior to administration of study treatment, have a negative pregnancy test and continue such precautions during all study treatment period and for 3 months after the last BCG treatment. 7. Signed and dated informed consent form 8. Patient is clinically fit enough to receive BCG bladder instillations. **Exclusion Criteria:** 1. Any previous intravesical BCG therapy 2. Presence of primary CIS only 3. Presence of histopathologically proven muscle invasive urothelial carcinoma of the bladder at first or (re-)re-TUR surgical specimens 4. Presence of any tumors in upper urinary tract or in the prostatic urethra at any time 5. Presence of any other histological type of resected tumor other than urothelial carcinoma on the first or second resection 6. Presence of another malignancy in the 5 years before randomisation except for basal cell carcinoma of the skin or localised prostate cancer in active surveillance 7. Presence of pregnancy or lactation 8. Presence of active tuberculosis, any form of immunodeficiency (eg HIV + serology, transplant recipients) and/or any other contraindication of BCG therapy 9. Patients who have received any systemic cytostatic agents or multi-instillation intravesical chemotherapy in the 3 months prior to randomisation. Early postoperative (within 6 hours of resection) single dose chemotherapy is allowed after the first resection. However, it should not be given after (re-)re-TUR if the patient is considered eligible for this study. 10. Patients with uncontrollable UTI.
Main study Endpoints	Primary endpoint: - time to first recurrence Secondary endpoints: - number and grade of recurrent tumors - rate of progression to a higher stage (T2 or higher) - incidence and severity of side effects As of Protocol Amendment 7, the primary and secondary endpoints of the NIMBUS study will not be assessed as planned (see added section Study Synopsis below and Section 2.2).
Nature and extent of the burden and	The burden and risks associated with participation in the study is considered minimal and acceptable. The number of visits and treatments is equal to or less compared what patients with these criteria is offered when they are treated on a

risks associated with participation and risk-benefit	standard way which is BCG intravesical instillation therapy. Extra in this study are the symptoms and quality of life questionnaires that need to be completed. A potential risk for patients in the reduced frequency arm is that the treatment is less effective with respect to the prevention of recurrence compared to the standard frequency arm. A potential benefit is that side effects, both in quantity and quality, are expected to be less in the reduced frequency arm compared to the standard frequency arm. The risks related to the expected treatment outcome, quality and quantity of side effects of the study medication can be considered as acceptable. Surgical procedures, laboratory and radiological evaluations are not considered extra and are performed according to standard practice or at the investigators discretion for monitoring eventual recurrence or progression of disease. Possible benefit for the patient is that the patient is followed according to the latest standards and guidelines of treatment of NMIBC.
Timing	As of Protocol Amendment 7, the timing of the NIMBUS has been changed (see added section Study Synopsis below and section 2.2). The recruitment phase was stopped as of October 17th 2019.~~The study includes a 6-year recruitment phase~~. Follow-up period will end at 17 November 2019 with the exception of; - patients that did not yet complete the 6 months follow-up period; for these patients follow-up will end after the Month 6, Week 3 visit~~,~~ ~~followed by a 3-year observation phase.~~ - patients that, on 17 November 2019, are in the middle of the treatment cycle of Month 12 (M12 W1-W3); follow-up will end after the Month 12 Week 3 visit (even if visits take place after 17 November 2019). Protocol ready: November 2012 Start EC submission procedure: December 2012 Start Initiation of the centers: November 2013 Study Closure: ~~2023~~2020.
Protocol Amendment 7	The Independent Data Monitoring Committee (IDMC) of NIMBUS has reviewed the trial's progress and conducted a safety analysis of the interim data (cut-off date July 1, 2019). The analysis of data showed a difference in recurrence percentages between the treatment groups (27.1% in the reduced frequency group compared to 12% in the standard group). The hazard ratio for first recurrence was 0.403 [95% CI: 0.241-0.676]. The study's primary objective was to show equivalence which was defined as the lower part of the one-sided CI higher than HR (hazardexperimental/-hazardstandard) for first recurrence of 0.75. However, this safety analysis showed inferiority which was defined in the study protocol as the upper part of the one-sided CI lower than HR 0.75. Therefore, on 17 October 2019, all sites that participate in the NIMBUS study were instructed to immediately stop recruitment of patients, inform patients and offer patients in Reduced Frequency arm the possibility to switch to Standard Frequency. The follow-up period will be shortened until all patients have at least 6 months of follow-up (i.e. performed visit Month 6 Week 3).

2.1 INTRODUCTION

Intravesical BCG therapy is considered the most effective form of treatment in patients with high-risk non-muscle invasive urothelial carcinoma of the bladder (NMIBC). Many years after the initial landmark report by Morales et al. which demonstrated the efficacy of BCG (1), there has been little change in the empirical dose and schedule described originally. Additional maintenance therapy consisting of 3 weekly instillations every 3 to 6 months improved long-term results following an initial induction course of 6-weekly instillations (2).

Futhermore, the 2 meta-analyses performed so far indicated that some form of maintenance following an induction therapy is required if the risk of progression is to be reduced (3,4).

In the analysis of 20 trials where BCG maintenance was given, a reduction of 37% in the odds of progression was observed (3). However, this meta-analysis could not determine which one of the BCG maintenance schedules was the most effective. In their meta-analysis, Bohle et al. concluded that at least one year of maintenance BCG was required (4).

However, toxicity associated with repeated instillations of BCG remains a major problem and requires dose modifications in an attempt to curb the side effects. It is noteworthy that only 16% of the patients in the SWOG study could receive all scheduled maintenance treatments due to substantial toxicity associated with this regimen (2).

Therefore, different schedules of BCG instillations were investigated in order to decrease the severity and frequency of side effects while maintaining the efficacy. The most common approach to reduce BCG toxicity has been dose reduction and a number of authors have proposed one third and one quarter dose instillations of BCG.

In a randomised study which compared one third dose to full dose BCG in 500 patients, CUETO found no overall difference in efficacy (5). Although fewer patients reported toxicity on the reduced dose, the incidence of severe systemic toxicity was similar in the standard and reduced dose groups.

In spite of the ongoing research concerning the optimum dose and schedule for BCG therapy, this has not been established yet, largely due to the absence of a complete understanding of mechanisms by which BCG mediates antitumor activity.

The exact mechanism of action of BCG remains uncertain, however, it is generally accepted that BCG therapy is immune dependent. After intravesical BCG instillation, the live BCG organisms bind to the urothelium and initiate an immune response and, most likely, activation of a so-called Th1 immune response is required for clinical efficacy (6). The Th1 response results in the production of cytokines as interferon (IFN)-γ, interleukin (IL)-2 and IL-12 which favour the development of cellular immune responses (delayed-type hypersensitivity, cytolysis and macrophage activation (7). The Th2 response is characterized by the synthesis of cytokines such as IL-4, IL-5, IL-6 and IL-10, and favours the generation of humoral immunity (antibodies) (8).

In general, following exposure to an antigen, the secondary immune response occurs more rapidly and is more vigorous. In an animal model, re-treatment with BCG effectively reduced the growth of transplanted transitional cell carcinoma but only when sufficient time had lapsed for the immune stimulation of previous BCG treatment to wane (9).

Development of the cytokine response would depend on the time interval during sensitization and challenge. During a repeat BCG instillation the immune system was shown to react more quickly which was reflected by a rapid increase in urinary IL-2 levels and this pattern was not influenced by the level of response to initial BCG challenge (10). Furthermore, IL-2 production can be down-regulated by repeated instillations with a short interval, presumably as a result of expression of regulatory cytokines. In a recent animal study, de Boer et al. demonstrated similar levels of IFN-γ, IL-2 and IL-12 (Th1) mRNA induction after a schedule of only two BCG instillations administered in week 1 and 6 (1 + 6 schedule), compared to 6 weekly instillations (7). Significantly lower levels of the Th2 cytokines of IL-10 and IL-4 mRNA by 1+6 schedule were observed in this study. However, reduction of the BCG instillation volume by 50% resulted in impaired Th1 responses. One additional instillation in week 2 or in week 5 under these suboptimal circumstances restored the cytokine responses completely, notably, for both the Th1 and Th2 cytokines. The authors concluded that to raise a Th1 cytokine response in the bladder, which is thought to be important for antitumor activity, BCG instillations at weeks 2, 3, 4, and 5 can be omitted, provided that the BCG dose is sufficient. Noteworthy, only one additional BCG instillation (half-dose, in week 2) was sufficient for restoring the Th1 cytokine response, which however also enhanced the Th2 response. Consequently, implementation of low frequency BCG instillation schedules should principally be meant to reduce the BCG dose and related adverse effects.

In conclusion, while the schedule with instillations at a regular dose in week 1 and 6 induced a cytokine response in which the Th1 response predominated, one extra instillation in week 2 or 5 will further increase the Th2 cytokine response. Since reduced number of instillations could provide equivalent Th1 cytokine expression to standard regimen and BCG-induced Th1/Th2 cytokine ratio was demonstrated to be associated with effective anti-tumor activity (11), novel reduced number of instillations strategy may provide an alternative way of BCG dose reduction.

Thus, the proposed investigation schedule is based on the hypothesis that after an initial sensitization to BCG antigens has occurred (as in the vaccination for Tuberculosis), intermediate instillations can be reduced for a proper anamnestic immune response and may result in similar clinical efficacy as standard BCG therapy.

2.2 PROTOCOL AMENDMENT 7

The Independent Data Monitoring Committee (IDMC) of NIMBUS has reviewed the trial's progress and conducted a safety analysis of the interim data (cut-off date July 1, 2019).
This data analysis showed a large difference in recurrence percentages between the treatment groups (27.1% in the reduced frequency group compared to 12% in the standard group). The hazard ratio for first recurrence was 0.403 [95% CI: 0.241 – 0.676].
The study's primary objective was to show equivalence which was defined as the lower part of the one-sided CI higher than HR (*hazardexperimental/-hazardstandard)* for first recurrence of 0.75.
However, this safety analysis showed inferiority which was defined in the study protocol as the upper part of the one-sided CI lower than HR 0.75. (see also 7. STATISTICAL CONSIDERATIONS)
Therefore, the IDMC has advised to terminate recruitment of the study immediately, inform investigators and patients and offer patients in the reduced frequency treatment arm the possibility to switch to the standard frequency. The Steering Committee agreed to follow up this advice.
On 17 October 2019, all sites that participate in the NIMBUS study were instructed to immediately stop recruitment of patients, inform patients and offer patients in Reduced Frequency arm the possibility to switch to Standard Frequency.
On 7 November 2019, the NIMBUS sites were informed that the follow-up period will end at 17 November 2019 with the exception of;
- patients that did not yet complete the 6 months follow-up period; for these patients follow-up will end after the Month 6 Week 3 visit.
- patients that, on 17 November 2019, are in the middle of the treatment cycle of Month 12 (M12 W1-W3); follow-up will end after the Month 12 Week 3 visit (even if visits take place after 17 November 2019).
On 7 November 2019, the NIMBUS sites were provided with a Letter for the Patient (see Appendix 13), written by the Sponsor, and the sites were instructed to hand-over, or send this letter to all patients that participated in the NIMBUS study at their institution.

3. STUDY OBJECTIVES & END POINTS

The primary objective of this study is to identify if reduced number of BCG instillations are not inferior to standard number and dose intravesical BCG treatment in patients with high grade NMIBC. Primary endpoint will be time to first recurrence.

Secondary endpoints are: number and grade of recurrent tumors; rate of progression to a higher stage (T2 or higher) of the disease and the incidence and severity of side effects, specifically the presence of treatment related toxicity > grade 2. These endpoints will be compared between the two study arms.

The objectives of a cytokines substudy and a DNA substudy that will take place in selected centres only are, to evaluate the impact of therapy on cytokines and to evaluate the results of DNA analysis as a prognostic factor, respectively (Appendices 11,12).

As of Protocol Amendment 7, the primary and secondary objectives of the NIMBUS study will not be assessed as planned (see added section 2.2).

4. DESIGN OF THE STUDY

This is an international multicentre prospective, randomized, parallel group, not blinded, trial to compare the efficacy and safety of two different adjuvant treatment schedules:

- Induction cycle BCG-full dose; weeks 1 through 6 plus maintenance cycles at months 3, 6 and 12 (wks 1,2,3) and
- Induction cycle BCG-full dose (reduced frequency); weeks 1, 2 and 6 plus maintenance cycles at months 3, 6 and 12 (wks 1,3).

As of Protocol Amendment 7, the timing of the NIMBUS study has been changed (see section 2.2). The recruitment phase was stopped as of October 17th 2019. Follow-up period will end at 17 November 2019 with the exception of;

- patients that did not yet complete the 6 months follow-up period; for these patients follow-up will end after the Month 6, Week 3 visit,
- patients that, on 17 November 2019, are in the middle of the treatment cycle of Month 12 (M12 W1-W3); follow-up will end after the Month 12 Week 3 visit (even if visits take place after 17 November 2019).~~The study includes a 6-year recruitment phase, followed by a 3-year observation phase. Each investigator will commit himself to a minimal number of patients to recruit within 4 years from the start of the study~~.

4.1 Treatment

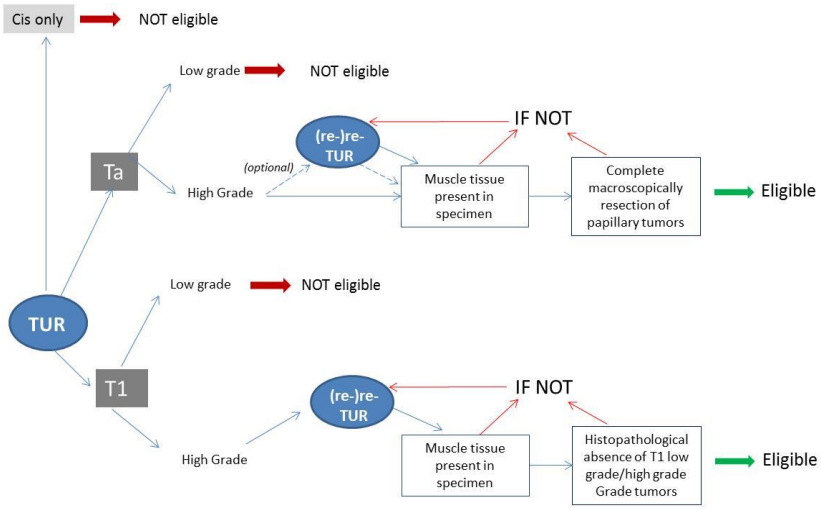
BCG intravesical instillation therapy is registered as adjuvant treatment for the prevention of recurrence of NMIBC and can be considered as standard treatment for the type of patients requested in this trial. For each individual centre, one of the three locally available BCG strains in Europe will be used: BCG Tice, BCG Medac or BCG Connaught. In case of a BCG shortage of one of these three strains, it is allowed to use another locally approved BCG strain, e.g., Moreau/Rio de Janeiro,

Copenhagen–1331, Tokyo–172-1, Moscow–368, Sofia–SL222. Preferably, one type of strain should be used within one patient.

BCG will be prescribed by the investigator according to usual daily practice.

Specification of BCG types and the standard procedures for preparation of BCG intravesical solutions that are available in the participating countries can be obtained via webaddresses as indicated in Appendix 5.

- In case of patients having Ta high grade tumor in the initial resection; a) patients ~~can be~~were included in the study provided muscle ~~is~~ was present and reported in the specimen and the Ta high grade tumor had~~s~~ been totally removed, or b) patients ~~undergo~~ underwent a re-TUR at the discretion of the investigator.
- Patients having T1 high grade tumor in the initial resection, should have undergone a re-TUR. Patients with histological detection of T1 tumor in the re-TUR should have undergone a second re-TUR. These patients ~~are~~ were eligible for the study provided muscle ~~is~~was present and reported in the specimen and the patients ~~are~~were, macroscopically and histologically confirmed, free of T1 tumors in the (re-)re-TUR specimen.



Flow chart for eligibility patients with CIS only, Ta and T1 tumors in TUR

A re-TUR (or re-reTUR) should have ~~be~~ been performed within 4-8 weeks after initial resection (or re-TUR).

Treatment with the randomised treatment schedule ~~will~~ should have started 2 weeks after and no later than 6 weeks after the last resection (initial resection, re-TUR or re-re-TUR). As of October 17th 2019 patients in the Reduced frequency treatment schedule were offered the possibility to switch to the Standard frequency treatment schedule.

The first maintenance therapy should be given at month 3 that is defined as 6-12 weeks after the last instillation of the induction BCG cycle (week 6) and hereafter at months 6 (18-24 weeks) and 12 (42-48 weeks) after the last instillation of the induction BCG cycle (Appendix ~~13~~14: Checklists). Standard Dose Instillations will take place with 1 vial of BCG. The weekly BCG instillations during induction and maintenance cycles have to be conducted within 7 ± 2 days. Follow up cystoscopy and cytology will be done every 3 months the first 2 years and bi-annually until the fifth year.

In case of side effects the instillation schedule can be modified. The rules for modification of the treatment in different side effects are mentioned in Appendix 6. Any deviation from the required dose or schedule as well as the reason for the deviation should be documented carefully in the eCRF by the investigator.
In case of cessation of BCG treatment, if possible, follow up cytology and cystoscopy should be continued according to protocol.
To evaluate if optimization of BCG instillation can help to influence side effects and efficacy of BCG instillations a substudy in a limited number of centres with interest to participate in this substudy will take place. Patients with fluid restriction will be compared with patients without fluid restriction and patients with rotation during the instillation procedure will be compared with patients without rotation with respect to side effects and efficacy. A limited number of extra questions in the CRF will be completed in case the investigator decides to participate in this substudy (Appendix 10).

4.2 Concomitant Medication

Concomitant medication has to be documented up to the visit at month 15 (last BCG instillation of the maintenance cycly = end of treatment). During the study, other treatments or the administration of other drugs for the prevention/treatment of NMIBC is not permitted. Any other non-experimental drug(s) in treatment for other indications are permitted, provided they are recorded in the eCRF.

4.3 Pre-Treatment Assessments

1. Demography data: gender, childbearing potential, race, height and weight.

2a. In case of Ta high grade tumor in the initial resection, a re-TUR can be performed at the discretion of the investigator. Initial resection or re-TUR should include deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the (initial) tumor site(s).

2b. In case of T1 high grade tumor in initial resection, a re-TUR (4-8 weeks after initial resection) or re-re-TUR (in case of T1 low/high grade tumor in re-TUR) should be performed and should include deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s).

3. Bladder wash cytology at the time of last resection (initial resection, re-TUR or re-re-TUR) or voided urine cytology preferably before last resection is required.

4. Cystoscopy before or at the time of initial resection

5. Upper urinary tract (UUT) tumors should be excluded. UUT investigations can be performed according to local standards (e.g., IVU, CT-Urography).

6. Any active urinary tract infection (UTI) should be excluded before the start of BCG instillations. UTI examination can be performed according to local practice (e.g., urine culture, urine strip test)

7. Laboratory examination (e.g., BUN, creatinine, AST, ALT, leucocytes, platelets) according to local practice.

8. For females of childbearing potential, a pregnancy test must be performed within 7 days before start BCG treatment.

9. ICIQ LUTS male and female questionnaires (Appendix 1).

10. EORTC QLQ-30 questionnaire (Appendix 2).

11. WHO Performance Score & ASA Performance Scale (Appendix 9).

4.4 Study Procedures & Follow-Up

1. During the first 2 years, all patients will be followed-up by 3 monthly control cystoscopies and voided urine cytology before follow-up cystoscopy or wash-out cytology at the time of follow-up cystoscopy. Procedure of bladder wash out cytology is as follows: After the introduction of rigid cystoscope, before draining the bladder, 3 times wash with ≥ 50 cc saline will be performed and collected for pathological examination. In case of the use of flexible cystoscope for control cystoscopy, 3 times wash with ≥ 20 ml saline will be performed through the working channel of the instrument and collected for examination. The first cystoscopy should be performed at 6-8 weeks after the completion of last

instillation of induction BCG. Follow up cystoscopy and cytology will be done every 3 months the first 2 years and bi-annually until the fifth year.

2. Any lesions with high suspicion for malignancy on follow-up cystoscopies will be resected completely with additional biopsies of the tumor bed to provide samples of muscle tissue for appropriate pathological examination.
3. No random biopsies are required during the control cystoscopies. However, any suspicious lesion(s) must be biopsied to rule out the presence of any type of tumor(s).
4. When a recurrence is suggested by positive cytology, a biopsy has to be performed because a recurrence can only be established on histological examination.
   If the cytology is positive in case of tumor-free cystoscopy, upper urinary tract imaging should be performed according to local standards (e.g. IVU, CT-Urography). If the results of these investigations are negative, the patient should have retrograde cytology from the upper urinary tract alongside with random-biopsies of the bladder and also prostatic urethra in males, within 4 to 6 weeks. If all are negative, the patient should continue the BCG instillations according to the assigned protocol arm during the first year. If the patient is beyond 2 years in the protocol, the next control cystoscopy should be performed after 3 months (not 6 months as in patients with completely normal findings) to ensure the absence of any tumor(s).
5. Patients with recurrent tumors will go-off study and will be treated at the discretion of the responsible physician.
6. Urine examination (e.g., urine culture, urine strip test) will be performed before the first instillation of BCG induction therapy to ensure the absence of a urinary tract infection (UTI). For subsequent instillations UTI examinations are not required unless the patient presents with persistent symptoms or gross hematuria (more than 48 h) in which case Löwenstein cultures and/or Mycobacterium DNA PCR should also be obtained.
   Discontinuation of BCG therapy and anti-tuberculosis drug therapy is indicated for at least 3 months if Löwenstein culture or PCR is positive.
7. Instillation(s) of BCG must be postponed in case of hematuria after traumatic catheterization and/or in non-treated urinary tract infection until complete resolution.
8. Questionnaires are to be completed prior to the first and last instillation of every cycle (ICIQ-LUTS and “EORTC QLQ 30” questionnaires (Appendix 1 and 2)). Also side effect evaluations of known local and systemic side effects (WHO Grading of Toxicity; Appendix 6) are to be peformed prior to the first and last instillation of every cycle. This is for the induction cycle prior to the first instillation, and prior to the week 6 instillation at the end of the 6 weeks BCG induction cycle or earlier in case of early stop of instillations. For the

maintenance cycles at months 3,6 and 12, this is prior to the first and the last instillations of the cycle (Wk1, 3) or earlier in case of stop of instillations. Other side effects or adverse events are to be reported according to the CTCAE criteria up to month 15 unless the AE is serious and either related to study participation or related to study treatment; these SAEs need to be reported throughout the study. (CTCAE; Appendix 4). See also 6.3.

9. Follow up of the upper urinary tract in the absence of positive cytology should be performed according to local standards.
10. During the treatment period, a pregnancy test will be done at months 3,6,12 and 3 months after the last BCG treatment, and should be performed at any time during the study for all women of childbearing potential if the investigator or patient suspects that pregnancy has occurred while the subject was being treated on protocol therapy.

Patients who become pregnant during the study treatment phase must not receive additional BCG instillations but may continue other study procedures at the discretion of the investigator (see also section 6.4).

As of Protocol Amendment 7, the follow-up period has been shortened (see section 2.2).

5. PATIENT SELECTION & WITHDRAWAL CRITERIA

5.1 Study Population

~~A total of 824 P~~patients with high grade* Ta-T1 urothelial papillary carcinoma of the bladder with or without CIS and who did not receive any BCG intravesical instillation therapy ~~are to be~~were recruited from urology departments in European hospitals participating in this study. At the time of the recruitment stop on 17 October 2019, 359 out of the 824 initially planned patients were randomised.

5.2 Inclusion Criteria

To be eligible for this study, patients needed to meet all of the following inclusion criteria:

1. Presence of high grade (Ta-T1) urothelial papillary carcinoma of the bladder with or without CIS

1.1. Tumors can be primary or recurrent

1.2. Tumors can be single or multiple

2a. In case of a Ta high grade tumor in the initial resection, a re-TUR can be performed at the discretion of the investigator. Initial resection or re-TUR must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the (initial) tumor site(s)

2b. In case of a T1 high grade tumor in the initial resection, a re-TUR should be performed at weeks 4-8 after initial resection, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s)

3. Re-re-TUR should be performed at weeks 4-8 after re-TUR in case of histological detection of T1 low/high grade tumor in the re-TUR, which must include the deep resection or cold cup biopsy (deep enough to obtain muscle tissue) of the initial tumor site(s)

4. Histopathologically confirmed absence of T1 low/high grade tumor(s) in the re-TUR specimen and/or re-re-TUR specimen

5. All visible papillary tumors must be completely resected

6. If the patient is male, he must use a condom during sexual intercourse during the first week after BCG treatment. If the patient is female, and of childbearing potential, she must practice adequate contraception for 30 days prior to administration of study treatment, have a negative pregnancy test

* Pathological Grading will be done according to WHO/ISUP classification (12)

and continue such precautions during all study treatment period and for 3 months after the last BCG treatment.

7. Signed and dated informed consent form
8. Patient is clinically fit enough to receive BCG bladder instillations.

5.3 Exclusion Criteria

1. Any previous intravesical BCG therapy
2. Presence of primary CIS only
3. Presence of histopathologically proven muscle invasive urothelial carcinoma of the bladder at first or (re-)re-TUR surgical specimens
4. Presence of any tumors in upper urinary tract or in the prostatic urethra at any time
5. Presence of any other histological type of resected tumor other than urothelial carcinoma on the first or second resection
6. Presence of another malignancy in the 5 years prior to randomisation, except for basal cell carcinoma of the skin or localised prostate cancer in active surveillance
7. Presence of pregnancy or lactation
8. Presence of active tuberculosis, any form of immunodeficiency (eg HIV + serology, transplant recipients) and/or any other contraindication of BCG therapy
9. Patients who have received any systemic cytostatic agents or multi-instillation intravesical chemotherapy in the 3 months prior to randomisation. Early postoperative (within 6 hours of resection) single dose chemotherapy is allowed after the first resection. However, it should not be given after (re-)re-TUR if the patient is considered eligible for this study.
10. Patients with uncontrollable UTI.

5.4 Patient Withdrawal and Early Dropouts (off study)

In the patient informed consent form the patients will be informed that they have the right to withdraw from the study at any time without affecting their subsequent care and may be withdrawn at the investigator's discretion at any time. In the event that the patient drops out, the investigator will, if possible, indicate the reason for withdrawal. Reasonable effort will be made to contact any patient lost to follow up during the course of the study in order to complete assessments and retrieve any outstanding data. Patients withdrawn from the trial will not be replaced.

Off study criteria:

- When the investigator considers it in the best interest of the patient that he/she will be withdrawn
- First recurrence
- Occurrence of new CIS
- Occurrence of urothelial carcinoma in the upper tract, or in the prostatic urethra
- Patient requests withdrawal of informed consent
- Lost to follow up
- Occurrence of distant metastases
- Occurence of a new malignancy requiring the use of sytemic chemotherapy.

6. STUDY METHODS

6.1 Randomisation procedure

Randomisation ~~will be~~was done via a web-based data management system. When a patient ~~is~~ was eligible to participate in the study and written informed consent ~~has~~ had been obtained (Appendix 8: Patient Information and Informed Consent Form), the patient ~~can be~~was randomised via the website. Treatment allocation ~~will be~~was displayed immediately on the screen after entry of the following information:

- Institutions name
- Name of investigator
- Patient identification / Patients date of birth
- Date of informed consent
- Number of tumors
- Type of BCG strain that will be used: BCG Tice, BCG Medac, BCG Connaught, or other.
- Pathology result (Tumor stage).
- CIS present: Y/N.

In this study, there ~~are~~were 5 stratification factors in which the marginal treatment totals ~~should b~~weree balanced. These stratification factors ~~are~~were: 1) Center 2) pathological Ta versus pathological T1 bladder tumor 3) bladder tumor with CIS versus without CIS 4) type of BCG strain used: BCG Tice, BCG Connaught, BCG Medac or other and 5) single or multiple tumors. The

validated randomisation program use~~d~~s the minimisation method with a random element as described by Pockock for treatment assignment [15].

At randomisation, a number ~~will be~~was allocated to the patient (patient sequential identification number). This number identifies the patient and ~~must be~~was reported on all eCRF's and other relevant documents. This patient sequential identification number identifies the patient for the Sponsor. The local investigator and his personnel maintain a list which identifies the patients' sequential identification number with the patients source data. This list is safeguarded by the local investigator and his personnel.

6.2 Study Organisation & Management

For this multicentre study, an initiating investigators meeting at a central location ~~will be~~was held to standardise data management procedures and resolve questions regarding protocol conduct. At the initiation meeting, the investigator and eventual other site study personnel ~~will be~~were instructed how to conduct the study- and data management procedures. In addition, the sites will be able to download the required materials via the EAU RF website. EAU RF's representatives may conduct field data review periodically. It is the responsibility of EAU RF's representatives to verify adherence to the protocol and the completeness, accuracy and consistency of the data. The investigator or a qualified employee will enter all relevant data into eCRF's, in accordance with the instructions provided. The investigator may be requested to provide a copy of the applicable pathology reports. These copies will be used as source verification. An explanation for the omission of any required data should appear on the appropriate e-page. The investigator ~~must~~ has signed an agreement thereby stating that she/he takes responsibility for the accuracy of the data in the entire eCRF.

Original patient records (e.g., hospital charts, clinical records, laboratory printouts) should be available at each study site for source document review by EAU RF's representatives. Source document review is the cross checking of information recorded on eCRF's with that recorded in the original patient records. In this study, source document review of specific types of information will be conducted for a percentage of patients (for example, 10 % of the patients enrolled). EAU RF's representatives ensure the privacy of the patient data by only collecting the patient data without the patient details that could identify the individual patient. The investigator should give the monitor access to all relevant patient data.

Queries to be issued to the investigator will consist of questions to clarify for instance missing data, inconsistencies, illegible data, illegal values and items that are not clearly corrected.

When all patient and visit data are received at EAU RF, all data problems have been resolved, all data checks and quality control checks have been performed, the study database is considered to be

clean and can be locked. This cleaning and locking process will be performed on a per patient and per visit basis. In addition, the study centre may be audited in depth for study quality assurance by EAU RF's representatives, and/or inspected by a national regulatory authority. This audit may include review of all source documents, drug records, original clinic case-notes, some or all of the facilities used in the trial, etc. Patient confidentiality will be maintained at all times and consent for this will be obtained prior to entry of the patient into the clinical trial.

6.3 Safety reporting

6.3.1 Adverse Events (AE's)

An adverse event is any undesirable clinical occurrence in a patient whether it is considered to be drug related or not. The observed or volunteered adverse events regardless of suspected causal relationship to the study treatment will be recorded on the adverse event page of the eCRF. An adverse event is classified by the investigator as mild (1), moderate (2), severe (3) life threatening (4) or death (5) according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE, Appendix 4).

Events involving adverse treatment reactions, illness with onset during the study, or exacerbations of pre-existing illness should be recorded. Objective test finding (e.g. laboratory results) that need treatment should also be recorded.

Note that the following examples of adverse events do not need to be recorded and, in case that one of the following examples fulfil the definition of an SAE, also do not need to be reported:

• Medical or surgical procedures (e.g. endoscopy, appendectomy); the condition that leads to the procedure is an AE.

• Hospitalisation for elective treatment of a pre-existing condition (known/diagnosed prior to informed consent signature) that did not worsen from baseline.

• Situations where an untoward medical occurrence did not occur (e.g. social and/or convenience admission to a hospital, admission for routine examination).

• Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

• The disease/disorder being studied, or expected recurrence, progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the patient's condition.

An example of events which are to be recorded in the medical history section of the eCRF and not as an AE is eg. pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e. prior to the first study product administration).

The investigator should also provide information on the duration (start and stop date), relation to study treatment, start of concomitant therapy and outcome of the adverse event. Follow up of the adverse event after therapy discontinuation, is required if the adverse event or its sequelae persist. Follow up is required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator. Adverse event information will be collected from the first instillation up to the visit at month 15 or as of Protocol Amendment 7 untill the last performed visit of the maintenance cycle . The Sponsor shall consider all adverse events and, if required, shall report them to the appropriate authorities.

6.3.2 Serious Adverse Events (SAE's)

A serious adverse event is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalization (except for elective hospitalization for a pre-existing condition that did not worsen from baseline; See 6.3.1)
- results in persistent or significant disability / incapacity or
- is a congenital anomaly/birth defect.

If, as a result of an adverse event during a clinical investigation, a patient has to be hospitalised, or their hospitalisation is unduly prolonged because of potential disability or danger to life or because an intervention has been necessitated or the event is terminal, the adverse event is regarded as serious. For example, if – according to the investigator - an adverse event causes foetal distress, foetal death or a congenital anomaly or malignancy results from the use of the drug during a clinical investigation, this would be processed as a serious adverse event.

All serious adverse events which occur from the first instillation up to the visit at month 15 or as of Protocol Amendment 7 untill the last performed visit of the maintenance cycle. All SAE's whether or not considered related to the treatment, must be reported immediately (within one day of the investigator becoming aware of the adverse event) by sending a completed Serious Adverse Event Report Form by e-mail or fax to EAU RF. Serious adverse events **related to either study participation or related to study treatment** should be reported throughout the entire study period. An event which is part of the natural course of the disease under study (i.e., disease recurrence or progression) is captured as an efficacy measure; therefore it does not need to be reported as a SAE. Progression/recurrence of the tumor will be recorded in the clinical assessments in the eCRF. Death due to a progressive disease is to be recorded on a specific form in the eCRF but not as a SAE.

However, if recurrence or progression of the underlying disease is more severe than what would normally be expected for the patient, or if the investigator considers that there was a causal relationship between treatment with BCG or protocol design/procedures and the disease progression/recurrence, then this must be reported as a SAE. Any new cancer (non-related to the cancer under study) must be reported as an SAE.
The Sponsor will report SAE's to the EC that approved the protocol and to the regulatory authorities via the annual development safety update reports (DSURs). (See chapter 9.4)

Table: Timing of reporting obligations of (S)AEs

Study activity	Treatment phase		Follow-up	Follow-up
	First BCG instillation visit	Last BCG instillation visit	Visit Month 15	Up to end of study
Reporting of AEs				
Reporting of SAEs				
Reporting of SAEs related to study participation				
Reporting of SAEs related to study treatment				

6.3.3 Suspected Unexpected Serious Adverse Reactions (SUSAR's)

Suspected unexpected adverse reactions are SAE's considered to be related to study treatment, of which the nature, or severity, is not consistent with the summary of product characteristics of the BCG strain used in this trial (See Appendix 5).
The Sponsor will report (expedited) all SUSARs to the investigators, competent authorities and EC's. The expedited reporting will occur within the per law defined time intervals which is currently not later than 15 days after the Sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term is currently a maximum of 7 days for a preliminary report, with another 8 days for completion of the report.

6.4 Pregnancy

Patients who become pregnant during the study treatment phase must not receive additional doses of study treatment but may continue other study procedures at the discretion of the investigator.
The investigator, or his/her designee, will collect pregnancy information on any patient who becomes pregnant while participating in this study i.e. from signature of informed consent till 3

months after the last BCG treatment.The investigator, or his/her designee, will record pregnancy information on the Pregnancy Report Form and submit it to the Sponsor within 24 hours of learning of a patient's pregnancy. The patient will be followed to determine the outcome of the pregnancy. At the end of the pregnancy, whether that be full-term or prematurely, information on the status of the mother and child will be forwarded to the Sponsor. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

While pregnancy itself is not considered an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded and followed as an AE or a SAE, as described in Section 6.3.1 and 6.3.2.

A spontaneous abortion is always considered to be a SAE and will be reported as described in Section 6.3.2. Furthermore, any SAE occurring as a result of a post-study pregnancy AND considered reasonably related in time to the investigational product by the investigator, will be reported to the Sponsor as described in Section 6.3.3. While the investigator is not obligated to actively seek this information from former study participants, he/she may learn of a pregnancy through spontaneous reporting.

6.5 Premature Termination of the Study

For a reasonable cause (see section 2.2), the Sponsor~~, may~~ will prematurely terminate this study. ~~provided~~ A~~a~~ written notice ~~is~~ to announce that the study will be prematurely terminated was communicated to the sites and submitted to the regulatory authorithies ~~at a reasonable time in advance of intended termination.~~.

7. STATISTICAL CONSIDERATIONS

As of Protocol Amendment 7, statistical analyses will not be assessed as planned. All clinical data collected in the study will be analysed descriptively. Please see section 2.2 for the rationale.

7.1 Patient Accrual, Study Duration and Calculation of Patient Numbers

The assumptions for the power calculations are the following.

- Primary endpoint on which sample size is based is time to first recurrence.
- The time to first recurrence for the study population is 60 months
- Recruitment period is 6 years with an average recruitment period of 4 years per country
- Follow up after recruitment is 3 years
- Nulhypothesis H0: "the experimental arm is inferior compared to the standard arm. Inferiority is defined as the true hazard ratio for first recurrence is lower than 0.75 (e.g. < 45 / 60 months).
- Alternative hypothesis H1: "the experimental arm is not inferior compared to the standard arm. Non-inferiority is defined as the true ratio for first recurrence is higher than or equal to 0.75 (e.g. ≥ 45 / 60 months).
- Anticipated drop out percentage is 15 %

nQuery 7.0 was used for the initial power calculations (13).
In order to establish therapeutic equivalence, the true hazard ratio for first recurrence ($t_{experimental}/t_{standard}$) must not be lower than 0.75. Taking this ratio as the lower margin of the one-sided equivalence range and given the above mentioned assumptions and using a one-sided error rate alpha of 2.5%, the following power calculations were simulated with the in the table indicated number of patients per arm.

N per arm	Number of events needed	power *
324	298	70
365	335	75
412	379	80
472	434	85
552	508	90

* Power to obtain a statistical significant non-inferior result of the reduced frequency arm in comparison with the standard arm.

From this table, the sample size needed per arm is 412 patients per arm which gives the total number of patients to be randomized at patients at an acceptable power of 80%.
Recruitment period will be on average 4 years and all patients will be followed for an additional 3 years or until recurrence or progression, if occurs before this period.

7.2 Final Statistical Analyses

Patient characteristics, demographics and baseline measurements will be summarized in order to provide a characterization of the patient population. Descriptive statistics, e.g. mean, standard

deviation, median, range, frequency distributions as appropriate will be presented for each randomization group: Standard frequency versus reduced frequency BCG arms.

The initial safety analysis will be performed when all patients have finished the treatment phase (after 3 years which is 1 year after the last patient was randomized). The incidence and severity of all adverse events will be tabulated per treatment group. Treatment related toxicity > grade 2 will be compared between arms.
The description of the safety data will be performed, first globally then for each of the study arms.

The efficacy analysis will be performed when the last included patient has a follow up of 3 years.
The intention to treat efficacy analysis will be performed including all patients who are randomized.
Another per protocol efficacy analysis will be performed with all patients randomized and treated with at least one BCG instillation and who have a regulary end of the study. This could be a recurrence during the study as well as the completed instillation schedule and follow up in case the patient does not develop a recurrence.
Efficacy variables to be analyzed per treatment group are:

- time to first recurrence
- number and grade of recurrent tumors
- rate of progression to a higher stage (T2 or higher) of the disease.

Time to first recurrence is the time between the first transurethral resection of the tumor till the time of first recurrence. Time to first recurrence will be estimated by means of the Kaplan Meier method and comparison between treatment groups will be done by means of the log-rank test.
A Cox proportional hazards model will be applied to correct for treatment effects and to assess the influence of prognostic and confounding factors.
Observed sample percentages will be compared between treatment groups by means of a Chi square test.
The analyses of other outcome measurements will be analyzed in an exploratory way with methods appropriate for the type of the variable. Both the safety data and the efficacy data will be summarized by appropriate descriptive statistics.
For each patient entering the reason for discontinuation (e.g. patient decision, urologists decision, lack of efficacy, adverse events) should be clarified. The description of the reason for discontinuation will be performed.
The results of questionnaires will be analysed per treatment group and compared between groups of patients with similar reasons for discontinuation.

All tests of efficacy hypotheses based on between-treatment comparisons will be performed at the 2.5% level of significance and will be one-sided. Statistical tests based on within-treatment comparisons will be performed at the 5% level of significance and will be two-sided. No adjustments will be made to nominal significance levels to account for multiple comparisons made on the same data.

For the primary endpoint analyses time to first recurrence, missing follow up data will be censored at the last known follow up date. This is common practice but does rely on the assumption that censoring is independent from the probability of an event. For this reason we will ask patients for reasons for dropping out of the trial when this is possible.

For missing questionnaire data, the following procedures are planned for missing values. We will first inspect and evaluate the reasons for the missing values. In the (possibly unlikely) event that the missing data can be labeled as missing at random, we will suffice with ordinary multiple imputation for the analyses. When no valid reasoning for missing at random can be made, we will use the delta adjustment procedure of Van Buuren for scenarios that are congruent to the reasons for the missing data (14). For the sake of completeness we will also perform complete case analyses and use Last Observation Carried Forward for questionnaires that are administered more than once.

7.3 Interim Analysis

An interim analysis will be performed on the primary end-point at the time that 50% of the patients are recruited and observed for at least 6 months since their randomisation in the study.

The reason for performing the interim analysis is based on ethical safety considerations. In the presence of evidence of inferiority of the reduced frequency arm, the study will be stopped. In case this result will not be reached, the study will continue as planned.

The interim analysis will be performed using a significance level of 2,5 % (one sided). Inferiority is defined as a true hazard ratio for first recurrence ($hazard_{experimental}/hazard_{standard}$) lower than 0.75. If there are doubts on the efficacy of the reduced frequency arm, further in depth analyses will be performed to investigate a possible imbalance in prognostic factors. The IDMC will advise to stop the study when the upper limit of the 95% CI is less than 0.75. No changes in the sample size are required because of the interim analysis.

The interim analysis on the hazard ratio for first recurrence will also be performed between the different BCG strains used. Statistical tests between BCG strains will be performed at the 5% level of significance and will be two-sided.

Results of the interim analysis will be evaluated by an Independent Data Monitoring Committee (IDMC). After evaluation of the data, the IDMC will communicate an advice to the Steering Committee members to continue or stop the trial. In order to maintain data integrity, the Steering Committee will be blinded to the analysis results and will remain blinded if the IDMC will suggest to continue the study.

As of Protocol Amendment 7, an interim Analyses will not be performed (see section 2.2).

8. ETHICAL CONSIDERATIONS

8.1 Regulation Statement

This study will be conducted according to the principles of the Declaration of Helsinki (version 19th October 2013, see for the most recent version: www.wma.net) and in accordance with the European and local regulations and applicable guidelines.

8.2 Recruitment / Consent and Ethical Review Procedure

Eligible patients will be fully informed by the local investigator and/or the local research coordinator and his research staff, whatever is applicable, about the study and asked to participate. The patient will receive a patient information sheet (Appendix 8) and will have ample opportunity to ask any question he/she might have. He/she will have sufficient time to consider the study's implications before deciding to participate in the study. Patient's consent will be noted on an informed consent form (Appendix 8).

If during the study the patient for whatever reason no longer wishes to participate he/she can withdraw his/her consent at any time, without any further consequences regarding his/her treatment.

Prior to the start of the study, in some countries, the protocol has to be approved by one recognized medical ethics review committee for all participating institutions (the accredited review committee). The EC shall form a conclusion on the scientific and medical-ethical aspects of the protocol. If the EC requires further information to form its decision or believes the protocol needs to be adjusted, it shall inform the Sponsor immediately. On the basis of the additional information or the adjusted protocol, the EC shall reach its conclusion about whether or not the protocol is acceptable in terms of the research's scientific and medical-ethical aspects. Approval will be indicated in writing with reference to the final protocol number, version and date. The use of medication as described in this protocol must not under any circumstances deviate from the agreed protocol. In exceptional circumstances, for example when the health of the patient is at risk, the investigator can use his clinical judgement and alterations may be made. The event must then be documented in detail to EAU RF and, if applicable, the EC's and the other investigators should be notified.

If in the opinion of the local investigator or the Sponsor the clinical observations in the study suggest it may be unwise to continue, they will be able to terminate the study locally or entirely, respectively. If it becomes apparent that patient enrolment is unsatisfactory or the quantity or quality of the data received is inaccurate or incomplete on a chronic basis, the Sponsor has the right to terminate the study and remove all study equipment from the investigational site. If the study is stopped early the EC should be informed about the reasons.

8.3 Benefit and Risks Assessment

The burden and risks associated with participation in the study is considered minimal and acceptable. The number of visits and treatments is equal to or less compared what patients with these criteria is offered when they are treated on a standard way which is BCG intravesical instillation therapy. Extra in this study are the symptoms and quality of life questionnaires that need to be completed. A potential risk for patients in the reduced frequency arm is that the treatment is less effective with respect to the prevention of recurrence compared to the standard frequency arm. A potential benefit is that side effects, both in quantity and quality, are expected to be less in the reduced frequency arm compared to the standard frequency arm. The risks related to the expected treatment outcome, quality and quantity of side effects of the study medication (Appendix 5) can be considered as acceptable. Surgical procedures, laboratory and radiological evaluations are not considered extra and are performed according to standard practice or at the investigators discretion for monitoring eventual recurrence or progression of disease. Possible benefit for the patient is that the patient is followed according to the latest standards and guidelines of treatment of NMIBC.

8.4 Compensation for Injury

If necessary, each participating site will arrange a liability insurance which is in accordance with the local legal requirements. The sponsor, EAU RF, will arrange a clinical trial insurance according to national and GCP requirements.

8.5 Incentives

There are no special incentives or financial compensations that patients will receive through participation in the study.

9. ADMINISTRATIVE ASPECTS AND PUBLICATION

9.1 Participating Local Investigator

The participating local investigator is authorised to randomise patients in this study as soon as EC approval has been obtained and, depending on local regulations, approval has been obtained from the managing board or the board of directors of the hospital. It is the responsibility of the investigator at the local site to verify adherence to the protocol, the protection of the rights of the patient, the completeness, accuracy and consistency of the data to be entered by eCRF and adherence to local regulations.

9.2 Sponsor

The Sponsor (EAU RF) is responsible for protocol writing and case report form design, patient registration and assigning patient sequential numbers, handling of SAE and SUSAR reports, performing consistency checks of the case report forms, issuing queries in case of inconsistencies, reviewing and confirming all objective tumor responses and the preparation of the manuscript for publication. Some of these responsibilities will be handled by third parties acting on behalf of the Sponsor.

9.3 Amendments

Amendments are changes made to the research protocol after a favourable opinion by the EC has been given. All amendments will be notified to the Managing Board of the participating centre that gave a favourable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the EC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:
the safety or physical or mental integrity of the patients of the trial; the scientific value of the trial; the conduct or management of the trial; or the quality or safety of any intervention used in the trial.
All substantial amendments will be notified to the EC that gave a favourable opinion.

Non-substantial amendments will not be notified to the EC, but will be recorded and filed by the sponsor. Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation.

Considering the long duration of this trial it is foreseen that participating sites may discontinue their participation, new sites will be added or that the coordinating investigator of individual sites changes. Any of these changes will not result in a substantial amendment if the reasons for these changes are of a logistic nature only and do not jeopardise the overall conduct of this study.

9.4 Annual Development Safety Update Report

The Sponsor will submit a summary of the progress of the trial and safety to the EC and the regulatory authorities once a year. Information will be provided on the date of inclusion of the first patient, numbers of patients included, medication exposure and numbers of patients that have completed the trial, serious adverse events / suspected unexpected serious adverse reactions, other problems, changes in safety information of BCG strains and amendments.

9.5 End of Study Report and Archiving

The Sponsor / investigator will notify the EC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor/investigator will notify the EC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the EC.

The investigator is obliged to archive the Investigator Site File according to the applicable law.

9.7 Public Disclosure and Publication Policy

Any formal presentation or publication of data collected from this trial will be considered as a joint publication by the investigator(s). The Lead investigators and the protocol writing committee members will be authors on presentations/publications. Every participating site should designate one member to be author on presentations/publications. Further authorship will be determined by the Sponsor according to the number of eligible patients enrolled and the quality of the patients' follow up at each participating site.

For multi-center studies, it is mandatory that the first publication is based on data from all centers, analysed as stipulated in the protocol by epidemiologists/statisticians in conjunction with the Sponsor, and not by the investigators themselves. Investigators participating in this multi-center study agree not to present data gathered from one center or a small group of centers before the full, initial publication, unless formally agreed to by the Sponsor.

The Sponsor must receive copies of any intended communication in advance of publication (at least 15 working days for an abstract or oral presentation and 45 working days for a journal submission). The Sponsor will review the communications for accuracy, verify that confidential information is not being inadvertently divulged and to provide any relevant supplementary information.

10. REFERENCES

1. Morales, A., Eidinger, D. and Bruce, A. W.: Intracavitary bacillus Calmette-Guerin in the treatment of superficial bladder tumors. J Urol, 116: 180, 1976.
2. Lamm, D. L., Blumenstein, B. A., Crissman, J. D., Montie, J. E., Gottesman, J. E., Lowe, B. A. et al: Maintenance bacillus Calmette-Guerin immunotherapy for recurrent TA, T1 and carcinoma in situ transitional cell carcinoma of the bladder: a randomized Southwest Oncology Group study. J Urol, 163: 1124, 2000.
3. Sylvester RJ, van der Meijden APM, Lamm DL. Intravesical bacillus Calmette-Gue´rin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol, 168:1964–70, 2002.
4. Bohle A, Jocham D, Bock PR. Intravesical bacillus Calmette-Guérin versus mitomycin C for superficial bladder cancer: a formal metaanalysis of comparative studies on recurrence and toxicity. J Urol,169:90–5, 2003.
5. Martinez-Pineiro JA, Flores N, Isorna S, Solsona E, Sebastian JL, Pertusa C, et al. Long-term follow-up of a randomized prospective trial comparing a standard 81 mg dose of intravesical bacille Calmette-Guérin with a reduced dose of 27 mg in superficial bladder cancer. BJU Int, 89:671–80, 2002.
6. Böhle A, Brandau S. Immune mechanisms in bacillus Calmette-Guerin immunotherapy for superficial bladder cancer J Urol, 170:964–9, 2003.
7. de Boer EC, Rooyakkers, S. J. Schamhart, D. H.et al. BCG dose reduction by decreasing the instillation frequency: effects on local Th1/Th2 cytokine responses in a mouse model. Eur Urol, 48:333-338, 2005.
8. DeBoer, E. C., De Jong, W. H., Steerenberg, P. A. et al: Induction of urinary interleukin-1 (IL-1), IL-2, IL-6, and tumour necrosis factor during intravesical immunotherapy with bacillus Calmette-Guerin in superficial bladder cancer. Cancer Immunol Immunother, 34: 306, 1992.
9. Reichert, D. F. and Lamm, D. L.: Long term protection in bladder cancer following intralesional immunotherapy. J Urol, 132:570, 1984.
10. de Reijke T M, de Boer E., Kurth KH et al. Urinary interleukin-2 monitoring during prolonged bacillus Calmette-Guerin treatment: can it predict the optimal number of instillations? J Urol, 161: 67-71, 1999.
11. Riemensberger J, Bohle A, Brandau S. IFN-gamma and IL-12 but not IL-10 are required for local tumour surveillance in a syngeneic model of orthotopic bladder cancer. Clin Exp Immunol, 127:20–6, 2002.

12. Epstein JI, Amin MB, Reuter VR, Mostofi FK. The World Health Organization/International Society of Urological Pathology consensus classification of urothelial (transitional cell) neoplasms of the urinary bladder. Am J Surg Pathol, 22:1435-1448, 1998.
13. Janet D. Elashoff (2007) nQuery Advisor Version 7.0 User's Guide.
14. van Buuren S, Boshuizen HC, Knook DL. Multiple imputation of missing blood pressure covariates in survival analysis. Stat Med. 1999 Mar 30;18(6):681-94.
15. Pocock SJ: Clinical Trials: a practical approach. John Wiley & Sons Ltd. ISBN 0 471 90155 5, © 1983, reprint 1993.
16. Abrams P, Avery K, Gardener N, Donovan J. The International Consultation on Incontinence Modular Questionnaire: www.iciq.net. J Urol. 2006;175:1063-1066; discussion 1066.
17. Donovan JL, Abrams P, Peters TJ, et al. The ICS-'BPH' Study: the psychometric validity and reliability of the ICSmale questionnaire. Br J Urol. 1996;77:554-562.
18. Groenwold M, Klee MC, Sprangers MA, Aaronson NK: Validation of the EORTC QLQ-C30 quality of life questionnaire through combined qualitative and quantitative assessment of patient-observer agreement. J Clin Epidemiol 50 (4): 441-450, 1997.
19. Rischmann P, Desgrandchamps F, Malavaud B, Chopin DK. BCG intravesical instillations: recommendations for side-effects management. Eur Urol 2000; 37 (Suppl 1):33–6.
20. Witjes JA, Palou J, Soloway M, Lamm D, Brausi M, Spermon JR, Persad R, Buckley R, Akaza H, Colombel M, Böhle A: Clinical Practice Recommendations for the Prevention and Management of Intravesical Therapy Associated Adverse Events European Urology Supplements October 2008 (Vol. 7, Issue 10, Pages 667-674).
21. Oken MM, Creech RH, Tormey DC, et al (1982). "Toxicity and response criteria of the Eastern Cooperative Oncology Group". Am. J. Clin. Oncol. 5 (6): 649–55.
22. Little JP. Consistency of ASA grading. Anaesthesia 1995; 59: 658-659.
23. Au JL, Badalament RA, Wientjes MG, et al: International Mitomycin C Consortium. Methods to improve efficacy of intravesical mitomycin C: results of a randomized phase II trial. J Natl Cancer Inst 2001; 93(8): 597-604.
24. Babjuk M, Oosterlinck W, Sylvester R et al.: EAU Guidelines on Non-Muscle-Invasive Urothelial Carcinoma of the Bladder – 2011 Update. Eur Urol 2011; 59: 997-1008.

Appendix 1 ICIQ LUTS female and male questionnaires

Initial number **CONFIDENTIAL** DAY MONTH YEAR **Today's date**

ICIQ-FLUTS 08/04

Female LUTS Questionnaire (Ref. 16,17)

Urinary symptoms

Many people experience urinary symptoms some of the time. We are trying to find out how many people experience urinary symptoms, and how much they bother them. We would be graeful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1. Please write in your date of birth:

DAY MONTH YEAR

2a. During the night, how many times do you have to get up to urinate, on average?

none	0
one	1
two	2
three	3
four or more	4

2b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all a great deal

3a. Do you have a sudden need to rush to the toilet to urinate?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

3b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all a great deal

4a. Do you have pain in your bladder?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

4b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all — a great deal

5a. How often do you pass urine during the day?

1 to 6 times	0
7 to 8 times	1
9 to 10 times	2
11 to 12 times	3
13 or more times	4

5b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all — a great deal

F score: sum scores 2a-5a ☐☐

6a. Is there a delay before you can start to urinate?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

6b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all — a great deal

7a. Do you have to strain to urinate?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

7b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all a great deal

8a. Do you stop and start more than once while you urinate?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

8b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all a great deal

V score: sum scores 6a+7a+8a ☐☐

9a. Does urine leak before you can get to the toilet?

never	0
occasionally	1
sometimes	2
most of the time	3
all of the time	4

9b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all a great deal

10a. How often do you leak urine?

never	☐	0
once or less per week	☐	1
two to three times per week	☐	2
once per day	☐	3
several times per day	☐	4

10b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all — a great deal

11a. Does urine leak when you are physically active, exert yourself, cough or sneeze?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

11b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all — a great deal

12a. Do you ever leak urine for no obvious reason and without feeling that you want to go?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

12b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all — a great deal

13a. Do you leak urine when you are asleep?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

13b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all — a great deal

I score: sum scores 9a-13a ☐☐

© BFLUTS-SF

Thank you very much for answering these questions.

Copyright © "ICIQ Group" : the ICIQ-FLUTS is based on the BFLUTS SF

Initial number

CONFIDENTIAL

DAY MONTH YEAR
Today's date

ICIQ-MLUTS 01/06

Male LUTS Questionnaire (Ref. 16,17)

Urinary symptoms

Many people experience urinary symptoms some of the time. We are trying to find out how many people experience urinary symptoms, and how much they bother them. We would be grateful if you could answer the following questions, thinking about how you have been, on average, over the PAST FOUR WEEKS.

1. Please write in your date of birth:

DAY MONTH YEAR

2a. Is there a delay before you can start to urinate?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

2b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

3a. Do you have to strain to <u>continue</u> urinating?

never ☐ 0
occasionally ☐ 1
sometimes ☐ 2
most of the time ☐ 3
all of the time ☐ 4

3b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

4a. Would you say that the strength of your urinary stream is…

normal	☐	0
occasionally reduced	☐	1
sometimes reduced	☐	2
reduced most of the time	☐	3
reduced all of the time	☐	4

4b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

5a. Do you stop and start more than once while you urinate?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

5b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

6a. How often do you feel that your bladder has not emptied properly after you have urinated?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

6b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

VS: sum scores 2-6 ☐☐

7a. Do you have a sudden need to rush to the toilet to urinate?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

7b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all a great deal

8a. Does urine leak before you can get to the toilet?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

8b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all a great deal

9a. Does urine leak when you cough or sneeze?

never	☐	0
occasionally	☐	1
sometimes	☐	2
most of the time	☐	3
all of the time	☐	4

9b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all a great deal

10a. Do you ever leak for no obvious reason and without feeling that you want to go?

never ☐	0
occasionally ☐	1
sometimes ☐	2
most of the time ☐	3
all of the time ☐	4

10b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

11a. Do you leak urine when you are asleep?

never ☐	0
occasionally ☐	1
sometimes ☐	2
most of the time ☐	3
all of the time ☐	4

11b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

12a. How often have you had a slight wetting of your pants a few minutes after you had finished urinating and had dressed yourself?

never ☐	0
occasionally ☐	1
sometimes ☐	2
most of the time ☐	3
all of the time ☐	4

12b. How much does this bother you?
Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**
not at all — a great deal

IS: sum scores 7-12 ☐☐

13a. How often do you pass urine during the day?

1 to 6 times	0
7 to 8 times	1
9 to 10 times	2
11 to 12 times	3
13 or more times	4

13b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all a great deal

14a. During the night, how many times do you have to get up to urinate, on average?

none	0
one	1
two	2
three	3
four or more	4

14b. How much does this bother you?

Please ring a number between 0 (not at all) and 10 (a great deal)

0 1 2 3 4 5 6 7 8 9 **10**

not at all a great deal

© ICS*male*SF

Thank you very much for answering these questions.

Copyright © "ICIQ Group" : the ICIQ-MLUTS is based on the ICSmaleSF

Appendix 2 QLQ-C30

THE QLQ-C30 VERSION 3.0 (Ref. 18)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are not « right » or « wrong » answers. The information that you provide will remain strictly confidential.

Please fill in your initials :
Your birthday (Day, Month, Year) :
Today's date (Day, Month, Year) :

		Not at all	A little	Quite a Bit	Very much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase ?	1	2	3	4
2.	Do you have any trouble taking a long walk ?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house ?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day ?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet ?	1	2	3	4

During the past week :		Not at all	A little	Quite a Bit	Very much
6.	Were you limited in doing either your work or other daily activities ?	1	2	3	4
7.	Were are you limited in pursuing your hobbies or other leisure time activities ?	1	2	3	4
8.	Were you short of breath ?	1	2	3	4
9.	Have you had pain ?	1	2	3	4
10.	Did you need to rest ?	1	2	3	4
11.	Have you had trouble sleeping ?	1	2	3	4
12.	Have you felt weak ?	1	2	3	4
13.	Have you lacked appetite ?	1	2	3	4
14.	Have you felt nauseated ?	1	2	3	4
15.	Have you vomited ?	1	2	3	4

During the past week :		Not at all	A little	Quite a Bit	Very much
16.	Have you been constipated ?	1	2	3	4
17.	Have you had diarrhea ?	1	2	3	4
18.	Were you tired ?	1	2	3	4
19.	Did pain interfere with your daily activities ?	1	2	3	4
20.	Have you had difficulty in concentrating on things, like reading a newspaper or watching television ?	1	2	3	4
21.	Did you feel tense ?	1	2	3	4
22.	Did you worry ?	1	2	3	4
23.	Did you feel irritable ?	1	2	3	4
24.	Did you feel depressed ?	1	2	3	4
25.	Have you had difficulty remembering things ?	1	2	3	4
26.	Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27.	Has your physical condition or medical treatment interfered with your social activities ?	1	2	3	4
28.	Has your physical condition or medical treatment caused you financial difficulties ?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week ?

1 2 3 4 5 6 7

Very poort Excellent

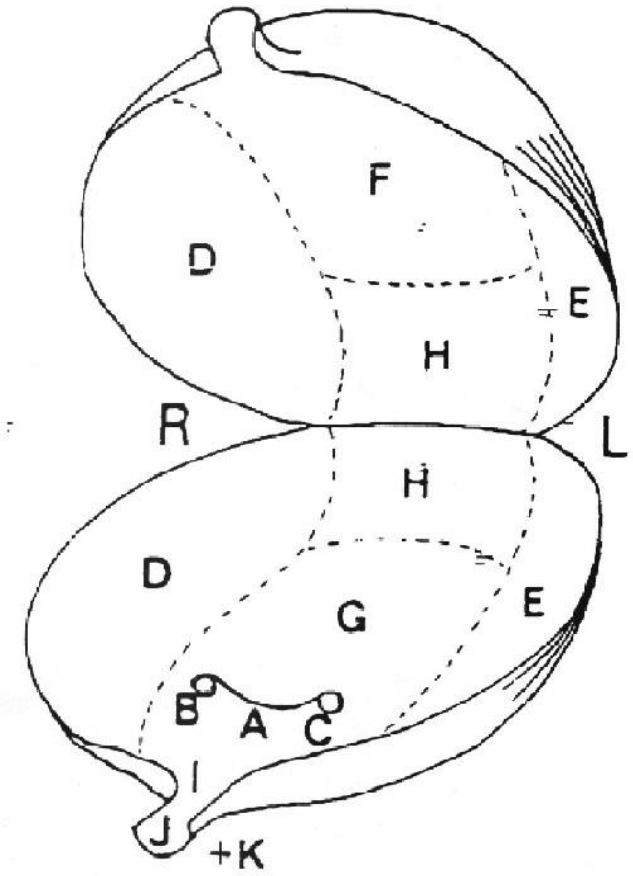
30. How would you rate your overall quality of life during the past week ?

1 2 3 4 5 6 7

Very poort Excellent

Appendix 3 Bladder Map

Bladder Map



A: Trigone:
B: Right ureteral orifice
C: Left ureteral orifice
D: Right wall
E: Left wall
F: Anterior wall
G: Posterior wall
H: Dome=fundus
I: Neck
J: Prostatic urethra
K: Prostatic substance

Appendix 4 Common Terminology Criteria for Adverse Events v 3.0 (CTCAE)

The Common Terminology Criteria for Adverse Events can be used via the internet:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf

This is a handy search engine in which the adverse event can be searched and graded easily.

On request, EAU RF will provide the participating sites with the CTCAE 72 pages pdf file or a paper version, if needed.

Appendix 5 Product Information BCG Strains

Product Information obtained via website:

BCG Tice:

https://www.medicines.org.uk/emc/product/1049/smpc

BCG Connaught:

http://www.vaccineshoppecanada.com/secure/pdfs/ca/immucyst_e.pdf

BCG Medac (other name: BCG RIVM):

https://www.geneesmiddeleninformatiebank.nl/smpc/h26876_smpc.pdf
http://www.pharmazie.com/graphic/A/20/1-24620.pdf
https://www.hpra.ie/HOMEPAGE/medicines/medicines-information/find-a-medicine/results/item?change=5741581&pano=PA0623/004/001&t=BCG-MEDAC

Information on other BCG substrains

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5777639/
http://www.bcg.gr.jp/english/menu1.html

Appendix 6 Definition and Management of Side Effects of BCG Treament

Grading of Toxicity:

World Health Organization grading of toxic drug effects, will be used as a guide for determining when intravesical therapy may be contraindicated (Ref. 19):

Grade 1: Moderate and <48 h (usually requires no modification of intravesical therapy)
Grade 2: Severe and/or >48 h (usually requires suspension of instillations until resolution of symptoms)
Grade 3: Local, regional, systemic, and immunoallergic (resumption of instillations must be evaluated in the light of the benefit-risk ratio with dose reduction)
Grade 4: Systemic BCG reactions (cessation of BCG therapy is required).

Table: International Bladder Cancer Group recommendations for the management of intravesical therapy–related local and systemic adverse events (© with permission of the authors (Ref. 20))

Side effect	Grade	Management options
Local side effects common to intravesical chemotherapy and BCG		
Non-bacterial or chemical cystitis	1	Oxybutynin, phenazopyridine, propantheline bromide, or anti-inflammatory agents (NSAIDs)
	2	Oxybutynin, phenazopyridine, propantheline bromide, or NSAIDs Consider postponement of intravesical therapy and subsequent dose reductions if cystitis persists beyond 48 h For prolonged BCG cystitis, consider use of a quinolone antibiotic
Gross hematuria	1–2	Perform urine culture to exclude hemorrhagic cystitis Suspend instillations until urine clears Catheterisation and bladder irrigation for clots may be required
Contracted bladder	≥2	Suspend instillations until resolution of symptoms Hydrodistention Cystectomy may be required in some instances
Ureteral obstruction	≥2	Usually temporary and self-limited Exclude presence of CIS or muscle-invasive (T2) bladder cancer Percutaneous drainage or stenting of the kidney may be required
Local side effects associated with BCG		
Symptomatic granulomatous prostatitis	>2	High-dose fluoroquinolones Isoniazid and rifampicin for 3 mo, plus quinolones and steroids Suspension of intravesical therapy
Epididymo-orchitis	>2	High-dose fluoroquinolones Isoniazid and rifampicin for 3 mo Suspension of intravesical therapy Orchidectomy if severe and persistent
Local side effects associated with intravesical chemotherapy		
Contact dermatitis	≥2	Prevention • Careful cleansing of hands after drug handling • Cleansing of genitals and perineum after voiding Cessation of therapy Topical steroids for relief of symptoms
Systemic side effects associated with BCG		
General malaise, fever	1	Generally resolve within 48 h with or without antipyretics
Persistent high-grade fever (>38.5 °C for >48 h)	≥2	Permanent discontinuation of BCG instillations Immediate evaluation Prompt treatment with two or more antimicrobial agents (eg, fluoroquinolones, isoniazid, rifampicin) while diagnostic evaluation, including cultures, is conducted Consultation with an infectious diseases specialist
Systemic BCG reactions	4	Prevention • Initiate BCG at least 2 wk post TURBT (if no signs and symptoms of hematuria) Cessation of BCG For severe infection • High-dose fluoroquinolones • Isoniazid, rifampicin, and ethambutol daily for 6 mo • Early, high-dose corticosteroids as long as symptoms persist • Consider an empirical non-specific antibiotic to treat Gram-negative bacteria and/or *Enterococcus*
Allergic reactions	1–2	Antihistamines and NSAIDs Consider suspension of BCG instillations
	3–4	Discontinue BCG instillations Consider isoniazid and rifampicin plus corticosteroids for persistent symptoms

Appendix 7 Protocol Signature Sheet

Investigator Signature:

I have read and agree to the **'Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAU RF number 2008-01 Amended final version ~~6~~7, ~~January~~ November 7th, 2019.**

I am aware of my responsibilities as an Investigator under the guidelines of Good Clinical Practice (GCP), local regulations (as applicable) and the study protocol. I agree to conduct the study according to these guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

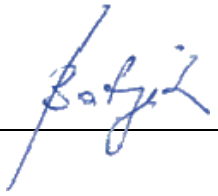
NAME:
TITLE: INVESTIGATOR: SIGNATURE: _____

DATE: _____

PLACE:

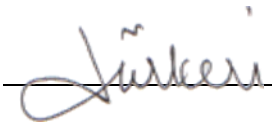
Full investigational site contact details, including telephone numbers, will be documented in the Trial Master File.

Principal Investigators:

NAME: Prof. Levent N. Türkeri SIGNATURE: 

DATE: 07-11-2019

PLACE: ISTANBUL

NAME: Prof. Marko M. Babjuk SIGNATURE: 

DATE: 07-11-2019

PLACE: PRAGUE

Appendix 8 Patient Information and Informed Consent Form

EAU RF nr 2008-01 Version 4, May 15th, 2017.

The European Association of Urology Research Foundation (EAU RF) is conducting a study on patients who have a disease similar to yours. The study will be conducted at the European level under the supervision of physicians recognized as experts in this area of expertise. In Germany, the study will be coordinated by Prof. Dr. M.-O. Grimm, Director of the department of urology, University Clinic, Jena. In the Netherlands, the study will be coordinated by Dr. T van der Heijden, Radboud UMC, Nijmegen. In France, the study will be coordinated by Prof. M. Colombel, Hôpital Edouard Herriot, Lyon, France. In Spain, the study will be coordinated by Prof. Luis Martínez-Piñeiro, El Hospital Universitario La Paz, Madrid. We would like to invite you to participate in this project after you have been given full information about this study.

In order to be able to take a knowledge-based decision whether or not you should participate in this study, you should be informed about its possible risks and benefits. This process is known as informed consent. This patient information form gives detailed information about the research study which your physician will discuss with you. Once you understand the study, you will be asked to sign the informed consent form if you wish to participate. When you have signed the form, you will receive a copy to keep as a record.

The research study being proposed to you is entitled:
"Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG.
A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAU RF number 2008-01 (AUO-Studie AB37/10)".

Introduction:
Your doctor has discovered that you have a high grade non-muscle invasive bladder tumor(s). This means that the tumor is not yet invading the urinary bladder muscle. The tumor is limited to the superficial part of the urinary bladder inside wall. The standard treatment consists of an operation through the urethra, the canal through which urine is discharged from the bladder (TUR-Bladder) where the tumor(s) are removed completely. A separate information folder supplied by employees of the department of urology will be used to inform you about the risks of this operation.
However, there is chance of over 50% that the disease may recur in the near future. It could also become more malignant. In order to avoid recurrence, an adjuvant treatment after the operation is necessary. This therapy consists of repeated bladder instillations through the urethra with a drug called Bacillus Calmette Guèrin (BCG). This drug was originally developed as a vaccine against lung tuberculosis. Independent from this indication, BCG has been found one of the best drugs to prevent recurrence of non-muscle invasive bladder cancer. Other known drugs that are used for instillation are chemotherapeutic drugs like Mitomycin, Doxorubicin and Epirubicin. However, these chemotherapeutic drugs are not used as standard of care to prevent recurrence of high grade non-muscle invasive bladder tumor(s). Unfortunately, it is unknown how many bladder instillations with BCG are necessary. Scientific evidence prones to the fact that the standard number of instillations can be reduced for a proper immune response resulting in similar clinical efficacy and potentially less side-effects and costs. In this study, we investigate the efficacy of BCG standard number versus BCG reduced number of bladder instillations. Moreover, we look carefully at the symptoms and side effects that may be caused by the drug or by the instillation procedure. A total of 824 patients will be asked to participate and the study duration will be in total 9 years. The incidence and severity of side effects may bother you and affect your quality of life during the treatment period. The symptoms and quality of life aspects have to be filled in by you in simple questionnaires. If this is difficult for you, ask us, we can help or advise you.

What do we expect from you ?
1. You will be examined clinically and undergo blood tests and urine examinations as usual. These tests do not differ from patients who do not participate in this study.
2. Specific care is taken that all tumors are completely resected. Four to eight weeks after the first surgical resection a control cystoscopy is performed where the site of the initial tumor will again be biopsied.

3. Randomization will decide which treatment will be given to you (standard number of instillations or the reduced number of instillations. The randomization is made by a computer after you have been registered onto the trial. Neither you nor your physician can anticipate which treatment you will receive. If you are randomized for the standard number of instillations, you will start with 6 weekly instillations with BCG (cycle 1) followed by 3 weekly instillations at months 3, 6 and 12 (cycles 2,3 and 4) after the operation – in total 15 instillations.
If you are randomized for the reduced frequency arm you will receive instillations at weeks 1, 2 and 6 (cycle 1) followed by instillations on week 1 and 3 at months 3, 6 and 12 (cycles 2,3 and 4) after the operation – in total 9 instillations.
Questionnaires are to be completed before the first and last instillation of each cycle which is in total 2 times in each of the four cycles – in total 8 times.
4. You will receive no payment for your participation. All medical examinations and analyses are standard and reimbursable by the health insurance as they are part of the normal routine.

After entering the study, you will be followed at fixed time periods: every three months the first 2 years and bi-annually until maximal the 6th year, when your physician will do a control cystoscopy. If your physician diagnoses a recurrence of your bladder tumor(s), the tumor will again be removed and further treatment will be decided at the discretion of you and your physician. Your study participation will end after a maximum of 5 years of follow up or earlier, when a recurrence is observed.
Your participation is entirely voluntary. You may decline from participating or withdraw your consent at any time. This will not affect your further treatment.

Are there risks, side-effects or discomforts when you decide to participate ?
The burden and risks associated with participation in the study is considered minimal and acceptable. The number of visits to the clinic and treatments is equal to or less compared with what patients with these criteria is offered when they are treated on a standard way which is BCG intravesical instillation therapy. Extra in this study are the lower urinary tract symptoms questionnaires (13 questions for females and 14 for males) and quality of life questions (30 questions) that need to be completed. This will take you an additional 15-20 minutes to complete.

A potential risk for patients in the reduced frequency arm is that the treatment is less effective with respect to the prevention of recurrence compared to the standard frequency arm. A potential benefit is that side effects, both in quantity and quality, are expected to be less in the reduced frequency arm compared to the standard frequency arm. The risks related to the expected treatment outcome and quality and quantity of side effects of the BCG treatment can be considered as low and acceptable.

Side effects that are common when using BCG instillations in the bladder are: fever, chills, malaise, flu-like symptoms, increased fatigue or an increase in urinary symptoms, (such as burning or pain on urination). You are advised to notify your physician if any of these symptoms last more than 48 hours or increase in severity. You should also notify your physician immediately if you experience any of the following less frequent occurring symptoms: joint pain, eye complaints (such as pain, irritation or redness), an increase in urinary symptoms (such as urgency, frequency of urination, blood in urine), cough, skin rash, jaundice, nausea or vomiting.

BCG contains live mycobacterium, that may be excreted with the urine. Therefore, you are advised to follow appropriate hygienic procedures to protect family and close contacts from infection. When you live with or in close quarters to persons who are immune-compromised (on chemotherapy, etc.), you should exercise special caution to avoid inadvertently transmitting BCG infection to such susceptible persons. After the instillation, BCG is retained in the bladder for as long as possible (up to 2 hours) and then voided. To avoid transmission of BCG to others, for 6 hours after treatment you should void while seated to avoid splashing of urine. Urine voided during this time should be disinfected with an equal volume of household bleach for 15 minutes before flushing or disposal. Unless medically contraindicated, you should increase fluid intake to "flush" the bladder for several hours following treatment with intravesical BCG. You may experience pain or burning with the first void after treatment. During the first week after BCG treatment a condom should be used during sexual intercourse.

The possible risks of BCG treatment to a pregnant woman and foetus are not known. Female patients capable of childbearing will be asked to take appropriate precautions to avoid pregnancy during the whole period of treatment administration (at least 30 days prior to the first treatment and up to three months after the last administration). Pregnant women may not participate at any time in the study, and, if applicable, pregnancy tests will be done to make sure that you are not pregnant at study entry and during the study.

<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
For selected centres which participate in the immunological substudy, the following should be added:

As part of the study you are invited to take part in optional research to better understand the immunological response to the BCG instillation. Therefore, we ask you to collect one urine sample prior to each installation and one urine sample between 4 and 8 hours after each instillation during the entire instillation process of the study. Collected samples will be transferred to the EAU RF or other laboratories working with the EAU RF where these urine samples are used to measure immunological important substances in the urine. The EAU RF will require anyone who works with your sample to hold the information and any results in confidence. These urine samples are extra and should not take place in case you should decide not to participate in this optional research. You will not have any individual benefit of the collection of urine samples.
<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

Additional laboratory and radiological evaluations are not foreseen in the study and are performed at the investigators discretion for monitoring eventual recurrence or progression of disease.

<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<
For selected centres which participate in the DNA substudy, the following should be added:

As part of the study you are invited to take part in optional research to better understand why some patients react favourably to BCG instillations and others experience a recurrence. Therefore, we ask you 10 ml of your blood in order to be able to investigate your DNA specifics. Collected samples will be transferred to the EAU RF or other laboratories working with the EAU RF where these blood samples are used to measure DNA specifics. The EAU RF will require anyone who works with your sample to hold the information and any results in confidence. This blood sample is extra and should not take place in case you should decide not to participate in this optional research. You will not have any individual benefit of the collection of your of your blood sample.
<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

Possible benefit for the patient is that the patient is treated according to the latest standards and guidelines of the treatment of non-muscle invasive bladder tumor(s).

For all patients participating in this study an insurance policy covers any damage that may occur during the course of this study.
Name of the insurer:
Policy number:
Contact person:
Telephone number contact person:

Together with this information sheet, you will receive a copy of the insurance details for your attention and consideration. See the attachment.

Privacy statement
For this study, the data related to your disease and your date of birth will be, dependent on the reason for collection, processed anonymously and only for the purpose of the study. This means that your full name and date of birth are only recognizable in the informed consent form that will be archived only in the hospital where you are treated for possible required verification of your willingness to participate in the study. For every patient that participates in the study the central research office will attribute a patient number that will consequently be used to identify the patient for processing the study data. This patient number cannot lead to the identification of the participant outside the hospital where you are treated. Anonymity of participants is strictly observed. When the study results are published, the anonymity of participants will be maintained.

If you do not have any further questions and you want to participate in this study, you are kindly invited to sign the informed consent form that is attached. You will receive a copy of this patient information as well as a copy of the informed consent for your records.

Thank you for your attention and your willingness to participate.

The study leader:

*Prof. Dr. med. M.-O. Grimm**
Chair dept. of Urology
University Hospital Jena

_____	_____
Place, Date	Signature Participant
_____	_____
Place, Date	Signature Physician
_____	_____
Place, Date (only applicable if the participant cannot read)	Signature Witness

** Italic part is hospital specific and has to be adapted for each of the participating centres.*

Patient Consent Form Standard Version 3 date July 9th, 2015: **Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations Versus Reduced Number of Intravesical Instillations with Standard Dose of BCG. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial EAU RF number 2008-01.**

- I have read and understand the patient information form related to this research study and my physician has answered all my questions regarding the study.
- I had sufficient time to consider my participation in this research study and I am aware that participation is completely voluntary.
- I realize that I may decide to withdraw my participation at any time without affecting the quality of my health care.
- I understand and agree that personal data will be collected from my medical records in a anonymised manner, used and processed by the EAU RF or any other designated third party that is involved in the study (e.g. hospital, physician, regulatory bodies and medical ethics committees).
-
- I authorize and instruct my physician(s) and institution to release the necessary personal - anonymised - data to the EAU RF and any other designated third party involved in the study.
- The EAU RF and all other designated third parties involved in the study shall maintain the confidentiality of all data provided compliant with all applicable data protection and privacy laws and shall not use my name or other identifying characteristics in publications.
- I have received a copy of the Patient Information and Consent Form and I hereby agree to participate in this study.

- I hereby consent to my personal and confidential data being:

1. processed by the EAU RF for the purposes as described above;
2. disclosed by the EAU RF to third parties as indicated in point 4 of this page for the purposes asdescribed above.

<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

For selected centres which participate in the immunological substudy, the following should be added:

- I have been given time and opportunity to consider taking part in optional immunological research.

By ticking the appropriate bullet in the next question, I freely give my consent to take part in this optional immunological research, as follows, and understand that if I select 'No' to such testing, it will not affect my participation in the clinical study.

- I agree that my urine samples will be used by the EAU RF or laboratories working with the EAU RF for "optional immunological research".

☐Yes ☐ No *Tick as appropriate*

<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

For selected centres which participate in the DNA substudy, the following should be added:

- I have been given time and opportunity to consider taking part in optional DNA research.

By ticking the appropriate bullet in the next question, I freely give my consent to take part in this optional DNA research, as follows, and understand that if I select 'No' to such testing, it will not affect my participation in the clinical study.

- I agree that my blood samples will be used by the EAU RF or laboratories working with the EAU RF for "optional immunological research".

☐Yes ☐ No *Tick as appropriate*

<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<<

type/print name

____________________	____________________	__________
(Patient)	Signature	Date

I hereby declare that I have fully informed the patient about this research study and explained to him its nature, aim, procedures and duration in full detail. I also declare that I have provided the patient with the information sheet and a dated and signed copy of the informed consent form.

type/print name

____________________	____________________	__________
(Physician) (has to sign always)	Signature	Date

type/print name

____________________	____________________	__________
(Name of presenter, if applicable) (who presented/explained the document)	Signature	Date

Appendix 9 WHO Performance Score & ASA Performance Scale

WHO Performance Score

The WHO score (published by Oken *et al* in 1982 (Ref. 21), also called the ECOG or Zubrod score (after C. Gordon Zubrod), runs from 0 to 5, with 0 denoting perfect health and 5 death:

0. Asymptomatic
1. Symptomatic but completely ambulatory
2. Symptomatic, <50% in bed during the day
3. Symptomatic, >50% in bed, but not bedbound
4. Bedbound
5. Death

ASA Performance Scale

ASA stands for American Society of Anesthesiologists. In 1963 the ASA adopted a five category physical status classification system for assessing a patient before surgery. A sixth category was later added (Ref. 22). These are:

1. A normal healthy patient.
2. A patient with mild systemic disease.
3. A patient with severe systemic disease.
4. A patient with severe systemic disease that is a constant threat to life.
5. A moribund patient who is not expected to survive without the operation.
6. A declared brain-dead patient whose organs are being removed for donor purposes.

Appendix 10 Substudy: "Prospective evaluation of the influence of fluid restrictions before BCG instillation and technique of BCG instillation on side-effects and efficacy of treatment"

The intravesical instillation of BCG is effective treatment of selected patients with NMIBC. The technique of instillation and measures used before and during instillation are not standardized. The role of optimization of instillation was shown after intravesical chemotherapy but has never been confirmed after BCG instillation (23,24).
There are measures that are recommended by some experts, like fluid restriction before instillation and patient rotation during instillation. Their impact on treatment efficacy and side-effects is not known.
The objective of the sub-study is to evaluate if optimization of BCG instillation can help to influence side effects and efficacy of BCG instillations. For this sub study a limited number of centres with interest to participate will be asked to participate. Patients with fluid restriction will be compared with patients without fluid restriction and patients with rotation during the instillation procedure will be compared with patients without rotation with respect to side effects and efficacy. Appropriate statistics will be used.

Design of the Sub-study:

Part A: Prospective, parallel evaluation of influence of fluid restriction.

Before the BCG instillation patients will be instructed according to standard practice:

1. Patients with fluid restriction: To drink only small cup of water (no tea or coffee) during breakfast (at least 4 hours before the scheduled instillation). Until the instillation and during instillation patient will not drink or eat food with large amounts of water (fruit, vegetables etc.)
2. Patients without fluid restriction: Patient will have usual fluid intake until one hour before instillation. Patient will not drink immediately before instillation and during the instillation.

The following parameters will be evaluated and compared before, during and after the instillation procedure:

- Whether the patient received fluid restriction: Yes or No.
- The urine volume drained from the bladder immediately pre-instillation.
- Whether patient achieved full length of retention of BCG (2 hours). The full length of retention will be registered in all patients, also in those patients who did not reach the full length of retention.
- The amount of urine in the bladder after two hours of instillation (either by opening the catheter and measuring the amount of urine in catheterized patients or voiding in patients in whom the catheter has been removed or by ultrasound in patients without catheter during instillation).

Part B: Prospective, controlled evaluation of influence of patient rotation during instillation.

Before the BCG instillation patients will be instructed according to standard practice:

1. Patients with rotation: The position of the patient during instillation will be changed each 30 minutes – supine position, left side, right side, prone position, vertical position.
2. The position of the patient during instillation will be random, it will not be actively influenced.

The following will be evaluated and compared after the instillation procedure:

Whether the patient was rotated: Yes or No.

Appendix 11 Substudy: "Prospective evaluation of cytokines following BCG instillations"

Urinary Cytokine Levels in Patients Treated with Reduced Number of BCG Intravesical Instillations Compared to Standard BCG Treatment

INTRODUCTION

Intravesical BCG therapy is considered the most effective form of treatment in patients with high-risk non-muscle invasive urothelial carcinoma of the bladder (NMIBC). Despite the fact that efficacy in not universal and side effects are quite common the empirical schedule which was proposed initially remained unchanged with limited modifications of the dose over the last four decades. Optimum dose and schedule for BCG therapy has not been established yet, largely due to the absence of a complete understanding of the exact mechanism of action of BCG in management of urothelial carcinoma of the bladder. One of the main questions remain unanswered after all of these years is the number and timing of instillations to achieve an optimal response with minimal side effects. After intravesical BCG instillation, the live BCG organisms bind to the urothelium via fibronectin and initiate an immune response and most likely, activation of a so-called Th1 immune response is required for clinical efficacy (1,2). The Th1 response results in the production of cytokines as interferon (IFN)-γ, interleukin (IL)-2 and IL-12 which favour the development of cellular immune responses (delayed-type hypersensitivity, cytolysis and macrophage activation which may then generate tumor-specific immunity and bladder tumor–killing cells comparable to lymphokine activated killer cells (3,4,5).
Development of the cytokine response would depend on the time interval during sensitization and challenge. IL-2 production can be down-regulated by repeated instillations with a short interval, presumably as a result of expression of regulatory cytokines (6). IL-2 was detected after the first instillation of BCG in patients with non-muscle invasive bladder cancer, however levels fell after the second and third instillations in both responders and nonresponders (7). Comparison of urinary IL-2 induction patterns during a repeat course with the intial BCG induction revealed that levels tended to be higher during the first and lower during the last weeks. These observations suggested an accelerated induction of urinary IL-2 during a subsequent instillation course of BCG (6).
However, there is also evidence in the literature that repeated instillations may down-regulate the response after a certain number. In a cohort of 19 patients treated with BCG urinary IFN-γ levels significantly increased by the second and peaked at the third instillation, followed by a decrease after the fourth instillation supporting the hypothesis of cytokine down-regulation due to repeated BCG stimulation (8).
Similar levels of IFN-γ, IL-2 and IL-12 (Th1) mRNA induction after a schedule of only two BCG instillations administered in week 1 and 6 (1 + 6 schedule), compared to 6 weekly instillations were demonstrated in an animal study (3). Significantly lower levels of the Th2 cytokines of IL-10 and IL-4 mRNA by 1+6 schedule were observed in this study. Since reduced number of instillations could provide equivalent Th1 cytokine expression to standard regimen and BCG-induced Th1/Th2 cytokine ratio was demonstrated to be associated with effective anti-tumor activity (9), a novel reduced number of instillations strategy may provide an alternative way of BCG dose reduction.
Unfortunately, clinical studies investigating the cytokine response to various BCG instillation frequencies (6 weekly instillations versus more spaced and less frequent instillations as proposed in phase III EAU-CRF NMIBC study) are lacking.
Thus, the proposed investigation is based on the hypothesis that after an initial BCG instillation which provides sensitization, number of subsequent instillations can be reduced for a proper anamnestic immune response and prevention of down-regulation of Th1 response by regulatory pathways is possible. This will then be reflected in similar Th1 and more favourable Th2 cytokine response at the end of the 6 week schedule as well as at the end of the 3rd week of maintanence of standard BCG treatment.
METHODS

One spot urine sample will be collected from each patient prior to each installation and one spot urine sample between 4 and 8 hr after each instillation both during the induction and maintenance period.
Samples will be immediately centrifuged for 10 min at 800 rpm to remove cells and debris. The urine samples will then be frozen at -20^{o}C. Levels of cytokines and IFN-γ will be determined in urine with commercially available, highly specific and reproducible enzyme-linked immunosorbent assays. Cytokine concentrations will be standardized to urine creatinine.
The levels of each investigated cytokine after individual instillations will be correlated with recurrence and progression rates as well as with side effects with in the standard and experimental arms.
This substudy will be performed in selected centres in consecutive patients who will be asked to participate in this optional research up to 40 patients. Since this is an exploratory study, no formal sample size calculations were performed.

REFERENCES

1. Kavoussi LR, Brown EJ, Ritchey JK, and Ratliff TL. Fibronectin-mediated Calmette-Guerin bacillus attachment to murine bladder mucosa. Requirement for the expression of an antitumor response. J Clin Invest 85:62-67, 1990.
2. Böhle A, Brandau S. Immune mechanisms in bacillus Calmette-Guerin immunotherapy for superficial bladder cancer J Urol, 170:964–9, 2003.
3. de Boer EC, Rooyakkers, S. J. Schamhart, D. H.et al. BCG dose reduction by decreasing the instillation frequency: effects on local Th1/Th2 cytokine responses in a mouse model. Eur Urol, 48:333-338, 2005.
4. Thalmann GN, Dewald B, Baggliolini M, Studer UE. Interleukin-8 expression in the urine after bacillus Calmette-Guerin therapy: a potential prognostic factor of tumor recurrence and progression. J Urol 158:1340–4, 1997.
5. Torrence RJ, Kavoussi LR, Catalona WJ, Ratliff TL. Prognostic factors in patients treated with intravesical bacillus Calmette-Guerin for superficial bladder cancer. J Urol 139:941–4, 1988.
6. de Reijke T M, de Boer E., Kurth KH et al. Urinary interleukin-2 monitoring during prolonged bacillus Calmette-Guerin treatment: can it predict the optimal number of instillations? J Urol, 161: 67-71, 1999.
7. Saint F, Kurth N, Maille P, Vordos D, Hoznek A, Soyeux P, Patard JJ, Abbou CC,Chopin DK. Urinary IL-2 assay for monitoring intravesical bacillus Calmette-Guérin response of superficial bladder cancer during induction course and maintenance therapy. Int J Cancer. 107(3):434-40, 2003.
8. Saint F, Patard JJ, Maille P, Soyeux P, Hoznek A, Salomon L, De La Taille A,Abbou CC, Chopin DK. T helper 1/2 lymphocyte urinary cytokine profiles in responding and nonresponding patients after 1 and 2 courses of bacillus Calmette-Guerin for superficial bladder cancer. J Urol. 66(6):2142-7, 2001.
9. Riemensberger J, Bohle A, Brandau S. IFN-gamma and IL-12 but not IL-10 are required for local tumour surveillance in a syngeneic model of orthotopic bladder cancer. Clin Exp Immunol, 127:20–6, 2002.

#

Appendix 12 Substudy: "Validation of predictive genetic markers for BCG response"

Prof. Dr. Bart Kiemeney
Department of Urology, Radboud university medical center,
Nijmegen, The Netherlands

INTRODUCTION

Bacillus Calmette–Guérin (BCG) has been used to treat non-muscle-invasive bladder cancer (NMIBC) for more than 30 years. In current clinical practice, intravesical BCG therapy is used as standard treatment for patients with high-risk NMIBC, including lamina-propria-invasive (stage T1) tumors, high-grade/G3 papillary tumors (stage Ta), and carcinoma in situ (CIS).[1] BCG is associated with a reduced risk of recurrence, and it can also decrease the risk of progression to muscle-invasive disease.[2-4] However, the initial response rate for BCG treatment is only 60–80%, and approximately a third of responders eventually still develop recurrence and progression.[5] Current prediction models that are based solely on clinico-pathological characteristics, such as the EORTC and CUETO risk tables, aid in crude discrimination of the risk of NMIBC recurrence and progression at the population level, but lack discriminative ability to accurately predict whether an individual patient will experience recurrence or progression.[6-8]

This is why there is a need for additional biomarkers that predict the response to BCG, and thereby guide urologists in their decision to treat high-risk patients with bladder-sparing, conservative treatment or to perform immediate radical cystectomy. Although multiple studies have been performed focusing on different clinical stages (from diagnosis until post-treatment), type of biomarkers (genetic, immunological, inflammatory, clinico-pathologic) and biospecimens (urine, blood), no suitable biomarkers have been identified yet.[5,9] And despite the extensive clinical experience with BCG, the exact mechanism of action underlying the effectiveness as therapeutic agent for bladder cancer requires further investigation.[10]

Evidence increases that germline genetic polymorphisms partly explain the inter-individual variability in BCG response.[11-15] The majority of studies performed up till now focused on genetic polymorphisms implicated in the immune response and DNA repair pathways. Most of these candidate-gene or candidate-pathway studies were characterized by a small sample size (among the BCG treated subgroup) and lack validation in independent patient series.[11] This emphasizes the need for larger studies among homogeneous patient series that systematically scan the whole genome for genetic markers related to BCG response, and with external validation of results.

Therefore, a genome-wide association study (GWAS) was performed among a population-based series of 250 high-risk NMIBC patients treated with at least one intravesical induction course (*i.e.*, six instillations) of BCG. This resulted in several interesting association signals in relation to BCG recurrence and progression that require extensive validation to distinguish true from false-positive findings. In addition to the requirement of large patient numbers for validation, the validation phase would greatly benefit from DNA collection in the context of randomized clinical trials (RCTs) characterized by standardized treatment schedules and prospective documentation of BCG response. Hence, the goal of this study is to validate the most promising GWAS signals among the homogeneous series of BCG-treated participants in this RCT.

METHODS

This substudy will be performed in selected centres in consecutive patients who will be asked to participate in this optional research. Since this is an exploratory study, no formal sample size calculations were performed. A 10 ml standard plastic EDTA tube (purple cap) will be used to collect a blood sample from trial participants who gave their informed consent for this substudy. For logistic reasons, blood sampling for this research project could be scheduled simultaneously with a clinical blood draw shortly after patient enrollment. Exact timing of sampling relative to start of BCG treatment is, however not crucial for this project. After collection, the (whole) blood samples

should ideally be frozen within 24 hours at -80°C, and stored until shipment. If hospitals do not have the facility to store at -80°C, storage at -40°C or even -20°C is also acceptable. Blood tubes should be labeled with the unique NIMBUS patient randomization number, gender, and date of birth for sample identification.

At the end of the enrollment phase of the trial, all participating centres will ship samples in one batch and frozen (on dry ice) to Radboud university medical center, Nijmegen, The Netherlands. Germline DNA will be isolated from the blood samples. Single-SNP Centaurus assays (or a genome-wide chip) will be used to genotype genetic polymorphisms. SNP genotypes will be tested for association with recurrence- and progression-free survival after BCG treatment among the overall group of trial participants (and stratified according to the standard and experimental arm) using Cox regression and Kaplan-Meier analyses.

REFERENCES

1) Babjuk M, Burger M, Zigeuner R, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2013. *Eur Urol* 2013;64:639-53.
2) Han RF, Pan JG. Can intravesical bacillus Calmette-Guerin reduce recurrence in patients with superficial bladder cancer? A meta-analysis of randomized trials. *Urology* 2006;67:1216-23.
3) Shelley MD, Kynaston H, Court J, et al. A systematic review of intravesical bacillus Calmette-Guérin plus transurethral resection vs transurethral resection alone in Ta and T1 bladder cancer. *BJU Int* 2001;88:209-16.
4) Sylvester RJ, van der Meijden AP, Lamm DL. Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. *J Urol* 2002;168:1964-70.
5) Lima L, Dinis-Ribeiro M, Longatto-Filho A, et al. Predictive biomarkers of bacillus calmette-guérin immunotherapy response in bladder cancer: where are we now? *Adv Urol* 2012; doi: 10.1155/2012/232609.
6) Sylvester RJ. How well can you actually predict which non-muscle-invasive bladder cancer patients will progress? *Eur Urol* 2011;60:431-3.
7) Xylinas E, Kent M, Kluth L, et al. Accuracy of the EORTC risk tables and of the CUETO scoring model to predict outcomes in non-muscle invasive urothelial carcinoma of the bladder. *Br J Cancer* 2012;109:1460-6.
8) Fernandez-Gomez J, Madero R, Solsona E, et al. The EORTC tables overestimate the risk of recurrence and progression in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guérin: external validation of the EORTC risk tables. *Eur Urol* 2011;60:423-30.
9) Zuiverloon TC, Nieuweboer AJ, Vékony H, et al. Markers predicting response to bacillus Calmette-Guérin immunotherapy in high-risk bladder cancer patients: a systematic review. *Eur Urol* 2012;61:128-45.
10) Redelman-Sidi G, Glickman MS, Bochner BH. The mechanism of action of BCG therapy for bladder cancer – a current perspective. *Nat Rev Urol* 2014;11:153-62.
11) Wei H, Kamat A, Chen M, et al. Association of polymorphisms in oxidative stress genes with clinical outcomes for bladder cancer treated with Bacillus Calmette-Guérin. *PLoS One* 2012; doi: 10.1371/journal.pone.0038533.
12) Chen M, Hildebrandt MA, Clague J, et al. Genetic variations in the sonic hedgehog pathway affect clinical outcomes in non-muscle-invasive bladder cancer. *Cancer Prev Res (Phila)* 2010;3:1235-45.
13) Kang HW, Tchey DU, Yan C, et al. The predictive value of GSTT1 polymorphisms in predicting the early response to induction BCG therapy in patients with non-muscle invasive bladder cancer. *Urol Oncol* 2014;32:458-65.
14) Ahirwar DK, Manchanda PK, Mittal RD, et al. BCG response prediction with cytokine gene variants and bladder cancer: where we are? *J Cancer Res Clin Oncol* 2011;137:1729-38.
15) Grotenhuis AJ, Vermeulen SH, Kiemeney LA. Germline genetic markers for urinary bladder cancer risk, prognosis and treatment response. *Future Oncol* 2010;6:1433-60.

Appendix 13 Letter to patient

European Association of Urology

EAU Research Foundation
PO Box 30016
6803 AA Arnhem
The Netherlands

T +31 (0)26 389 0677
F +31 (0)26 389 0679

researchfoundation@uroweb.org
www.uroweb.org

Bank ING Bank N.V.
Arnhem - Netherlands
Acc no 677216688
BIC INGBNL2A
IBAN NL37INGB0677216688
Chamber of Commerce 09165573
VAT-ID nr. NL8183.32.979.B01

EAU Research Foundation
is the trade name of
Stichting EAU Foundation
for Urological Research

EAU Research Foundation Board

Chairman:
Prof. A.S. Bjartell
Malmö (SE)

Members:
Clinical Studies Committee
Prof. C.M. Moore
London (GB)
Prof. A. Necchi
Milan (IT)

Basic Research Committee
Prof. G.W. Jenster
Rotterdam (NL)

Registries Committee
Prof. L.A.L.M. Kiemeney
Nijmegen (NL)
Prof. S.F. Shariat
Vienna (AT)

Central Research Office
Dr. W.P.J. Witjes
Arnhem (NL)

Ex-officio:
European Urological Scholarship
Prof. V.G. Mirone
Naples (IT)

Arnhem, 6 November 2019

Subject: Information for Patient NIMBUS study

Title of the study:
Treatment of High Grade Non-Muscle Invasive Urothelial Carcinoma of the Bladder by Standard Number and Dose of Intravesical BCG Instillations versus Reduced Number of Intravesical Instillations with Standard Dose of BCG. A European Association of Urology Research Foundation Randomized Phase III Clinical Trial
Short title: NIMBUS

Sponsor: European Association of Urology Research Foundation (EAU RF)

Eudra CT No .: 2010-019181-91

Dear Madam/Sir,

You are participating or have participated in the NIMBUS clinical trial.
New information is available for this study, which we have summarized for you below.
We also explain what this means for your participation in the NIMBUS study.

Early termination trial

Every year an independent committee of experts (independent data monitoring committee) reviews the interim data of the NIMBUS trial. This committee especially monitors the number of patients that have a recurrence of bladder tumor. Recent analyses showed a higher recurrence rate (frequency of recurrence of a bladder tumor) in the treatment group with a reduced number of treatments compared to the standard number of treatments. As a result, EAU RF has stopped to include new patients in the NIMBUS study after 17 October 2019. The period of data collection will also be shortened dependent on the study phase of the patient.

Will the early termination of the study affect my treatment with BCG?

If you are still receiving BCG with the reduced number of treatments, you have been informed by your doctor on the possibility of switching to the standard study arm. This is the routine standard number of BCG instillations recommended for treating your condition.

European Association of Urology

EAU Research Foundation
PO Box 30016
6803 AA Arnhem
The Netherlands

T +31 (0)26 389 0677
F +31 (0)26 389 0679

researchfoundation@uroweb.org
www.uroweb.org

Bank ING Bank N.V.
Arnhem - Netherlands
Acc no 6772166 88
BIC INGBNL2A
IBAN NL37INGB0677216688
Chamber of Commerce 09165573
VAT-ID nr. NL8183.32.979.B01

EAU Research Foundation
is the trade name of
Stichting EAU Foundation
for Urological Research

EAU Research Foundation Board

Chairman:
Prof. A.S. Bjartell

Members:
Clinical Studies Committee
Prof. C.M. Moore
Prof. A. Necchi
Basic Research Committee
Prof. G.W. Jenster
Registries Committee
Prof. L.A.L.M. Kiemeney
Prof. S.F. Shariat
Central Research Office
Dr. W.P.J. Witjes

Ex-officio:

If you are still receiving BCG with the standard number of treatments, your treatment schedule will not be changed, you will continue to have the standard number of BCG instillations.

Collection of your study data

The period of data collection will be shortened dependent on the study phase you are currently in.

If you are still receiving BCG treatment:

Treatment schedule NIMBUS study

	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12
Standard Frequency arm	Week 1,2,3,4	Week 5,6	Week 1,2,3	Week 1,2,3		Week 1,2,3
Reduced Frequency arm	Week 1,2	Week 6	Week 1,3	Week 1,3		Week 1,3

- We will collect your study data until you completed the third week (W3) visit of the 6th month (M6) of BCG treatment
- If you have already received the BCG treatment of M6W3 and your next visit is the visit of Month 9 (M9) or Month 12 (M12) we will collect the study data of the visit of M9 or M12 if the visit has been taken place or will take place before 17 Nov 2019.
- If, at 17 November 2019, you are receiving BCG instillations of the 12th month, we will collect your study data until you have completed the third week (W3) visit of the 12th month (M12) of BCG treatment, even if these visits take place after 17 November 2019.

If you have already finished your BCG treatment:

We collect data on your follow-up examinations until November 17th 2019.

When will my study participation end?

Your study participation will end after we have collected your study data as described above, or earlier, when a recurrence is observed.

After study end you will continue to have the treatment or care for as part of the medical routine. Because the standard number of BCG instillations and follow-up

European Association of Urology

EAU Research Foundation
PO Box 30016
6803 AA Arnhem
The Netherlands

T +31 (0)26 389 0677
F +31 (0)26 389 0679

researchfoundation@uroweb.org
www.uroweb.org

Bank ING Bank N.V.
Arnhem - Netherlands
Acc no 677216688
BIC INGBNL2A
IBAN NL37INGB0677216688
Chamber of Commerce 09165573
VAT-ID nr. NL8183.32.979.B01

EAU Research Foundation
is the trade name of
Stichting EAU Foundation
for Urological Research

examinations in the study are in accordance with the clinical routine described in the guidelines, nothing will change with the premature termination of the study.

The study will end when all patients have at least a follow period of 6 months (i.e. finished week 3 of the 6th month BCG instillations).

After the study has ended and all data are analysed, your doctor will inform you on the most important results.

Your personal data will stay confidential and are only accessible to the designated authorised people.

As before, your participation is entirely voluntary. You may decline from participating or withdraw your consent at any time. This will not affect your further treatment.

The EAU Research foundation wishes to thank you for participating in the NIMBUS study.

Despite the premature ending of the trial, the data collected in this trial will enable to answer some important scientific questions concerning the use of BCG therapy in the treatment of bladder cancer.

If you have participated in the Cytokine-substudy and/or DNA-substudy, we want to thank you for providing the urine samples and/or a blood sample.
With these samples we are able to investigate which immune responses are important in BCG treatment of bladder and to better understand why some patients react favourably to BCG instillations and others experience a recurrence.

Do you still have questions after reading this information? please contact your study urologist or her/his staff members at your hospital.

On behalf of the EAU RF,

Dr. Wim Witjes
Scientific & Clinical Research Director

Prof. Anders Bjartell
Chairman of the EAU Research Foundation

EAU Research Foundation Board

Chairman:
Prof. A.S. Bjartell
Malmö (SE)

Members:

Clinical Studies Committee
Prof. C.M. Moore
London (GB)
Prof. A. Necchi
Milan (IT)

Basic Research Committee
Prof. G.W. Jenster
Rotterdam (NL)

Registries Committee
Prof. L.A.L.M. Kiemeney
Nijmegen (NL)
Prof. S.F. Shariat
Vienna (AT)

Central Research Office
Dr. W.P.J. Witjes
Arnhem (NL)

Ex-officio:

European Urological Scholarship
Prof. V.G. Mirone
Naples (IT)

Appendix 1~~4~~3 Checklists

Checklist Standard Frequency Arm *Note that the follow-up period is shortened (see section 2.2)*

			Induction cycle						Maintenance cycle										Follow-up	
	Screening*	Randomisation	month 1				month 2		mth 3			mth 6			mth 9	mth 12			mth 15	mth 18-21-24-30-36-42-48-54-60
			wk1	wk2	wk3	wk4	wk5	wk6	wk1	wk2	wk3	wk1	wk2	wk3		wk1	wk2	wk3		
Demography data	X																			
BCG Instillation			X	X	X	X	X	X	X	X	X	X	X	X		X	X	X		
Bladder Wash / voided urine Cytology (1)	X								X			X			X	X			X	X
Cystoscopy (Bladder map)	X								X			X			X	X			X	X
ICIQ LUTS and QLQ-30 (2)			X					X	X		X	X		X		X		X		
Laboratory Examination (3)	X																			
Upper Urinary Tract Investigation (4)	X																			
Informed consent		X																		
Medical History		X																		
In and Exclusion criteria		X																		
Physical Examination including WHO/ASA score		X																		
Concomitant Medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urine examination prior to start of BCG instillations (5)		X																		
Pregnancy test (6)	X								X			X				X			X	
(Serious) Adverse Events (CTCAE) (7)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
SAE's related to study participation/treatment (CTCAE) (7)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

* standard procedures according to local practice, retrospective documentation after written informed consent.

[1] Voided urine cytology preferably before last resection (initial resection, re-TUR or re-re-TUR) and follow up cystoscopies or wash-out cytology at the time of last resection and at the time of follow up cystoscopies

[2] Prior to the first instillation and prior to the 6th instillation at the end of the induction course or earlier in case of early stop of instillations. Also, at months 3, 6 and 12 also prior to the first and the last instillations (Wk1,3) or earlier in case of stop of instillations.

[3] Laboratory examination preferably before last resection according to local practice (e.g., BUN, creatinine, AST, ALT, leucocytes, platelets).

[4] Upper Urinary Tract Investigation (UUTI) according to local practice (e.g., IVU, CT-Urography) to exclude upper urinary tract tumors.

[5] Urine examination between last resection and prior to 1st BCG-instillation.

[6] For females of childbearing potential, a pregnancy test must be performed within 7 days before start BCG treatment. During the treatment period, a pregnancy test will be done at months 3,6,12 and 3 months after the last BCG treatment, and should be performed at any time during the study for all women of childbearing potential if the investigator or patient suspects that pregnancy has occurred while the subject was being treated on protocol therapy.

[7] WHO toxicity grading of known local and systemic side effects (Appendix 6) are to be performed prior to the first instillation, and prior to the 6th instillation at the end of the induction course or earlier in case of early stop of instillations. Also, at months 3,6 and 12 prior to the first and the last instillations (Wk1,3) or earlier in case of stop of instillations. All Adverse Events are to be reported according CTCAE up to month 15 unless the AE is serious and either related to study participation or related to study treatment; these SAEs need to be reported throughout the study.

eau rf Research Foundation

Checklist Reduced Frequency Arm

Note that on 17th November 2019 patients in the Reduced frequency treatment schedule were offered the possibility to switch to the Standard frequency treatment schedule and that that the follow-up period is shortened (see section 2.2)

			Induction cycle						Maintenance cycle										Follow-up	
	Screening*	Randomisation	month 1				month 2		mth 3			mth 6			mth 9	mth 12			mth 15	mth 18-21-24-30-36-42-48-54-60
			wk1	wk2	wk3	wk4	wk5	wk6	wk1	wk2	wk3	wk1	wk2	wk3		wk1	wk2	wk3		
Demograhy data	X																			
BCG Instillation			X	X				X	X		X	X		X		X		X		
Bladder Wash / voided urine Cytology (1)	X								X			X			X	X			X	X
Cystoscopy (Bladder map)	X								X			X			X	X			X	X
ICIQ LUTS and QLQ-30 (2)			X					X	X		X	X		X		X		X		
Laboratory Examination (3)	X																			
Upper Urinary Tract Investigation (4)	X																			
Informed consent		X																		
Medical History		X																		
In and Exclusion criteria		X																		
Physical Examination including WHO/ASA score		X																		
Concomitant Medication		X	X	X				X	X		X	X		X	X	X		X	X	
Urine examination prior to start of BCG instillations (5)		X																		
Pregnancy test (6)	X								X			X				X			X	
(Serious) Adverse Events (CTCAE) (7)			X	X				X	X		X	X		X	X	X		X	X	
SAE's related to study participation/treatment (CTCAE) (7)			X	X				X	X		X	X		X	X	X		X	X	X

[*] standard procedures according to local practice, retrospective documentation after written informed consent.
[1] Voided urine cytology preferably before last resection (initial resection, re-TUR or re-reTUR) and follow up cystoscopies or wash-out cytology at the time of last resection and at the time of follow up cystoscopies
[2] Prior to the first instillation and prior to the 6th instillation at the end of the induction course or earlier in case of early stop of instillations. Also, at months 3, 6 and 12 also prior to the first and the last instillations (Wk1,3) or earlier in case of stop of instillations.
[3] Laboratory examination preferably before last resection according to local practice (e.g., BUN, creatinine, AST, ALT, leucocytes, platelets)
[4] Upper Urinary Tract Investigation (UUTI) according to local practice (e.g., IVU, CT-Urography) to exclude upper urinary tract tumors.
[5] Urine examination between last resection and prior to 1st BCG-instillation.
[6.] For females of childbearing potential, a pregnancy test must be performed within 7 days before start BCG treatment. During the treatment period, a pregnancy test will be done at months 3,6,12 and 3 months after the last BCG treatment, and should be performed at any time during the study for all women of childbearing potential if the investigator or patient suspects that pregnancy has occurred while the subject was being treated on protocol therapy.
[7] WHO toxicity grading of known local and systemic side effects (Appendix 6) are to be performed prior to the first instillation, and prior to the 6th instillation at the end of the induction course or earlier in case of early stop of instillations. Also, at months 3,6 and 12 prior to the first and the last instillations (Wk1,3) or earlier in case of stop of instillations. All Adverse Events are to be reported according CTCAE up to month 15 unless the AE is serious and either related to study participation or related to study treatment; these SAEs need to be reported throughout the study.

Appendix 13

Questionnaires

EORTC QLQ-C30 (version 3)

Scoring of QLQ-C30 questionnaire was done as described in EORTC QLQ-C30 Scoring manual.
To account for missing values the following method has been used (as described in the Scoring manual: if at least half of the items from the scale have been answered, assume that the missing items have values equal to the average of those items which *are* present for that respondent.

Scoring of the QLQ-C30 Summary Score
The EORTC QLQ-C30 Summary Score is calculated from the mean of 13 of the 15 QLQ-C30 scales (the Global Quality of Life scale and the Financial Impact scale are not included). Prior to calculating the mean, the symptom scales need to be reversed to obtain a uniform direction of all scales. The summary score should only be calculated if all of the required 13 scale scores are available (using scale scores based on the completed items, provided that at least 50% of the items in that scale have been completed.

Note: The EORTC Quality of Life Group cautions strongly against the use of total, global score based upon the sum of all items and advises to use the Global health status/QoL scale as the overall summary measure.

Questionnaires have been completed prior to the first and last instillation of every cycle (ICIQ-LUTS and “EORTC QLQ 30” questionnaires).

According to protocol the questionnaires should be completed prior to BCG instillation. In some cases questionnaires have been completed after BCG instillation.

Month 1 Week 1

QLQ C30 completed?	Reduced	Standard	Total
Yes	166 (96.5%)	166 (94.3%)	332 (95.4%)
No	6 (3.5%)	10 (5.7%)	16 (4.6%)
	172 (100%)	176 (100%)	348 (100%)

Total group	n	Mean	SD	median	min	max
Physical functioning	332	84,62	19,01	93,33	13,33	100
Role functioning	331	82,38	26,01	100,00	0,00	100
Emotional functioning	329	79,27	20,79	83,33	0,00	100
Cognitive functioning	329	89,56	17,77	100,00	0,00	100
Social functioning	329	84,65	22,62	100,00	0,00	100
Fatigue	332	22,17	24,25	11,11	0,00	100
Nausea / Vomiting	329	2,18	9,36	0,00	0,00	100
Pain	332	15,01	21,83	0,00	0,00	100
Dyspnea	331	16,21	26,76	0,00	0,00	100
Insomnia	332	25,20	31,59	0,00	0,00	100
Appetite loss	332	5,32	16,65	0,00	0,00	100
Constipation	328	11,28	21,13	0,00	0,00	100
Diarrhea	329	5,98	16,09	0,00	0,00	100
Financial difficulties	328	5,69	17,34	0,00	0,00	100
Global health and quality of life	327	71,61	20,28	75,00	0,00	100

Reduced frequency group	n	Mean	SD	median	min	max
Physical functioning	166	84,09	18,92	93,33	20	100
Role functioning	166	82,03	25,69	100,00	0	100
Emotional functioning	165	79,76	21,27	83,33	0	100
Cognitive functioning	165	90,00	17,92	100,00	0	100
Social functioning	165	84,85	22,30	100,00	0	100
Fatigue	166	23,09	25,10	16,67	0	100
Nausea / Vomiting	165	1,92	6,99	0,00	0	50
Pain	166	14,86	21,87	0,00	0	100
Dyspnea	165	15,96	25,39	0,00	0	100
Insomnia	166	26,51	32,93	0,00	0	100
Appetite loss	166	6,22	18,57	0,00	0	100
Constipation	164	12,20	20,89	0,00	0	66,67
Diarrhea	165	6,67	17,73	0,00	0	100
Financial difficulties	165	7,07	20,09	0,00	0	100
Global health and quality of life	165	70,51	19,31	75,00	0	100

Standard frequency group	n	Mean	SD	median	min	max
Physical functioning	166	85,16	19,15	93,33	13,33	100

Role functioning	165	82,73	26,41	100,00	0	100
Emotional functioning	164	78,78	20,35	83,33	8,33	100
Cognitive functioning	164	89,13	17,67	100,00	33,33	100
Social functioning	164	84,45	22,99	100,00	0	100
Fatigue	166	21,25	23,40	11,11	0	100
Nausea / Vomiting	164	2,44	11,27	0,00	0	100
Pain	166	15,16	21,85	0,00	0	100
Dyspnea	166	16,47	28,13	0,00	0	100
Insomnia	166	23,90	30,23	0,00	0	100
Appetite loss	166	4,42	14,47	0,00	0	100
Constipation	164	10,37	21,39	0,00	0	100
Diarrhea	164	5,28	14,27	0,00	0	66,67
Financial difficulties	163	4,29	13,93	0,00	0	66,67
Global health and quality of life	162	72,74	21,22	79,17	0	100

Month 2 Week 6

QLQ C30 completed?	reduced	standard	Total
Yes	152 (91.0%)	153 (89.5%)	305 (90.2%)
No	15 (9.0%)	18 (10.5%)	33 (9.8%)
	167 (100%)	171 (100%)	338 (100%)

Total group	n	Mean	SD	median	min	max
Physical functioning	304	84,10	18,97	93,33	0	100
Role functioning	304	80,92	26,91	100,00	0	100
Emotional functioning	302	81,26	21,17	83,33	0	100
Cognitive functioning	302	88,25	17,79	100,00	0	100
Social functioning	302	85,21	22,12	100,00	0	100
Fatigue	304	27,38	25,69	22,22	0	100
Nausea / Vomiting	304	3,67	10,93	0,00	0	100
Pain	305	17,49	24,97	0,00	0	100
Dyspnea	304	17,00	26,39	0,00	0	100
Insomnia	303	21,67	28,51	0,00	0	100
Appetite loss	304	8,00	19,10	0,00	0	100
Constipation	300	11,00	22,67	0,00	0	100
Diarrhea	301	6,76	15,71	0,00	0	100
Financial difficulties	302	6,07	17,71	0,00	0	100
Global health and quality of life	302	70,34	20,36	75,00	8,33	100

Reduced frequency group	n	Mean	SD	median	min	max
Physical functioning	152	83,86	18,70	90,00	20	100
Role functioning	152	81,80	26,67	100,00	0	100
Emotional functioning	151	81,57	21,40	91,67	0	100
Cognitive functioning	151	88,19	18,82	100,00	0	100
Social functioning	151	86,64	21,00	100,00	0	100
Fatigue	152	26,54	25,77	22,22	0	100
Nausea / Vomiting	151	3,31	9,23	0,00	0	50
Pain	152	18,75	26,53	0,00	0	100
Dyspnea	152	18,64	27,32	0,00	0	100
Insomnia	151	22,74	27,59	0,00	0	100
Appetite loss	152	9,21	21,08	0,00	0	100
Constipation	150	11,33	23,12	0,00	0	100
Diarrhea	151	6,62	15,41	0,00	0	66,67
Financial difficulties	151	7,28	19,96	0,00	0	100
Global health and quality of life	151	70,92	21,38	75,00	16,67	100

Standard frequency group	n	Mean	SD	median	min	max

Physical functioning	152	84,34	19,31	93,33	0	100
Role functioning	152	80,04	27,20	100,00	0	100
Emotional functioning	151	80,96	21,00	83,33	0	100
Cognitive functioning	151	88,30	16,75	100,00	33,33	100
Social functioning	151	83,77	23,17	100,00	0	100
Fatigue	152	28,22	25,67	22,22	0	100
Nausea / Vomiting	153	4,03	12,39	0,00	0	100
Pain	153	16,23	23,33	0,00	0	100
Dyspnea	152	15,35	25,41	0,00	0	100
Insomnia	152	20,61	29,45	0,00	0	100
Appetite loss	152	6,80	16,87	0,00	0	100
Constipation	150	10,67	22,29	0,00	0	100
Diarrhea	150	6,89	16,06	0,00	0	100
Financial difficulties	151	4,86	15,10	0,00	0	66,67
Global health and quality of life	151	69,76	19,33	66,67	8,33	100

Month 3 Week 1

QLQ C30 completed?	reduced	standard	Total
Yes	127 (81.4%)	138 (83.6%)	265 (82.6%)
No	29 (18.6%)	27 (16.4%)	56 (17,4%)
	156 (100%)	165 (100%)	321 (100%)

Total group	n	Mean	SD	median	min	max
Physical functioning	265	83,70	19,00	91,67	13,33	100
Role functioning	265	82,96	26,86	100,00	0	100
Emotional functioning	262	80,95	22,53	91,67	0	100
Cognitive functioning	262	87,21	19,65	100,00	0	100
Social functioning	262	85,18	22,12	100,00	0	100
Fatigue	265	23,90	25,19	22,22	0	100
Nausea / Vomiting	263	2,79	10,23	0,00	0	100
Pain	265	14,97	23,35	0,00	0	100
Dyspnea	265	17,74	27,21	0,00	0	100
Insomnia	264	23,23	29,20	0,00	0	100
Appetite loss	265	6,16	17,64	0,00	0	100
Constipation	262	9,92	19,87	0,00	0	100
Diarrhea	261	6,39	15,25	0,00	0	66,67
Financial difficulties	261	7,28	20,10	0,00	0	100
Global health and quality of life	261	73,31	20,92	75,00	0	100

Reduced frequency group	n	Mean	SD	median	min	max
Physical functioning	127	81,29	19,63	86,67	13,33	100
Role functioning	127	81,23	28,17	100,00	0	100
Emotional functioning	125	81,60	22,03	91,67	8,33	100
Cognitive functioning	125	87,20	20,65	100,00	0	100
Social functioning	125	84,53	22,42	100,00	0	100
Fatigue	127	27,91	27,00	22,22	0	100
Nausea / Vomiting	126	3,04	7,72	0,00	0	50
Pain	127	17,72	24,28	0,00	0	100
Dyspnea	127	21,00	28,42	0,00	0	100
Insomnia	127	26,77	31,99	33,33	0	100
Appetite loss	127	7,87	18,99	0,00	0	100
Constipation	125	12,53	21,86	0,00	0	100
Diarrhea	124	6,99	17,15	0,00	0	66,67
Financial difficulties	124	8,06	22,24	0,00	0	100
Global health and quality of life	125	70,87	21,21	75,00	0	100

Standard frequency group	n	Mean	SD	median	min	max
Physical functioning	138	85,92	18,19	93,33	25	100

Role functioning	138	84,54	25,60	100,00	0	100
Emotional functioning	137	80,35	23,04	91,67	0	100
Cognitive functioning	137	87,23	18,77	100,00	16,67	100
Social functioning	137	85,77	21,91	100,00	0	100
Fatigue	138	20,21	22,87	11,11	0	100
Nausea / Vomiting	137	2,55	12,11	0,00	0	100
Pain	138	12,44	22,25	0,00	0	100
Dyspnea	138	14,73	25,79	0,00	0	100
Insomnia	137	19,95	26,03	0,00	0	100
Appetite loss	138	4,59	16,21	0,00	0	100
Constipation	137	7,54	17,62	0,00	0	100
Diarrhea	137	5,84	13,34	0,00	0	66,67
Financial difficulties	137	6,57	18,00	0,00	0	100
Global health and quality of life	136	75,55	20,47	83,33	0	100

Month 3 Week 3

QLQ C30 completed?	reduced	standard	Total
Yes	122 (93.8%)	122 (84.1%)	244 (88.7%)
No	8 (6.2%)	23 (15.9%)	31 (11.3%)
	130 (100%)	145 (100%)	275 (100%)

Total group	n	Mean	SD	median	min	max
Physical functioning	242	83,71	19,36	92,50	13,33	100
Role functioning	242	79,06	27,33	100,00	0	100
Emotional functioning	243	82,65	20,31	91,67	0	100
Cognitive functioning	243	86,63	19,54	100,00	0	100
Social functioning	243	84,64	21,84	100,00	0	100
Fatigue	242	25,71	24,55	22,22	0	100
Nausea / Vomiting	243	3,36	11,09	0,00	0	100
Pain	242	17,77	24,88	0,00	0	100
Dyspnea	242	16,94	26,86	0,00	0	100
Insomnia	242	21,63	28,42	0,00	0	100
Appetite loss	242	6,75	16,78	0,00	0	100
Constipation	242	9,92	20,21	0,00	0	100
Diarrhea	243	6,72	17,29	0,00	0	100
Financial difficulties	242	5,65	18,23	0,00	0	100
Global health and quality of life	243	71,12	20,94	75,00	0	100

Reduced frequency group	n	Mean	SD	median	min	max
Physical functioning	120	80,61	20,96	86,67	13,33	100
Role functioning	120	77,92	27,43	83,33	0	100
Emotional functioning	121	83,03	20,37	91,67	0	100
Cognitive functioning	121	87,05	19,54	100,00	0	100
Social functioning	121	84,71	22,93	100,00	0	100
Fatigue	120	25,93	24,67	22,22	0	100
Nausea / Vomiting	121	4,27	13,36	0,00	0	100
Pain	120	19,31	26,02	0,00	0	100
Dyspnea	120	21,11	29,29	0,00	0	100
Insomnia	120	20,56	27,39	0,00	0	100
Appetite loss	120	5,83	15,38	0,00	0	100
Constipation	120	12,78	23,34	0,00	0	100
Diarrhea	121	6,89	19,21	0,00	0	100
Financial difficulties	121	7,44	21,73	0,00	0	100
Global health and quality of life	121	69,97	22,11	66,67	8,33	100

Standard frequency group	n	Mean	SD	median	min	max
Physical functioning	122	86,75	17,19	93,33	33,33	100

Role functioning	122	80,19	27,30	100,00	0	100
Emotional functioning	122	82,26	20,32	91,67	8,33	100
Cognitive functioning	122	86,20	19,60	100,00	33,33	100
Social functioning	122	84,56	20,79	100,00	33,33	100
Fatigue	122	25,50	24,52	22,22	0	100
Nausea / Vomiting	122	2,46	8,21	0,00	0	66,67
Pain	122	16,26	23,71	0,00	0	100
Dyspnea	122	12,84	23,65	0,00	0	100
Insomnia	122	22,68	29,46	0,00	0	100
Appetite loss	122	7,65	18,07	0,00	0	100
Constipation	122	7,10	16,17	0,00	0	66,67
Diarrhea	122	6,56	15,24	0,00	0	66,67
Financial difficulties	121	3,86	13,74	0,00	0	66,67
Global health and quality of life	122	72,27	19,74	75,00	0	100

Month 6 Week 1

QLQ C30 completed?	reduced	standard	Total
Yes	103 (84.4%)	124 (89.2%)	227 (87.0%)
No	19 (15.6%)	15 (10.8%)	34 (13.0%)
	122 (100%)	139 (100%)	261 (100%)

Total group	n	Mean	SD	median	min	max
Physical functioning	227	84,23	19,61	93,33	0	100
Role functioning	227	82,67	25,05	100,00	0	100
Emotional functioning	225	81,54	21,47	83,33	0	100
Cognitive functioning	225	86,30	19,44	100,00	0	100
Social functioning	225	86,81	21,97	100,00	0	100
Fatigue	227	22,61	22,83	22,22	0	100
Nausea / Vomiting	227	2,13	7,12	0,00	0	50
Pain	227	16,08	23,82	0,00	0	100
Dyspnea	226	17,26	27,26	0,00	0	100
Insomnia	227	22,91	28,46	0,00	0	100
Appetite loss	227	4,41	14,38	0,00	0	100
Constipation	224	8,04	18,81	0,00	0	100
Diarrhea	225	6,22	16,99	0,00	0	100
Financial difficulties	225	6,37	18,47	0,00	0	100
Global health and quality of life	224	74,18	21,77	83,33	8,33	100

Reduced frequency group	n	Mean	SD	median	min	max
Physical functioning	103	82,78	20,31	86,67	0	100
Role functioning	103	83,01	25,24	100,00	0	100
Emotional functioning	102	82,90	22,68	91,67	0	100
Cognitive functioning	102	87,42	20,37	100,00	0	100
Social functioning	102	85,46	24,22	100,00	0	100
Fatigue	103	23,73	23,08	22,22	0	100
Nausea / Vomiting	103	2,91	8,86	0,00	0	50
Pain	103	17,80	26,02	0,00	0	100
Dyspnea	103	19,42	27,82	0,00	0	100
Insomnia	103	22,98	28,78	0,00	0	100
Appetite loss	103	5,50	16,89	0,00	0	100
Constipation	102	8,82	17,50	0,00	0	66,67
Diarrhea	102	6,21	18,00	0,00	0	100
Financial difficulties	102	7,52	20,93	0,00	0	100
Global health and quality of life	101	70,87	23,88	83,33	8,33	100

Standard frequency group	n	Mean	SD	median	min	max

Physical functioning	124	85,43	19,00	93,33	13,33	100
Role functioning	124	82,39	24,99	100,00	0	100
Emotional functioning	123	80,42	20,44	83,33	16,67	100
Cognitive functioning	123	85,37	18,67	83,33	16,67	100
Social functioning	123	87,94	19,94	100,00	0	100
Fatigue	124	21,68	22,66	22,22	0	100
Nausea / Vomiting	124	1,48	5,21	0,00	0	33,33
Pain	124	14,65	21,84	0,00	0	100
Dyspnea	123	15,45	26,75	0,00	0	100
Insomnia	124	22,85	28,31	0,00	0	100
Appetite loss	124	3,49	11,89	0,00	0	66,67
Constipation	122	7,38	19,88	0,00	0	100
Diarrhea	123	6,23	16,17	0,00	0	100
Financial difficulties	123	5,42	16,18	0,00	0	100
Global health and quality of life	123	76,90	19,55	83,33	25	100

Month 6 Week 3

QLQ C30 completed?	reduced	standard	Total
Yes	107 (92.2%)	119 (89.5%)	226 (90.8%)
No	9 (7.8%)	14 (10.5%)	23 (9.2%)
	116 (100%)	133 (100%)	249 (100%)

Total group	n	Mean	SD	median	min	max
Physical functioning	226	85,10	17,65	93,33	20	100
Role functioning	225	79,63	27,02	100,00	0	100
Emotional functioning	226	81,07	23,77	91,67	0	100
Cognitive functioning	226	85,91	19,93	100,00	0	100
Social functioning	226	84,14	22,78	100,00	0	100
Fatigue	226	25,59	24,65	22,22	0	100
Nausea / Vomiting	225	2,37	6,99	0,00	0	50
Pain	225	20,52	26,91	16,67	0	100
Dyspnea	225	17,48	26,92	0,00	0	100
Insomnia	225	23,70	29,40	0,00	0	100
Appetite loss	225	4,89	13,76	0,00	0	100
Constipation	225	10,37	21,62	0,00	0	100
Diarrhea	225	7,26	18,14	0,00	0	100
Financial difficulties	226	6,49	18,78	0,00	0	100
Global health and quality of life	226	70,65	22,65	75,00	8,33	100

Reduced frequency group	n	Mean	SD	median	min	max
Physical functioning	107	83,33	17,78	86,67	26,67	100
Role functioning	107	80,84	25,98	100,00	0	100
Emotional functioning	107	82,35	23,81	91,67	0	100
Cognitive functioning	107	87,07	19,47	100,00	0	100
Social functioning	107	83,64	24,87	100,00	0	100
Fatigue	107	24,97	25,02	22,22	0	100
Nausea / Vomiting	106	2,36	7,43	0,00	0	50
Pain	106	21,38	26,90	16,67	0	100
Dyspnea	107	19,00	28,27	0,00	0	100
Insomnia	106	23,27	30,23	0,00	0	100
Appetite loss	106	5,66	16,25	0,00	0	100
Constipation	106	11,95	21,67	0,00	0	66,67
Diarrhea	106	5,35	14,65	0,00	0	66,67
Financial difficulties	107	8,72	22,59	0,00	0	100
Global health and quality of life	107	70,56	23,72	75,00	16,67	100

Standard frequency group	n	Mean	SD	median	min	max

Physical functioning	119	86,68	17,46	93,33	20	100
Role functioning	118	78,53	28,00	100,00	0	100
Emotional functioning	119	79,93	23,77	91,67	0	100
Cognitive functioning	119	84,87	20,35	100,00	0	100
Social functioning	119	84,59	20,83	100,00	0	100
Fatigue	119	26,14	24,40	22,22	0	100
Nausea / Vomiting	119	2,38	6,61	0,00	0	33,33
Pain	119	19,75	27,01	16,67	0	100
Dyspnea	118	16,10	25,68	0,00	0	100
Insomnia	119	24,09	28,76	33,33	0	100
Appetite loss	119	4,20	11,11	0,00	0	33,33
Constipation	119	8,96	21,57	0,00	0	100
Diarrhea	119	8,96	20,67	0,00	0	100
Financial difficulties	119	4,48	14,34	0,00	0	100
Global health and quality of life	119	70,73	21,75	75,00	8,33	100

Month 12 Week 1

QLQ C30 completed?	reduced	standard	Total
Yes	79 (87.8%)	92 (83.6%)	171 (85.5%)
No	11 (12.2%)	18 (16.4%)	29 (14.5%)
	90 (100%)	110 (100%)	200 (100%)

Total group	n	Mean	SD	median	min	max
Physical functioning	171	86,71	17,56	93,33	6,67	100
Role functioning	171	84,70	24,48	100,00	0	100
Emotional functioning	171	83,71	19,25	91,67	8,33	100
Cognitive functioning	170	87,75	18,45	100,00	33,33	100
Social functioning	171	87,23	22,02	100,00	0	100
Fatigue	171	21,67	22,22	22,22	0	100
Nausea / Vomiting	171	2,44	8,02	0,00	0	66,67
Pain	171	13,94	21,21	0,00	0	100
Dyspnea	171	17,74	26,88	0,00	0	100
Insomnia	171	23,20	27,08	0,00	0	100
Appetite loss	171	3,70	12,23	0,00	0	66,67
Constipation	170	7,25	17,94	0,00	0	100
Diarrhea	171	6,04	15,21	0,00	0	66,67
Financial difficulties	170	5,69	16,23	0,00	0	66,67
Global health and quality of life	170	75,05	22,09	83,33	0	100

Reduced frequency group	n	Mean	SD	median	min	max
Physical functioning	79	86,75	16,73	93,33	26,67	100
Role functioning	79	85,23	23,11	100,00	0	100
Emotional functioning	79	84,63	20,47	91,67	8,33	100
Cognitive functioning	79	86,50	20,51	100,00	33,33	100
Social functioning	79	86,29	23,68	100,00	0	100
Fatigue	79	23,77	23,11	22,22	0	88,89
Nausea / Vomiting	79	2,32	6,39	0,00	0	33,33
Pain	79	13,71	22,76	0,00	0	100
Dyspnea	79	16,46	24,39	0,00	0	100
Insomnia	79	24,47	28,60	33,33	0	100
Appetite loss	79	2,95	9,53	0,00	0	33,33
Constipation	78	8,12	19,51	0,00	0	100
Diarrhea	79	5,91	14,87	0,00	0	66,67
Financial difficulties	78	6,41	17,04	0,00	0	66,67
Global health and quality of life	78	74,79	20,37	75,00	16,67	100

Standard frequency group	n	Mean	SD	median	min	max
Physical functioning	92	86,67	18,33	93,33	6,67	100

Role functioning	92	84,24	25,72	100,00	0	100
Emotional functioning	92	82,91	18,20	87,50	25	100
Cognitive functioning	91	88,83	16,49	100,00	33,33	100
Social functioning	92	88,04	20,57	100,00	0	100
Fatigue	92	19,87	21,39	13,89	0	100
Nausea / Vomiting	92	2,54	9,22	0,00	0	66,67
Pain	92	14,13	19,91	0,00	0	83,33
Dyspnea	92	18,84	28,94	0,00	0	100
Insomnia	92	22,10	25,81	0,00	0	100
Appetite loss	92	4,35	14,17	0,00	0	66,67
Constipation	92	6,52	16,57	0,00	0	66,67
Diarrhea	92	6,16	15,57	0,00	0	66,67
Financial difficulties	92	5,07	15,58	0,00	0	66,67
Global health and quality of life	92	75,27	23,55	83,33	0	100

Month 12 Week 3

QLQ C30 completed?	reduced	standard	Total
Yes	76 (90.5%)	92 (89.3%)	168 (89.8%)
No	8 (9.5%)	11 (10.7%)	19 (10.2%)
	84 (100%)	103 (100%)	187 (100%)

Total group	n	Mean	SD	median	min	max
Physical functioning	167	85,95	17,22	93,33	20	100
Role functioning	168	79,76	26,57	100,00	0	100
Emotional functioning	167	82,83	20,69	91,67	8,33	100
Cognitive functioning	168	86,81	20,94	100,00	0	100
Social functioning	167	85,33	21,78	100,00	0	100
Fatigue	168	26,12	24,47	22,22	0	100
Nausea / Vomiting	168	2,28	8,73	0,00	0	83,33
Pain	168	22,32	28,07	16,67	0	100
Dyspnea	167	15,97	24,77	0,00	0	100
Insomnia	168	23,61	29,49	0,00	0	100
Appetite loss	168	5,75	15,48	0,00	0	100
Constipation	168	10,52	21,93	0,00	0	100
Diarrhea	167	7,19	15,14	0,00	0	66,67
Financial difficulties	167	4,19	12,77	0,00	0	66,67
Global health and quality of life	166	70,38	23,58	75,00	0	100

Reduced frequency group	n	Mean	SD	median	min	max
Physical functioning	76	86,84	16,00	93,33	26,67	100
Role functioning	76	83,55	23,17	100,00	0	100
Emotional functioning	76	84,87	20,98	91,67	8,33	100
Cognitive functioning	76	89,04	18,17	100,00	16,67	100
Social functioning	76	86,84	22,66	100,00	0	100
Fatigue	76	24,71	25,05	22,22	0	88,89
Nausea / Vomiting	76	1,97	5,42	0,00	0	16,67
Pain	76	17,32	23,95	0,00	0	100
Dyspnea	75	16,44	23,49	0,00	0	100
Insomnia	76	21,93	30,58	0,00	0	100
Appetite loss	76	5,70	14,80	0,00	0	66,67
Constipation	76	10,53	21,23	0,00	0	100
Diarrhea	76	6,58	14,42	0,00	0	66,67
Financial difficulties	76	4,39	13,71	0,00	0	66,67
Global health and quality of life	76	71,05	24,21	79,17	0	100

Standard frequency group	n	Mean	SD	median	min	max

Physical functioning	91	85,20	18,24	86,67	20	100
Role functioning	92	76,63	28,82	91,67	0	100
Emotional functioning	91	81,14	20,41	83,33	16,67	100
Cognitive functioning	92	84,96	22,92	100,00	0	100
Social functioning	91	84,07	21,07	100,00	16,67	100
Fatigue	92	27,29	24,06	22,22	0	100
Nausea / Vomiting	92	2,54	10,75	0,00	0	83,33
Pain	92	26,45	30,58	16,67	0	100
Dyspnea	92	15,58	25,89	0,00	0	100
Insomnia	92	25,00	28,66	33,33	0	100
Appetite loss	92	5,80	16,10	0,00	0	100
Constipation	92	10,51	22,61	0,00	0	100
Diarrhea	91	7,69	15,77	0,00	0	66,67
Financial difficulties	91	4,03	12,00	0,00	0	66,67
Global health and quality of life	90	69,81	23,16	75,00	0	100

ICIQ-MLUTS

Scoring

It is scored on a scale from 0-20 for voiding symptoms and 0-24 for incontinence symptoms. The existing domain scores for each module were derived through statistical analysis that identifies the items that relate to each other to assess a common element. Therefore it is scientifically justified to use these to compare the condition of groups of patients over time. The part b for each question (which measures the degree of "bother" of a particular symptom by a particular patient) is not used in the scoring but it can be helpful in determining the patient's priority for treatment. (*from website: https://iciq.net/faq*)

MLUTS

2a. Is there a delay before you can start to urinate? (*Hesitancy*)
3a. Do you have to strain to continue urinating? (*Straining*)
4a. Would you say that the strength of your urinary stream is… (*Weak stream*)
5a. Do you stop and start more than once while you urinate? (*Intermittency*)
6a. How often do you feel that your bladder has not emptied properly after you have urinated? (*Feeling incomplete emptying*)
7a. Do you have a sudden need to rush to the toilet to urinate? (*Urgency*)
8a. Does urine leak before you can get to the toilet? (*Urge leakage*)
9a. Does urine leak when you cough or sneeze? (*Stress leakage*)
10a. Do you ever leak for no obvious reason and without feeling that you want to go? (*Leakage*)
11a. Do you leak urine when you are asleep? (*Nocturnal enuresis*)
12a. How often have you had a slight wetting of your pants a few minutes after you had finished urinating and had dressed yourself? (*Post micturition dribble*)
13a. How often do you pass urine during the day? (*Frequency*)
14a. During the night, how many times do you have to get up to urinate, on average? (*Nocturia*)

ICIQ-MLUTS Month 1 Week 1

MLUTS completed?	reduced	standard	Total
Yes	136 (96.5%)	138 (94.5%)	274 (95.5%)
No	5 (3.5%)	8 (5.5%)	13 (4.5%)
	141 (100%)	146 (100%)	287 (100%)

Total group	**n**	**Mean**	**SD**	**median**	**min**	**max**
Hesitancy	274	0,78	0,98	0	0	4
Bother hesitancy	269	1,44	2,35	0	0	10
Straining	274	0,72	0,94	0	0	4
Bother straining	269	1,26	2,16	0	0	10
Weak stream	273	1,27	1,31	1	0	4
Bother weak stream	270	1,83	2,41	1	0	10
Intermittency	273	0,99	0,95	1	0	4
Bother intermittency	268	1,34	2,08	0	0	10
Feeling incomplete emptying	274	1,02	1,01	1	0	4
Bother feeling incomplete emptying	269	1,58	2,31	1	0	10
Voiding Score	**273**	**4,76**	**3,64**	**4**	**0**	**17**
Urgency	274	1,61	1,18	2	0	4
Bother urgency	271	2,8	3,06	2	0	10
Urge leakage	274	0,76	0,95	0	0	4
Bother urge leakage	270	2,1	3,11	0	0	10
Stress leakage	274	0,19	0,58	0	0	4
Bother stress leakage	266	0,52	1,67	0	0	10
Leakage	272	0,33	0,75	0	0	4
Bother leakage	267	0,93	2,17	0	0	10
Nocturnal enuresis	273	0,18	0,61	0	0	4
Bother nocturnal enuresis	267	0,45	1,59	0	0	10
Post micturition dribble	273	0,63	0,83	0	0	4
Bother post micturition dribble	271	1,28	2,18	0	0	10
Incontinence Score	**272**	**3,71**	**3,54**	**3**	**0**	**24**
Frequency	273	1,15	1,20	1	0	4
Bother frequency	271	2,49	3,16	1	0	10
Nocturia	273	2,07	1,15	2	0	4
Bother nocturia	272	2,75	3,13	2	0	10

Reduced frequency group	n	Mean	SD	median	min	max
Hesitancy	136	0,82	1,02	0,5	0	4
Bother hesitancy	132	1,58	2,53	0	0	10
Straining	136	0,79	1,01	0	0	4
Bother straining	133	1,47	2,37	0	0	10
Weak stream	136	1,27	1,33	1	0	4
Bother weak stream	134	2,03	2,64	1	0	10
Intermittency	136	1	0,97	1	0	4
Bother intermittency	132	1,52	2,32	0	0	10
Feeling incomplete emptying	136	1,04	1,11	1	0	4
Bother feeling incomplete emptying	133	1,71	2,51	1	0	10
Voiding Score	**136**	**4,93**	**3,92**	**4**	**0**	**17**
Urgency	136	1,5	1,19	1	0	4
Bother urgency	134	2,54	3,04	1	0	10
Urge leakage	136	0,83	1,04	1	0	4
Bother urge leakage	133	2,15	3,19	0	0	10
Stress leakage	136	0,26	0,70	0	0	4
Bother stress leakage	131	0,76	2,05	0	0	10
Leakage	135	0,39	0,88	0	0	4
Bother leakage	131	1,17	2,54	0	0	10
Nocturnal enuresis	136	0,24	0,77	0	0	4
Bother nocturnal enuresis	131	0,69	2,06	0	0	10
Post micturition dribble	136	0,73	0,93	0	0	4
Bother post micturition dribble	134	1,6	2,55	0	0	10
Incontinence Score	**135**	**3,96**	**4,19**	**3**	**0**	**24**
Frequency	136	1,02	1,18	1	0	4
Bother frequency	133	2,29	3,08	1	0	10
Nocturia	136	2,05	1,15	2	0	4
Bother nocturia	134	2,69	3,11	2	0	10

Standard treatment group	**n**	**Mean**	**SD**	**median**	**min**	**max**
Hesitancy	138	0,73	0,93	0	0	4
Bother hesitancy	137	1,31	2,16	0	0	10
Straining	138	0,65	0,88	0	0	4
Bother straining	136	1,04	1,91	0	0	10
Weak stream	137	1,27	1,30	1	0	4
Bother weak stream	136	1,63	2,16	0,5	0	9
Intermittency	137	0,97	0,92	1	0	4
Bother intermittency	136	1,17	1,82	0	0	9
Feeling incomplete emptying	138	1,01	0,91	1	0	4
Bother feeling incomplete emptying	136	1,44	2,10	0,5	0	10
Voiding Score	**137**	**4,59**	**3,35**	**4**	**0**	**15**
Urgency	138	1,72	1,17	2	0	4
Bother urgency	137	3,07	3,06	2	0	10
Urge leakage	138	0,68	0,85	0	0	3
Bother urge leakage	137	2,05	3,05	0	0	10
Stress leakage	138	0,12	0,40	0	0	3
Bother stress leakage	135	0,29	1,15	0	0	9
Leakage	137	0,27	0,60	0	0	2
Bother leakage	136	0,69	1,71	0	0	9
Nocturnal enuresis	137	0,12	0,39	0	0	2
Bother nocturnal enuresis	136	0,22	0,88	0	0	8
Post micturition dribble	137	0,53	0,70	0	0	3
Bother post micturition dribble	137	0,96	1,69	0	0	8
Incontinence Score	**137**	**3,46**	**2,75**	**3**	**0**	**13**
Frequency	137	1,28	1,21	1	0	4
Bother frequency	138	2,68	3,23	1	0	10
Nocturia	137	2,09	1,16	2	0	4
Bother nocturia	138	2,8	3,16	1	0	10

ICIQ-MLUTS Month 2 Week 6

MLUTS completed?	reduced	standard	Total
Yes	124 (91.2%)	128 (88.9%)	252 (90%)
No	12 (8.8%)	16 (11.1%)	28 (10%)
	136 (100%)	144 (100%)	280 (100%)

Total group	**n**	**Mean**	**SD**	**median**	**min**	**max**
Hesitancy	252	0,66	0,81	0	0	4
Bother hesitancy	248	1,2	2,12	0	0	10
Straining	252	0,69	0,85	0	0	4
Bother straining	248	1,11	1,92	0	0	10
Weak stream	250	1,1	1,22	1	0	4
Bother weak stream	246	1,38	2,00	0	0	10
Intermittency	249	0,95	0,88	1	0	4
Bother intermittency	244	1,18	1,84	0	0	10
Feeling incomplete emptying	248	0,93	0,93	1	0	4
Bother feeling incomplete emptying	245	1,41	2,10	0	0	10
Voiding Score	**248**	**4,35**	**3,53**	**4**	**0**	**17**
Urgency	251	1,39	1,11	1	0	4
Bother urgency	246	2,45	2,85	1	0	10
Urge leakage	252	0,75	0,90	1	0	4
Bother urge leakage	246	1,82	2,81	0	0	10
Stress leakage	252	0,19	0,57	0	0	4
Bother stress leakage	247	0,46	1,56	0	0	10
Leakage	250	0,36	0,78	0	0	4
Bother leakage	244	0,88	2,08	0	0	10
Nocturnal enuresis	248	0,23	0,63	0	0	4
Bother nocturnal enuresis	242	0,61	1,84	0	0	10
Post micturition dribble	248	0,65	0,85	0	0	4
Bother post micturition dribble	244	1,31	2,22	0	0	10
Incontinence Score	**247**	**3,57**	**3,69**	**3**	**0**	**22**
Frequency	248	1,12	1,13	1	0	4
Bother frequency	244	2,19	2,97	1	0	10
Nocturia	248	2,08	1,21	2	0	4
Bother nocturia	246	2,57	3,08	1	0	10

Reduced frequency group	n	Mean	SD	median	min	max
Hesitancy	124	0,65	0,79	0	0	4
Bother hesitancy	120	1,28	2,28	0	0	10
Straining	124	0,75	0,92	0,5	0	4
Bother straining	120	1,27	2,24	0	0	10
Weak stream	124	1,16	1,23	1	0	4
Bother weak stream	121	1,45	2,07	0	0	10
Intermittency	124	0,93	0,87	1	0	3
Bother intermittency	120	1,15	1,85	0	0	10
Feeling incomplete emptying	123	0,96	0,98	1	0	4
Bother feeling incomplete emptying	120	1,51	2,21	0,5	0	10
Voiding Score	**123**	**4,48**	**3,63**	**4**	**0**	**14**
Urgency	124	1,27	1,11	1	0	4
Bother urgency	122	2,26	2,89	1	0	10
Urge leakage	124	0,74	0,97	0	0	4
Bother urge leakage	120	1,84	2,91	0	0	10
Stress leakage	124	0,27	0,74	0	0	4
Bother stress leakage	119	0,71	2,04	0	0	10
Leakage	124	0,4	0,91	0	0	4
Bother leakage	119	1,12	2,56	0	0	10
Nocturnal enuresis	124	0,23	0,65	0	0	4
Bother nocturnal enuresis	119	0,65	2,01	0	0	10
Post micturition dribble	124	0,73	0,89	1	0	4
Bother post micturition dribble	120	1,5	2,47	0	0	10
Incontinence Score	**124**	**3,64**	**4,24**	**2**	**0**	**22**
Frequency	122	1,03	1,04	1	0	4
Bother frequency	119	1,98	3,01	0	0	10
Nocturia	122	1,93	1,20	2	0	4
Bother nocturia	120	2,49	3,03	1	0	10

Standard treatment group	n	Mean	SD	median	min	max
Hesitancy	128	0,66	0,84	0	0	4
Bother hesitancy	128	1,13	1,97	0	0	9
Straining	128	0,63	0,77	0	0	3
Bother straining	128	0,97	1,57	0	0	8
Weak stream	126	1,04	1,21	1	0	4
Bother weak stream	125	1,3	1,93	0	0	8
Intermittency	125	0,98	0,90	1	0	4
Bother intermittency	124	1,22	1,83	0	0	9
Feeling incomplete emptying	125	0,9	0,88	1	0	4
Bother feeling incomplete emptying	125	1,32	1,98	0	0	9
Voiding Score	**125**	**4,22**	**3,44**	**3**	**0**	**17**
Urgency	127	1,51	1,09	1	0	4
Bother urgency	124	2,63	2,80	2	0	10
Urge leakage	128	0,76	0,83	1	0	3
Bother urge leakage	126	1,79	2,73	0	0	10
Stress leakage	128	0,1	0,33	0	0	2
Bother stress leakage	128	0,23	0,87	0	0	8
Leakage	126	0,33	0,62	0	0	2
Bother leakage	125	0,65	1,47	0	0	9
Nocturnal enuresis	124	0,23	0,62	0	0	4
Bother nocturnal enuresis	123	0,58	1,67	0	0	9
Post micturition dribble	124	0,58	0,81	0	0	4
Bother post micturition dribble	124	1,12	1,94	0	0	10
Incontinence Score	**123**	**3,51**	**3,05**	**3**	**0**	**14**
Frequency	126	1,2	1,20	1	0	4
Bother frequency	125	2,39	2,94	1	0	10
Nocturia	126	2,21	1,21	2	0	4
Bother nocturia	126	2,65	3,13	2	0	10

ICIQ-MLUTS Month 3 Week 1

MLUTS completed?	reduced	standard	Total
Yes	106 (83.5%)	113 (82.5%)	219 (83%)
No	21 (16.5%)	24 (17.5%)	45 (17%)
	127 (100%)	137 (100%)	264 (100%)

Total group	**n**	**Mean**	**SD**	**median**	**min**	**max**
Hesitancy	219	0,81	0,83	1	0	4
Bother hesitancy	216	1,17	1,91	0	0	10
Straining	218	0,72	0,89	0,5	0	4
Bother straining	216	1,19	1,95	0	0	10
Weak stream	219	1,11	1,25	1	0	4
Bother weak stream	218	1,49	2,13	0	0	10
Intermittency	218	0,95	0,82	1	0	4
Bother intermittency	215	1,29	1,82	1	0	10
Feeling incomplete emptying	218	0,99	0,92	1	0	4
Bother feeling incomplete emptying	218	1,53	2,12	1	0	10
Voiding Score	**217**	**4,59**	**3,62**	**4**	**0**	**19**
Urgency	217	1,17	1,03	1	0	4
Bother urgency	216	2	2,62	1	0	10
Urge leakage	217	0,66	0,86	0	0	4
Bother urge leakage	215	1,53	2,53	0	0	10
Stress leakage	217	0,23	0,61	0	0	4
Bother stress leakage	214	0,57	1,59	0	0	10
Leakage	218	0,35	0,74	0	0	4
Bother leakage	215	0,8	1,79	0	0	10
Nocturnal enuresis	218	0,22	0,61	0	0	4
Bother nocturnal enuresis	215	0,61	1,76	0	0	10
Post micturition dribble	218	0,68	0,83	0,5	0	4
Bother post micturition dribble	217	1,33	2,18	0	0	10
Incontinence Score	**217**	**3,31**	**3,60**	**2**	**0**	**20**
Frequency	215	1,02	1,06	1	0	4
Bother frequency	215	1,92	2,59	1	0	10
Nocturia	217	1,89	1,12	2	0	4
Bother nocturia	216	2,19	2,70	1	0	10

Reduced frequency group	n	Mean	SD	median	min	max
Hesitancy	106	0,84	0,86	1	0	4
Bother hesitancy	106	1,24	1,95	0	0	10
Straining	105	0,73	0,93	0	0	4
Bother straining	106	1,23	2,03	0	0	10
Weak stream	106	1,12	1,33	1	0	4
Bother weak stream	106	1,53	2,23	0	0	10
Intermittency	106	0,93	0,80	1	0	4
Bother intermittency	106	1,32	1,89	1	0	10
Feeling incomplete emptying	106	1,08	0,95	1	0	4
Bother feeling incomplete emptying	106	1,7	2,31	1	0	10
Voiding Score	**105**	**4,73**	**3,79**	**4**	**0**	**16**
Urgency	106	1,18	1,09	1	0	4
Bother urgency	106	2,01	2,84	1	0	10
Urge leakage	106	0,73	0,99	0	0	4
Bother urge leakage	105	1,69	2,82	0	0	10
Stress leakage	106	0,33	0,78	0	0	4
Bother stress leakage	106	0,79	1,96	0	0	10
Leakage	106	0,38	0,82	0	0	4
Bother leakage	106	0,94	2,02	0	0	10
Nocturnal enuresis	106	0,29	0,74	0	0	4
Bother nocturnal enuresis	106	0,75	2,09	0	0	10
Post micturition dribble	106	0,72	0,86	1	0	4
Bother post micturition dribble	106	1,44	2,33	0,5	0	10
Incontinence Score	**106**	**3,62**	**4,29**	**2**	**0**	**20**
Frequency	104	1,06	1,04	1	0	4
Bother frequency	104	1,97	2,74	1	0	10
Nocturia	104	1,99	1,22	2	0	4
Bother nocturia	104	2,21	2,83	1	0	10

Standard treatment group	**n**	**Mean**	**SD**	**median**	**min**	**max**
Hesitancy	113	0,78	0,80	1	0	4
Bother hesitancy	110	1,11	1,89	0	0	10
Straining	113	0,7	0,84	1	0	4
Bother straining	110	1,16	1,88	0	0	10
Weak stream	113	1,11	1,17	1	0	4
Bother weak stream	112	1,46	2,05	1	0	10
Intermittency	112	0,96	0,85	1	0	3
Bother intermittency	109	1,27	1,76	1	0	10
Feeling incomplete emptying	112	0,89	0,88	1	0	4
Bother feeling incomplete emptying	112	1,37	1,91	1	0	10
Voiding Score	**112**	**4,46**	**3,46**	**4**	**0**	**19**
Urgency	111	1,16	0,97	1	0	4
Bother urgency	110	1,99	2,40	1	0	10
Urge leakage	111	0,59	0,72	0	0	3
Bother urge leakage	110	1,39	2,22	0	0	9
Stress leakage	111	0,14	0,37	0	0	2
Bother stress leakage	108	0,34	1,08	0	0	8
Leakage	112	0,32	0,66	0	0	4
Bother leakage	109	0,65	1,54	0	0	10
Nocturnal enuresis	112	0,15	0,43	0	0	2
Bother nocturnal enuresis	109	0,47	1,35	0	0	9
Post micturition dribble	112	0,64	0,80	0	0	3
Bother post micturition dribble	111	1,22	2,03	0	0	9
Incontinence Score	**111**	**3,02**	**2,77**	**2**	**0**	**14**
Frequency	111	0,98	1,08	1	0	4
Bother frequency	111	1,86	2,45	1	0	10
Nocturia	113	1,8	1,02	2	0	4
Bother nocturia	112	2,16	2,58	1	0	10

ICIQ-MLUTS Month 3 Week 3

MLUTS completed?	reduced	standard	Total
Yes	99 (92.5%)	99 (83.2%)	198 (87.6%)
No	8 (7.5%)	20 (16.8%)	28 (12.4%)
	107 (1000%)	119 (100%)	226 (100%)

Total group	n	Mean	SD	median	min	max
Hesitancy	198	0,73	0,77	1	0	4
Bother hesitancy	191	1,1	1,69	0	0	10
Straining	198	0,75	0,95	1	0	4
Bother straining	192	1,14	1,74	0	0	10
Weak stream	198	1,25	1,23	1	0	4
Bother weak stream	192	1,44	2,04	0	0	10
Intermittency	197	0,99	0,87	1	0	4
Bother intermittency	192	1,2	1,74	0	0	10
Feeling incomplete emptying	196	1,01	0,94	1	0	4
Bother feeling incomplete emptying	193	1,45	1,90	1	0	10
Voiding Score	**196**	**4,71**	**3,65**	**4**	**0**	**20**
Urgency	197	1,27	1,01	1	0	4
Bother urgency	195	2,17	2,61	1	0	10
Urge leakage	197	0,63	0,83	0	0	4
Bother urge leakage	196	1,45	2,32	0	0	10
Stress leakage	198	0,22	0,61	0	0	4
Bother stress leakage	191	0,58	1,64	0	0	10
Leakage	198	0,39	0,79	0	0	4
Bother leakage	193	0,97	2,09	0	0	10
Nocturnal enuresis	197	0,22	0,68	0	0	4
Bother nocturnal enuresis	190	0,58	1,77	0	0	10
Post micturition dribble	197	0,66	0,78	1	0	4
Bother post micturition dribble	193	1,32	2,20	0	0	10
Incontinence Score	**196**	**3,41**	**3,61**	**2**	**0**	**21**
Frequency	195	1,09	1,07	1	0	4
Bother frequency	193	1,96	2,59	1	0	10
Nocturia	194	2,02	1,17	2	0	4
Bother nocturia	193	2,06	2,61	1	0	10

Reduced frequency group	n	Mean	SD	median	min	max
Hesitancy	99	0,84	0,83	1	0	4
Bother hesitancy	96	1,33	1,97	0	0	10
Straining	99	0,82	1,05	1	0	4
Bother straining	95	1,37	2,07	0	0	10
Weak stream	99	1,26	1,37	1	0	4
Bother weak stream	96	1,49	2,24	0	0	10
Intermittency	99	1,05	0,89	1	0	4
Bother intermittency	96	1,42	1,92	1	0	10
Feeling incomplete emptying	99	1,12	1,02	1	0	4
Bother feeling incomplete emptying	96	1,7	2,14	1	0	10
Voiding Score	**99**	**5,09**	**4,13**	**5**	**0**	**20**
Urgency	99	1,16	1,00	1	0	4
Bother urgency	97	2,05	2,66	1	0	10
Urge leakage	98	0,71	0,94	0	0	4
Bother urge leakage	97	1,66	2,63	0	0	10
Stress leakage	99	0,32	0,78	0	0	4
Bother stress leakage	96	0,91	2,06	0	0	10
Leakage	99	0,47	0,91	0	0	4
Bother leakage	97	1,24	2,41	0	0	10
Nocturnal enuresis	99	0,27	0,78	0	0	4
Bother nocturnal enuresis	96	0,79	2,21	0	0	10
Post micturition dribble	99	0,74	0,86	1	0	4
Bother post micturition dribble	96	1,56	2,52	0,5	0	10
Incontinence Score	**98**	**3,69**	**4,30**	**2,5**	**0**	**21**
Frequency	97	0,98	0,99	1	0	4
Bother frequency	95	2,07	2,83	1	0	10
Nocturia	95	2,02	1,22	2	0	4
Bother nocturia	94	2,12	2,77	1	0	10

Standard treatment group	n	Mean	SD	median	min	max
Hesitancy	99	0,62	0,70	1	0	3
Bother hesitancy	95	0,87	1,32	0	0	5
Straining	99	0,69	0,83	1	0	4
Bother straining	97	0,92	1,31	0	0	6
Weak stream	99	1,24	1,09	1	0	4
Bother weak stream	96	1,39	1,83	0	0	7
Intermittency	98	0,93	0,85	1	0	4
Bother intermittency	96	0,99	1,53	0	0	7
Feeling incomplete emptying	97	0,89	0,83	1	0	4
Bother feeling incomplete emptying	97	1,2	1,61	0	0	7
Voiding Score	**97**	**4,32**	**3,04**	**4**	**0**	**14**
Urgency	98	1,38	1,01	1	0	4
Bother urgency	98	2,29	2,57	1	0	10
Urge leakage	99	0,56	0,69	0	0	3
Bother urge leakage	99	1,24	1,95	0	0	8
Stress leakage	99	0,11	0,35	0	0	2
Bother stress leakage	95	0,24	0,95	0	0	8
Leakage	99	0,31	0,63	0	0	4
Bother leakage	96	0,7	1,69	0	0	10
Nocturnal enuresis	98	0,17	0,56	0	0	4
Bother nocturnal enuresis	94	0,36	1,13	0	0	8
Post micturition dribble	98	0,58	0,69	0	0	3
Bother post micturition dribble	97	1,07	1,82	0	0	8
Incontinence Score	**98**	**3,12**	**2,73**	**2**	**0**	**14**
Frequency	98	1,2	1,13	1	0	4
Bother frequency	98	1,85	2,34	1	0	10
Nocturia	99	2,02	1,13	2	0	4
Bother nocturia	99	2,01	2,47	1	0	10

ICIQ-MLUTS Month 6 Week 1

MLUTS completed?	reduced	standard	Total
Yes	87 (87%)	105 (92.1%)	192 (89.7%)
No	13 (13%)	9 (7.9%)	22 (10.3%)
	100 (100%)	114 (100%)	214 (100%)

Total group	n	Mean	SD	median	min	max
Hesitancy	192	0,75	0,77	1	0	3
Bother hesitancy	190	1,04	1,62	0	0	7
Straining	192	0,71	0,89	0	0	4
Bother straining	191	1,05	1,72	0	0	10
Weak stream	192	1,16	1,23	1	0	4
Bother weak stream	192	1,31	2,06	0	0	10
Intermittency	191	0,92	0,85	1	0	4
Bother intermittency	191	1,04	1,55	0	0	8
Feeling incomplete emptying	191	0,95	0,85	1	0	4
Bother feeling incomplete emptying	190	1,23	1,74	0	0	10
Voiding Score	**191**	**4,49**	**3,38**	**4**	**0**	**14**
Urgency	190	1,13	1,01	1	0	4
Bother urgency	191	1,82	2,33	1	0	10
Urge leakage	192	0,58	0,73	0	0	4
Bother urge leakage	192	1,42	2,24	0	0	10
Stress leakage	192	0,23	0,55	0	0	4
Bother stress leakage	192	0,5	1,32	0	0	10
Leakage	192	0,32	0,60	0	0	2
Bother leakage	191	0,76	1,66	0	0	10
Nocturnal enuresis	191	0,17	0,49	0	0	3
Bother nocturnal enuresis	188	0,47	1,43	0	0	10
Post micturition dribble	191	0,64	0,80	0	0	4
Bother post micturition dribble	190	1,24	1,94	0	0	10
Incontinence Score	**190**	**3,09**	**3,15**	**2**	**0**	**18**
Frequency	191	0,97	1,00	1	0	4
Bother frequency	191	1,58	2,19	1	0	10
Nocturia	192	1,87	1,08	2	0	4
Bother nocturia	192	2,01	2,39	1	0	10

Reduced frequency group	n	Mean	SD	median	min	max
Hesitancy	87	0,84	0,83	1	0	3
Bother hesitancy	86	1,15	1,59	0	0	5
Straining	87	0,71	0,89	0	0	4
Bother straining	86	1,16	1,90	0	0	10
Weak stream	87	1,18	1,34	1	0	4
Bother weak stream	87	1,4	2,22	0	0	10
Intermittency	87	0,93	0,89	1	0	4
Bother intermittency	87	1,1	1,68	0	0	8
Feeling incomplete emptying	87	1,02	0,93	1	0	4
Bother feeling incomplete emptying	87	1,37	1,96	1	0	10
Voiding Score	**87**	**4,69**	**3,63**	**4**	**0**	**14**
Urgency	86	1,07	1,10	1	0	4
Bother urgency	87	1,82	2,60	1	0	10
Urge leakage	87	0,6	0,80	0	0	4
Bother urge leakage	87	1,45	2,37	0	0	10
Stress leakage	87	0,31	0,69	0	0	4
Bother stress leakage	87	0,71	1,75	0	0	10
Leakage	87	0,33	0,64	0	0	2
Bother leakage	87	0,9	1,95	0	0	10
Nocturnal enuresis	87	0,21	0,57	0	0	3
Bother nocturnal enuresis	86	0,62	1,79	0	0	10
Post micturition dribble	87	0,71	0,89	0	0	4
Bother post micturition dribble	87	1,31	2,11	0	0	10
Incontinence Score	**86**	**3,26**	**3,72**	**2**	**0**	**18**
Frequency	87	0,91	1,04	1	0	4
Bother frequency	87	1,71	2,51	1	0	10
Nocturia	87	1,8	1,12	2	0	4
Bother nocturia	87	1,95	2,47	1	0	10

Standard treatment group	**n**	**Mean**	**SD**	**median**	**min**	**max**
Hesitancy	105	0,68	0,71	1	0	2
Bother hesitancy	104	0,94	1,64	0	0	7
Straining	105	0,7	0,89	0	0	4
Bother straining	105	0,95	1,57	0	0	6
Weak stream	105	1,14	1,14	1	0	4
Bother weak stream	105	1,24	1,92	0	0	9
Intermittency	104	0,9	0,82	1	0	3
Bother intermittency	104	0,98	1,44	0	0	6
Feeling incomplete emptying	104	0,89	0,79	1	0	3
Bother feeling incomplete emptying	103	1,12	1,54	0	0	7
Voiding Score	**104**	**4,32**	**3,15**	**4**	**0**	**12**
Urgency	104	1,17	0,92	1	0	4
Bother urgency	104	1,82	2,10	1	0	7
Urge leakage	105	0,57	0,68	0	0	2
Bother urge leakage	105	1,39	2,13	0	0	8
Stress leakage	105	0,16	0,40	0	0	2
Bother stress leakage	105	0,32	0,78	0	0	4
Leakage	105	0,3	0,57	0	0	2
Bother leakage	104	0,64	1,37	0	0	7
Nocturnal enuresis	104	0,14	0,40	0	0	2
Bother nocturnal enuresis	102	0,34	1,03	0	0	7
Post micturition dribble	104	0,59	0,72	0	0	2
Bother post micturition dribble	103	1,18	1,80	0	0	8
Incontinence Score	**104**	**2,95**	**2,59**	**2**	**0**	**11**
Frequency	104	1,02	0,97	1	0	4
Bother frequency	104	1,46	1,90	1	0	7
Nocturia	105	1,92	1,04	2	0	4
Bother nocturia	105	2,05	2,32	1	0	10

ICIQ-MLUTS Month 6 Week 3

MLUTS completed?	reduced	standard	Total
Yes	88 (92.6%)	98 (89.1%)	186 (90.7%)
No	7 (7.4%)	12 (10.9%)	19 (9.3%)
	95 (100%)	110 (100%)	205 (100%)

Total group	**n**	**Mean**	**SD**	**median**	**min**	**max**
Hesitancy	186	0,79	0,82	1	0	3
Bother hesitancy	183	1,05	1,66	0	0	8
Straining	186	0,82	0,87	1	0	4
Bother straining	184	1,21	1,88	0	0	10
Weak stream	185	1,24	1,26	1	0	4
Bother weak stream	185	1,46	2,06	0	0	9
Intermittency	185	1,04	0,87	1	0	4
Bother intermittency	185	1,25	1,79	1	0	8
Feeling incomplete emptying	185	1,06	0,97	1	0	4
Bother feeling incomplete emptying	185	1,44	1,96	1	0	10
Voiding Score	**185**	**4,96**	**3,66**	**4**	**0**	**15**
Urgency	185	1,29	1,03	1	0	4
Bother urgency	186	2,12	2,52	1	0	10
Urge leakage	186	0,63	0,78	0	0	4
Bother urge leakage	184	1,51	2,32	0	0	10
Stress leakage	186	0,27	0,64	0	0	4
Bother stress leakage	184	0,52	1,40	0	0	10
Leakage	185	0,39	0,73	0	0	4
Bother leakage	184	0,89	1,85	0	0	10
Nocturnal enuresis	185	0,26	0,67	0	0	4
Bother nocturnal enuresis	183	0,55	1,46	0	0	10
Post micturition dribble	185	0,68	0,81	1	0	4
Bother post micturition dribble	185	1,25	1,95	0	0	10
Incontinence Score	**184**	**3,54**	**3,41**	**3**	**0**	**23**
Frequency	185	1,34	1,20	1	0	4
Bother frequency	184	2,22	2,66	1	0	10
Nocturia	184	2,13	1,25	2	0	4
Bother nocturia	185	2,43	2,71	2	0	10

Reduced frequency group	n	Mean	SD	median	min	max
Hesitancy	88	0,85	0,88	1	0	3
Bother hesitancy	85	1,24	1,99	0	0	8
Straining	88	0,89	0,95	1	0	4
Bother straining	86	1,43	2,15	0	0	10
Weak stream	88	1,25	1,41	1	0	4
Bother weak stream	88	1,65	2,22	1	0	8
Intermittency	88	1,09	0,89	1	0	4
Bother intermittency	88	1,44	1,98	1	0	8
Feeling incomplete emptying	88	1,15	1,12	1	0	4
Bother feeling incomplete emptying	88	1,57	2,21	1	0	10
Voiding Score	**88**	**5,23**	**4,07**	**4**	**0**	**15**
Urgency	87	1,16	1,03	1	0	4
Bother urgency	88	1,93	2,56	1	0	10
Urge leakage	88	0,67	0,88	0	0	4
Bother urge leakage	86	1,58	2,46	0	0	10
Stress leakage	88	0,36	0,79	0	0	4
Bother stress leakage	87	0,74	1,83	0	0	10
Leakage	87	0,46	0,85	0	0	4
Bother leakage	86	1,05	2,10	0	0	10
Nocturnal enuresis	87	0,31	0,75	0	0	4
Bother nocturnal enuresis	86	0,72	1,80	0	0	10
Post micturition dribble	87	0,78	0,91	1	0	4
Bother post micturition dribble	87	1,46	2,17	1	0	10
Incontinence Score	**86**	**3,8**	**4,12**	**2,5**	**0**	**23**
Frequency	87	1,2	1,17	1	0	4
Bother frequency	86	2,2	2,93	1	0	10
Nocturia	87	1,91	1,26	2	0	4
Bother nocturia	87	2,36	2,94	1	0	10

Standard treatment group	n	Mean	SD	median	min	max
Hesitancy	98	0,73	0,75	1	0	3
Bother hesitancy	98	0,89	1,30	0	0	5
Straining	98	0,76	0,79	1	0	3
Bother straining	98	1,01	1,60	0	0	8
Weak stream	97	1,24	1,13	1	0	4
Bother weak stream	97	1,3	1,91	0	0	9
Intermittency	97	1	0,85	1	0	3
Bother intermittency	97	1,08	1,58	0	0	8
Feeling incomplete emptying	97	0,98	0,80	1	0	3
Bother feeling incomplete emptying	97	1,32	1,71	1	0	8
Voiding Score	**97**	**4,71**	**3,25**	**4**	**0**	**13**
Urgency	98	1,4	1,01	1	0	4
Bother urgency	98	2,29	2,49	2	0	10
Urge leakage	98	0,59	0,67	0	0	2
Bother urge leakage	98	1,45	2,21	0	0	8
Stress leakage	98	0,18	0,44	0	0	2
Bother stress leakage	97	0,32	0,81	0	0	5
Leakage	98	0,34	0,61	0	0	2
Bother leakage	98	0,74	1,60	0	0	8
Nocturnal enuresis	98	0,21	0,58	0	0	4
Bother nocturnal enuresis	97	0,39	1,07	0	0	7
Post micturition dribble	98	0,59	0,70	0	0	3
Bother post micturition dribble	98	1,07	1,73	0	0	8
Incontinence Score	**98**	**3,32**	**2,63**	**3**	**0**	**10**
Frequency	98	1,46	1,22	1	0	4
Bother frequency	98	2,23	2,40	1,5	0	10
Nocturia	97	2,33	1,21	2	0	4
Bother nocturia	98	2,49	2,49	2	0	10

ICIQ-MLUTS Month 12 Week 1

MLUTS completed?	reduced	standard	Total
Yes	63 (86.3%)	75 (85.2%)	138 (85.7%)
No	10 (13.7%)	13 (14.8%)	23 (14.3%)
	73 (100%)	88 (100%)	161 (100%)

Total group	n	Mean	SD	median	min	max
Hesitancy	138	0,75	0,83	1	0	3
Bother hesitancy	135	0,95	1,74	0	0	10
Straining	138	0,64	0,79	0	0	3
Bother straining	134	0,96	1,54	0	0	8
Weak stream	138	1,12	1,22	1	0	4
Bother weak stream	134	1,33	2,03	0	0	10
Intermittency	138	0,93	0,79	1	0	4
Bother intermittency	135	1,1	1,62	0	0	8
Feeling incomplete emptying	138	0,93	0,89	1	0	4
Bother feeling incomplete emptying	136	1,28	1,94	0	0	10
Voiding Score	**138**	**4,38**	**3,56**	**4**	**0**	**15**
Urgency	137	1,02	0,92	1	0	4
Bother urgency	136	1,57	2,21	1	0	10
Urge leakage	136	0,49	0,69	0	0	3
Bother urge leakage	133	1,17	2,14	0	0	10
Stress leakage	136	0,26	0,61	0	0	4
Bother stress leakage	132	0,52	1,42	0	0	10
Leakage	136	0,32	0,66	0	0	4
Bother leakage	133	0,71	1,82	0	0	10
Nocturnal enuresis	137	0,23	0,61	0	0	3
Bother nocturnal enuresis	133	0,6	1,73	0	0	10
Post micturition dribble	137	0,63	0,74	0	0	4
Bother post micturition dribble	135	1,15	1,88	0	0	9
Incontinence Score	**135**	**2,97**	**3,23**	**2**	**0**	**18**
Frequency	137	1,07	1,12	1	0	4
Bother frequency	135	1,67	2,42	1	0	10
Nocturia	138	1,8	1,19	2	0	4
Bother nocturia	136	1,99	2,65	1	0	10

Reduced frequency group	n	Mean	SD	median	min	max
Hesitancy	63	0,76	0,89	1	0	3
Bother hesitancy	63	1,02	1,87	0	0	8
Straining	63	0,68	0,91	0	0	3
Bother straining	62	1,13	1,92	0	0	8
Weak stream	63	1,16	1,35	1	0	4
Bother weak stream	62	1,53	2,27	0	0	9
Intermittency	63	1	0,84	1	0	4
Bother intermittency	63	1,38	1,92	0	0	8
Feeling incomplete emptying	63	1,02	1,01	1	0	4
Bother feeling incomplete emptying	63	1,6	2,35	0	0	10
Voiding Score	**63**	**4,62**	**3,94**	**4**	**0**	**15**
Urgency	62	1	1,01	1	0	4
Bother urgency	63	1,65	2,53	0	0	10
Urge leakage	63	0,51	0,74	0	0	3
Bother urge leakage	63	1,27	2,32	0	0	10
Stress leakage	63	0,3	0,75	0	0	4
Bother stress leakage	62	0,69	1,86	0	0	10
Leakage	63	0,35	0,79	0	0	4
Bother leakage	62	0,76	2,08	0	0	10
Nocturnal enuresis	63	0,25	0,65	0	0	3
Bother nocturnal enuresis	62	0,71	2,03	0	0	10
Post micturition dribble	63	0,71	0,83	1	0	4
Bother post micturition dribble	63	1,44	2,20	0	0	9
Incontinence Score	**62**	**3,16**	**3,80**	**2**	**0**	**18**
Frequency	63	1,05	1,11	1	0	4
Bother frequency	63	1,86	2,72	1	0	10
Nocturia	63	1,71	1,21	1	0	4
Bother nocturia	63	2,32	2,98	1	0	10

Standard treatment group	**n**	**Mean**	**SD**	**median**	**min**	**max**
Hesitancy	75	0,75	0,77	1	0	3
Bother hesitancy	72	0,89	1,62	0	0	10
Straining	75	0,61	0,68	1	0	2
Bother straining	72	0,81	1,11	0	0	4
Weak stream	75	1,08	1,11	1	0	4
Bother weak stream	72	1,15	1,80	0	0	10
Intermittency	75	0,88	0,75	1	0	3
Bother intermittency	72	0,85	1,25	0	0	4
Feeling incomplete emptying	75	0,85	0,78	1	0	3
Bother feeling incomplete emptying	73	1	1,44	0	0	7
Voiding Score	**75**	**4,17**	**3,22**	**4**	**0**	**12**
Urgency	75	1,04	0,85	1	0	4
Bother urgency	73	1,49	1,90	1	0	8
Urge leakage	73	0,48	0,65	0	0	2
Bother urge leakage	70	1,07	1,99	0	0	8
Stress leakage	73	0,23	0,46	0	0	2
Bother stress leakage	70	0,37	0,84	0	0	3
Leakage	73	0,29	0,54	0	0	2
Bother leakage	71	0,68	1,57	0	0	7
Nocturnal enuresis	74	0,2	0,57	0	0	3
Bother nocturnal enuresis	71	0,51	1,43	0	0	7
Post micturition dribble	74	0,55	0,64	0	0	2
Bother post micturition dribble	72	0,89	1,53	0	0	6
Incontinence Score	**73**	**2,81**	**2,68**	**2**	**0**	**10**
Frequency	74	1,09	1,14	1	0	4
Bother frequency	72	1,51	2,13	1	0	8
Nocturia	75	1,87	1,17	2	0	4
Bother nocturia	73	1,7	2,31	1	0	9

ICIQ-MLUTS Month 12 Week 3

MLUTS completed?	reduced	standard	Total
Yes	61 (91%)	72 (86.7%)	133 (88.7%)
No	6 (9%)	11 (13.3%)	17 (11.3%)
	67 (100%)	83 (100%)	150 (100%)

Total group	n	Mean	SD	median	min	max
Hesitancy	133	0,78	0,84	1	0	4
Bother hesitancy	130	1,08	1,82	0	0	8
Straining	133	0,72	0,83	1	0	3
Bother straining	130	1,09	1,88	0	0	10
Weak stream	133	1,17	1,19	1	0	4
Bother weak stream	131	1,45	2,15	0	0	10
Intermittency	132	1,05	0,85	1	0	4
Bother intermittency	130	1,34	1,92	1	0	10
Feeling incomplete emptying	132	0,97	0,83	1	0	3
Bother feeling incomplete emptying	129	1,4	2,00	1	0	10
Voiding Score	**132**	**4,7**	**3,59**	**5**	**0**	**16**
Urgency	132	1,23	1,03	1	0	4
Bother urgency	131	2,02	2,50	1	0	10
Urge leakage	132	0,57	0,72	0	0	3
Bother urge leakage	130	1,29	2,02	0	0	10
Stress leakage	132	0,26	0,63	0	0	4
Bother stress leakage	130	0,59	1,45	0	0	10
Leakage	132	0,33	0,61	0	0	4
Bother leakage	130	0,73	1,73	0	0	10
Nocturnal enuresis	133	0,29	0,64	0	0	3
Bother nocturnal enuresis	130	0,65	1,67	0	0	10
Post micturition dribble	133	0,62	0,69	1	0	3
Bother post micturition dribble	132	1,14	1,82	0	0	10
Incontinence Score	**132**	**3,3**	**3,37**	**2**	**0**	**18**
Frequency	133	1,31	1,23	1	0	4
Bother frequency	131	2,13	2,72	1	0	10
Nocturia	133	2,08	1,17	2	0	4
Bother nocturia	132	2,34	2,71	1	0	10

Reduced frequency group	n	Mean	SD	median	min	max
Hesitancy	61	0,72	0,82	1	0	3
Bother hesitancy	59	1	1,98	0	0	8
Straining	61	0,72	0,90	0	0	3
Bother straining	59	1,27	2,46	0	0	10
Weak stream	61	1,13	1,31	1	0	4
Bother weak stream	60	1,43	2,49	0	0	10
Intermittency	60	1,07	0,97	1	0	4
Bother intermittency	59	1,36	2,26	0	0	10
Feeling incomplete emptying	60	1	0,92	1	0	3
Bother feeling incomplete emptying	58	1,57	2,41	0	0	10
Voiding Score	**60**	**4,65**	**4,13**	**4**	**0**	**16**
Urgency	60	0,97	1,03	1	0	4
Bother urgency	59	1,64	2,62	0	0	10
Urge leakage	60	0,5	0,73	0	0	3
Bother urge leakage	59	1,17	2,19	0	0	10
Stress leakage	60	0,32	0,75	0	0	4
Bother stress leakage	59	0,68	1,82	0	0	10
Leakage	60	0,28	0,72	0	0	4
Bother leakage	59	0,63	1,83	0	0	10
Nocturnal enuresis	61	0,28	0,64	0	0	3
Bother nocturnal enuresis	59	0,64	1,82	0	0	10
Post micturition dribble	61	0,66	0,79	0	0	3
Bother post micturition dribble	60	1,13	2,02	0	0	10
Incontinence Score	**60**	**3**	**3,86**	**2**	**0**	**18**
Frequency	61	1,05	1,09	1	0	4
Bother frequency	60	2,02	2,91	0,5	0	10
Nocturia	61	1,85	1,15	2	0	4
Bother nocturia	60	2,42	2,93	1	0	10

Standard treatment group	**n**	**Mean**	**SD**	**median**	**min**	**max**
Hesitancy	72	0,83	0,86	1	0	4
Bother hesitancy	71	1,15	1,68	1	0	8
Straining	72	0,72	0,77	1	0	3
Bother straining	71	0,94	1,22	0	0	6
Weak stream	72	1,21	1,09	1	0	4
Bother weak stream	71	1,46	1,84	1	0	8
Intermittency	72	1,04	0,74	1	0	3
Bother intermittency	71	1,32	1,60	1	0	8
Feeling incomplete emptying	72	0,94	0,75	1	0	3
Bother feeling incomplete emptying	71	1,25	1,58	1	0	8
Voiding Score	**72**	**4,75**	**3,10**	**5**	**0**	**13**
Urgency	72	1,46	0,99	1	0	4
Bother urgency	72	2,33	2,36	2	0	9
Urge leakage	72	0,63	0,72	0	0	2
Bother urge leakage	71	1,39	1,87	1	0	8
Stress leakage	72	0,21	0,50	0	0	2
Bother stress leakage	71	0,52	1,04	0	0	4
Leakage	72	0,36	0,51	0	0	2
Bother leakage	71	0,82	1,65	0	0	8
Nocturnal enuresis	72	0,29	0,64	0	0	3
Bother nocturnal enuresis	71	0,65	1,54	0	0	7
Post micturition dribble	72	0,6	0,60	1	0	2
Bother post micturition dribble	72	1,15	1,65	0	0	8
Incontinence Score	**72**	**3,54**	**2,91**	**3**	**0**	**11**
Frequency	72	1,53	1,30	1	0	4
Bother frequency	71	2,23	2,56	2	0	10
Nocturia	72	2,28	1,15	2	0	4
Bother nocturia	72	2,28	2,52	1	0	10

ICIQ-FLUTS

Scoring

It is scored on a scale from 0-16 for symptoms of filling, 0-12 for voiding symptoms and 0-20 for incontinence symptoms. The existing domain scores for each module were derived through statistical analysis that identifies the items that relate to each other to assess a common element. Therefore it is scientifically justified to use these to compare the condition of groups of patients over time. The part b for each question (which measures the degree of "bother" of a particular symptom by a particular patient) is not used in the scoring but it can be helpful in determining the patient's priority for treatment. (*from website: https://iciq.net/faq*)

FLUTS

2a. During the night, how many times do you have to get up to urinate, on average? (*Nocturia*)
3a. Do you have a sudden need to rush to the toilet to urinate? (*Urgency*)
4a. Do you have pain in your bladder? (*Bladder pain*)
5a. How often do you pass urine during the day? (*Frequency*)
6a. Is there a delay before you can start to urinate? (*Hesitancy*)
7a. Do you have to strain to urinate? (*Straining*)
8a. Do you stop and start more than once while you urinate? (*Intermittency*)
9a. Does urine leak before you can get to the toilet? (*Urge leakage*)
10a. How often do you leak urine? (*Leakage frequency*)
11a. Does urine leak when you are physically active, exert yourself, cough or sneeze? (*Stress leakage*)
12a. Do you ever leak urine for no obvious reason and without feeling that you want to go? (*Leakage*)
13a. Do you leak urine when you are asleep? (*Nocturnal enuresis*)

ICIQ-FLUTS Month 1 Week 1

FLUTS completed?	reduced	standard	Total
Yes	30 (96.8%)	28 (93.3%)	58 (95.1%)
No	1 (3.2%)	2 (6.7%)	3 (4.9%)
	31 (100%)	30 (100%)	61 (100%)

Total group	n	Mean	SD	median	min	max
Nocturia	58	1,88	1,26	2	0	4
Bother nocturia	57	2,46	3,05	1	0	10
Urgency	58	1,14	1,10	1	0	4
Bother urgency	56	2,29	3,05	1	0	10
Bladder pain	58	0,69	0,88	0	0	4
Bother bladder pain	56	1,93	2,85	0	0	10
Frequency	58	0,91	1,10	1	0	4
Bother frequency	58	2,09	2,81	1	0	10
Filling Score	**58**	**4,62**	**3,01**	**4**	**0**	**13**
Hesitancy	58	0,43	0,65	0	0	2
Bother hesitancy	55	0,71	1,32	0	0	6
Straining	58	0,24	0,60	0	0	2
Bother straining	54	0,46	1,08	0	0	5
Intermittency	58	0,47	0,82	0	0	4
Bother intermittency	55	0,62	1,23	0	0	5
Voiding Score	**58**	**1,14**	**1,72**	**0,5**	**0**	**8**
Urge leakage	58	0,62	0,75	0	0	2
Bother urge leakage	56	1,62	2,71	0	0	10
Leakage frequency	58	0,76	1,05	0	0	4
Bother leakage frequency	56	1,63	2,73	0	0	10
Stress leakage	58	0,72	0,93	0	0	4
Bother stress leakage	57	1,21	2,08	0	0	8
Leakage	58	0,14	0,54	0	0	3
Bother leakage	54	0,44	1,24	0	0	5
Nocturnal enuresis	58	0,07	0,32	0	0	2
Bother nocturnal enuresis	54	0,2	0,71	0	0	4
Incontinence Score	**58**	**2,31**	**2,70**	**2**	**0**	**15**

Reduced frequency group	n	Mean	SD	median	min	max
Nocturia	30	2,03	1,33	2	0	4
Bother nocturia	30	3,07	3,38	1,5	0	10
Urgency	30	1,4	1,10	1	0	4
Bother urgency	28	2,86	3,15	1,5	0	9
Bladder pain	30	0,77	0,97	0,5	0	4
Bother bladder pain	30	2,17	2,83	1	0	9
Frequency	30	1	1,20	1	0	4
Bother frequency	30	2,53	2,96	1,5	0	10
Filling Score	**30**	**5,2**	**3,10**	**4**	**0**	**13**
Hesitancy	30	0,5	0,68	0	0	2
Bother hesitancy	28	0,71	1,15	0	0	4
Straining	30	0,3	0,65	0	0	2
Bother straining	27	0,48	1,05	0	0	4
Intermittency	30	0,57	0,94	0	0	4
Bother intermittency	28	0,93	1,59	0	0	5
Voiding Score	**30**	**1,37**	**1,97**	**1**	**0**	**8**
Urge leakage	30	0,77	0,77	1	0	2
Bother urge leakage	28	2,18	3,03	1	0	10
Leakage frequency	30	1	1,11	1	0	4
Bother leakage frequency	29	2,21	2,99	0	0	10
Stress leakage	30	0,77	1,01	0,5	0	4
Bother stress leakage	29	1,21	2,01	0	0	8
Leakage	30	0,27	0,74	0	0	3
Bother leakage	27	0,74	1,66	0	0	5
Nocturnal enuresis	30	0,13	0,43	0	0	2
Bother nocturnal enuresis	27	0,33	0,96	0	0	4
Incontinence Score	**30**	**2,93**	**3,26**	**3**	**0**	**15**

Standard treatment group	n	Mean	SD	median	min	max
Nocturia	28	1,71	1,18	2	0	4
Bother nocturia	27	1,78	2,52	1	0	8
Urgency	28	0,86	1,04	0,5	0	3
Bother urgency	28	1,71	2,89	0	0	10
Bladder pain	28	0,61	0,79	0	0	2
Bother bladder pain	26	1,65	2,90	0	0	10
Frequency	28	0,82	0,98	0,5	0	3
Bother frequency	28	1,61	2,60	0	0	8
Filling Score	**28**	**4**	**2,83**	**4**	**0**	**9**
Hesitancy	28	0,36	0,62	0	0	2
Bother hesitancy	27	0,7	1,49	0	0	6
Straining	28	0,18	0,55	0	0	2
Bother straining	27	0,44	1,12	0	0	5
Intermittency	28	0,36	0,68	0	0	2
Bother intermittency	27	0,3	0,54	0	0	2
Voiding Score	**28**	**0,89**	**1,40**	**0**	**0**	**5**
Urge leakage	28	0,46	0,69	0	0	2
Bother urge leakage	28	1,07	2,26	0	0	9
Leakage frequency	28	0,5	0,92	0	0	3
Bother leakage frequency	27	1	2,30	0	0	9
Stress leakage	28	0,68	0,86	0	0	3
Bother stress leakage	28	1,21	2,18	0	0	8
Leakage	28	0	0,00	0	0	0
Bother leakage	27	0,15	0,46	0	0	2
Nocturnal enuresis	28	0	0,00	0	0	0
Bother nocturnal enuresis	27	0,07	0,27	0	0	1
Incontinence Score	**28**	**1,64**	**1,77**	**1**	**0**	**6**

ICIQ-FLUTS Month 2 Week 6

FLUTS completed?	reduced	standard	Total
Yes	29 (93.5%)	24 (88.9%)	53 (91.4%)
No	2 (6.5%)	3 (11.1%)	5 (8.6%)
	31 (100%)	27 (100%)	58 (100%)

Total group	n	Mean	SD	median	min	max
Nocturia	53	1,79	1,17	2	0	4
Bother nocturia	51	2,04	2,60	1	0	9
Urgency	53	1,15	1,03	1	0	4
Bother urgency	51	2,49	3,08	1	0	10
Bladder pain	53	0,57	0,80	0	0	3
Bother bladder pain	52	1,6	2,31	0	0	9
Frequency	53	1,06	0,99	1	0	4
Bother frequency	51	2,1	2,76	1	0	10
Filling Score	**53**	**4,57**	**2,41**	**4**	**0**	**11**
Hesitancy	53	0,47	0,72	0	0	2
Bother hesitancy	51	0,76	1,52	0	0	7
Straining	53	0,3	0,58	0	0	2
Bother straining	51	0,63	1,28	0	0	6
Intermittency	53	0,42	0,69	0	0	3
Bother intermittency	50	0,86	1,64	0	0	6
Voiding Score	**53**	**1,19**	**1,59**	**1**	**0**	**6**
Urge leakage	53	0,7	0,75	1	0	3
Bother urge leakage	49	1,55	2,71	0	0	10
Leakage frequency	52	0,81	1,05	0	0	4
Bother leakage frequency	50	1,46	2,71	0	0	10
Stress leakage	53	0,7	0,91	0	0	3
Bother stress leakage	51	1,29	2,18	0	0	9
Leakage	52	0,23	0,68	0	0	3
Bother leakage	51	0,53	1,69	0	0	8
Nocturnal enuresis	53	0,08	0,33	0	0	2
Bother nocturnal enuresis	51	0,16	0,61	0	0	4
Incontinence Score	**51**	**2,59**	**2,97**	**2**	**0**	**15**

Reduced frequency group	n	Mean	SD	median	min	max
Nocturia	29	1,72	1,22	1	0	4
Bother nocturia	28	2,29	3,00	0,5	0	9
Urgency	29	1,07	1,07	1	0	3
Bother urgency	28	2,46	3,23	0	0	10
Bladder pain	29	0,59	0,87	0	0	3
Bother bladder pain	29	1,69	2,44	0	0	7
Frequency	29	0,97	0,94	1	0	4
Bother frequency	28	2,11	2,91	0	0	10
Filling Score	**29**	**4,34**	**2,44**	**4**	**0**	**11**
Hesitancy	29	0,55	0,78	0	0	2
Bother hesitancy	28	0,86	1,53	0	0	5
Straining	29	0,31	0,66	0	0	2
Bother straining	28	0,79	1,62	0	0	6
Intermittency	29	0,45	0,78	0	0	3
Bother intermittency	27	1,07	1,86	0	0	6
Voiding Score	**29**	**1,31**	**1,87**	**0**	**0**	**6**
Urge leakage	29	0,76	0,69	1	0	2
Bother urge leakage	26	1,81	3,02	0	0	10
Leakage frequency	29	0,9	1,08	1	0	4
Bother leakage frequency	27	1,59	2,93	0	0	10
Stress leakage	29	0,72	0,92	0	0	3
Bother stress leakage	28	1,18	1,96	0	0	8
Leakage	28	0,29	0,71	0	0	3
Bother leakage	28	0,43	1,55	0	0	8
Nocturnal enuresis	29	0,07	0,26	0	0	1
Bother nocturnal enuresis	28	0,07	0,26	0	0	1
Incontinence Score	**28**	**2,82**	**2,75**	**2**	**0**	**11**

Standard treatment group	n	Mean	SD	median	min	max
Nocturia	24	1,88	1,12	2	0	4
Bother nocturia	23	1,74	2,03	1	0	5
Urgency	24	1,25	0,99	1	0	4
Bother urgency	23	2,52	2,95	2	0	10
Bladder pain	24	0,54	0,72	0	0	2
Bother bladder pain	23	1,48	2,19	1	0	9
Frequency	24	1,17	1,05	1	0	4
Bother frequency	23	2,09	2,63	1	0	9
Filling Score	**24**	**4,83**	**2,41**	**5**	**0**	**9**
Hesitancy	24	0,38	0,65	0	0	2
Bother hesitancy	23	0,65	1,53	0	0	7
Straining	24	0,29	0,46	0	0	1
Bother straining	23	0,43	0,66	0	0	2
Intermittency	24	0,37	0,58	0	0	2
Bother intermittency	23	0,61	1,34	0	0	6
Voiding Score	**24**	**1,04**	**1,20**	**1**	**0**	**4**
Urge leakage	24	0,63	0,82	0	0	3
Bother urge leakage	23	1,26	2,34	0	0	9
Leakage frequency	23	0,7	1,02	0	0	4
Bother leakage frequency	23	1,3	2,48	0	0	10
Stress leakage	24	0,67	0,92	0	0	3
Bother stress leakage	23	1,43	2,47	0	0	9
Leakage	24	0,17	0,64	0	0	3
Bother leakage	23	0,65	1,87	0	0	7
Nocturnal enuresis	24	0,08	0,41	0	0	2
Bother nocturnal enuresis	23	0,26	0,86	0	0	4
Incontinence Score	**23**	**2,3**	**3,25**	**2**	**0**	**15**

ICIQ-FLUTS Month 3 Week 1

FLUTS completed?	reduced	standard	Total
Yes	23 (79.3%)	23 (82.1%)	46 (80.7%)
No	6 (20.7%)	5 (17.9%)	11 (19.3%)
	29 (100%)	28 (100%)	57 (100%)

Total group	n	Mean	SD	median	min	max
Nocturia	46	1,78	1,11	2	0	4
Bother nocturia	44	1,77	2,75	0	0	10
Urgency	46	0,83	0,80	1	0	3
Bother urgency	45	1,47	2,23	0	0	9
Bladder pain	46	0,39	0,71	0	0	3
Bother bladder pain	46	0,98	2,10	0	0	9
Frequency	46	0,65	0,90	0	0	4
Bother frequency	44	1,41	2,39	0	0	10
Filling Score	**46**	**3,65**	**2,17**	**4**	**0**	**12**
Hesitancy	46	0,5	0,72	0	0	3
Bother hesitancy	44	0,48	1,09	0	0	4
Straining	46	0,26	0,58	0	0	2
Bother straining	45	0,38	1,09	0	0	6
Intermittency	46	0,43	0,78	0	0	4
Bother intermittency	44	0,61	1,48	0	0	8
Voiding Score	**46**	**1,2**	**1,78**	**0,5**	**0**	**8**
Urge leakage	46	0,67	0,76	0,5	0	2
Bother urge leakage	44	1,52	2,65	0	0	10
Leakage frequency	46	0,76	1,06	0	0	4
Bother leakage frequency	44	1,45	2,78	0	0	10
Stress leakage	46	0,57	0,81	0	0	3
Bother stress leakage	44	1,27	2,47	0	0	10
Leakage	46	0,13	0,50	0	0	3
Bother leakage	43	0,47	1,55	0	0	8
Nocturnal enuresis	46	0,15	0,47	0	0	2
Bother nocturnal enuresis	44	0,34	1,26	0	0	7
Incontinence Score	**46**	**2,28**	**2,75**	**2**	**0**	**12**

Reduced frequency group	n	Mean	SD	median	min	max
Nocturia	23	1,96	1,26	2	0	4
Bother nocturia	22	2,32	3,18	0,5	0	10
Urgency	23	0,96	0,88	1	0	3
Bother urgency	22	1,82	2,67	0,5	0	9
Bladder pain	23	0,52	0,85	0	0	3
Bother bladder pain	23	1,35	2,23	0	0	7
Frequency	23	0,57	0,99	0	0	4
Bother frequency	22	1,86	2,68	0,5	0	10
Filling Score	**23**	**4**	**2,63**	**4**	**0**	**12**
Hesitancy	23	0,65	0,89	0	0	3
Bother hesitancy	22	0,73	1,32	0	0	4
Straining	23	0,35	0,71	0	0	2
Bother straining	23	0,65	1,43	0	0	6
Intermittency	23	0,61	0,94	0	0	4
Bother intermittency	22	1,05	1,91	0	0	8
Voiding Score	**23**	**1,61**	**2,19**	**1**	**0**	**8**
Urge leakage	23	0,74	0,75	1	0	2
Bother urge leakage	22	2	3,16	0,5	0	10
Leakage frequency	23	0,96	1,15	1	0	4
Bother leakage frequency	22	1,86	3,27	0	0	10
Stress leakage	23	0,52	0,79	0	0	3
Bother stress leakage	22	1,32	2,61	0	0	10
Leakage	23	0,22	0,67	0	0	3
Bother leakage	21	0,67	1,93	0	0	8
Nocturnal enuresis	23	0,17	0,49	0	0	2
Bother nocturnal enuresis	22	0,68	1,73	0	0	7
Incontinence Score	**23**	**2,61**	**3,16**	**2**	**0**	**12**

Standard treatment group	n	Mean	SD	median	min	max
Nocturia	23	1,61	0,94	2	0	3
Bother nocturia	22	1,23	2,18	0	0	9
Urgency	23	0,7	0,70	1	0	2
Bother urgency	23	1,13	1,71	0	0	7
Bladder pain	23	0,26	0,54	0	0	2
Bother bladder pain	23	0,61	1,95	0	0	9
Frequency	23	0,74	0,81	1	0	3
Bother frequency	22	0,95	2,01	0	0	8
Filling Score	**23**	**3,3**	**1,58**	**4**	**0**	**6**
Hesitancy	23	0,35	0,49	0	0	1
Bother hesitancy	22	0,23	0,75	0	0	3
Straining	23	0,17	0,39	0	0	1
Bother straining	22	0,09	0,43	0	0	2
Intermittency	23	0,26	0,54	0	0	2
Bother intermittency	22	0,18	0,66	0	0	3
Voiding Score	**23**	**0,78**	**1,17**	**0**	**0**	**4**
Urge leakage	23	0,61	0,78	0	0	2
Bother urge leakage	22	1,05	1,96	0	0	8
Leakage frequency	23	0,57	0,95	0	0	3
Bother leakage frequency	22	1,05	2,19	0	0	9
Stress leakage	23	0,61	0,84	0	0	3
Bother stress leakage	22	1,23	2,39	0	0	10
Leakage	23	0,04	0,21	0	0	1
Bother leakage	22	0,27	1,08	0	0	5
Nocturnal enuresis	23	0,13	0,46	0	0	2
Bother nocturnal enuresis	22	0	0,00	0	0	0
Incontinence Score	**23**	**1,96**	**2,29**	**1**	**0**	**8**

ICIQ-FLUTS Month 3 Week 3

FLUTS completed?	reduced	standard	Total
Yes	22 (95.7%)	22 (84.6%)	44 (89.8%)
No	1 (4.3%)	4 (15.4%)	5 (10.2%)
	23 (100%)	26 (100%)	49 (100%)

Total group	n	Mean	SD	median	min	max
Nocturia	44	1,93	1,11	2	0	4
Bother nocturia	42	1,98	2,83	1	0	10
Urgency	44	1	0,78	1	0	3
Bother urgency	40	1,83	2,63	1	0	10
Bladder pain	44	0,7	1,00	0	0	4
Bother bladder pain	42	1,1	2,30	0	0	10
Frequency	44	1,02	1,11	1	0	4
Bother frequency	43	1,81	2,81	0	0	10
Filling Score	44	4,66	2,74	4	1	15
Hesitancy	44	0,48	0,79	0	0	3
Bother hesitancy	39	1,03	2,30	0	0	10
Straining	44	0,3	0,67	0	0	3
Bother straining	39	0,44	1,19	0	0	5
Intermittency	44	0,52	0,82	0	0	3
Bother intermittency	40	0,75	1,93	0	0	10
Voiding Score	**44**	**1,3**	**1,79**	**0,5**	**0**	**6**
Urge leakage	44	0,68	0,71	1	0	2
Bother urge leakage	39	1,59	2,84	0	0	10
Leakage frequency	43	0,79	1,04	0	0	4
Bother leakage frequency	39	1,49	2,84	0	0	10
Stress leakage	44	0,57	0,76	0	0	3
Bother stress leakage	41	0,95	1,83	0	0	9
Leakage	44	0,11	0,44	0	0	2
Bother leakage	39	0,46	1,50	0	0	8
Nocturnal enuresis	44	0,09	0,42	0	0	2
Bother nocturnal enuresis	39	0,13	0,66	0	0	4
Incontinence Score	**43**	**2,28**	**2,29**	**2**	**0**	**8**

Reduced frequency group	n	Mean	SD	median	min	max
Nocturia	22	1,95	1,25	2	0	4
Bother nocturia	20	2,2	3,17	0,5	0	10
Urgency	22	1,05	0,90	1	0	3
Bother urgency	19	2,05	2,64	1	0	8
Bladder pain	22	0,77	1,07	0	0	3
Bother bladder pain	21	1,29	2,43	0	0	8
Frequency	22	0,91	1,11	1	0	4
Bother frequency	21	2,29	3,00	1	0	10
Filling Score	**22**	**4,68**	**2,84**	**4**	**1**	**12**
Hesitancy	22	0,64	1,00	0	0	3
Bother hesitancy	18	1,39	2,43	0	0	8
Straining	22	0,32	0,65	0	0	2
Bother straining	18	0,67	1,65	0	0	5
Intermittency	22	0,5	0,86	0	0	3
Bother intermittency	19	0,74	1,59	0	0	5
Voiding Score	**22**	**1,45**	**2,04**	**0**	**0**	**6**
Urge leakage	22	0,68	0,72	1	0	2
Bother urge leakage	18	1,83	3,03	0	0	9
Leakage frequency	22	0,86	1,04	0,5	0	3
Bother leakage frequency	19	1,79	3,08	0	0	9
Stress leakage	22	0,64	0,85	0	0	3
Bother stress leakage	20	1,3	2,34	0	0	9
Leakage	22	0,23	0,61	0	0	2
Bother leakage	19	0,79	2,07	0	0	8
Nocturnal enuresis	22	0,09	0,43	0	0	2
Bother nocturnal enuresis	19	0,21	0,92	0	0	4
Incontinence Score	**22**	**2,5**	**2,50**	**2**	**0**	**8**

Standard treatment group	n	Mean	SD	median	min	max
Nocturia	22	1,91	0,97	2	1	4
Bother nocturia	22	1,77	2,54	1	0	10
Urgency	22	0,95	0,65	1	0	3
Bother urgency	21	1,62	2,67	1	0	10
Bladder pain	22	0,64	0,95	0	0	4
Bother bladder pain	21	0,9	2,21	0	0	10
Frequency	22	1,14	1,13	1	0	4
Bother frequency	22	1,36	2,59	0	0	10
Filling Score	**22**	**4,64**	**2,70**	**4**	**2**	**15**
Hesitancy	22	0,32	0,48	0	0	1
Bother hesitancy	21	0,71	2,19	0	0	10
Straining	22	0,27	0,70	0	0	3
Bother straining	21	0,24	0,54	0	0	2
Intermittency	22	0,55	0,80	0	0	3
Bother intermittency	21	0,76	2,23	0	0	10
Voiding Score	**22**	**1,14**	**1,52**	**1**	**0**	5
Urge leakage	22	0,68	0,72	1	0	2
Bother urge leakage	21	1,38	2,71	0	0	10
Leakage frequency	21	0,71	1,06	0	0	4
Bother leakage frequency	20	1,2	2,63	0	0	10
Stress leakage	22	0,5	0,67	0	0	2
Bother stress leakage	21	0,62	1,12	0	0	4
Leakage	22	0	0,00	0	0	0
Bother leakage	20	0,15	0,49	0	0	2
Nocturnal enuresis	22	0,09	0,43	0	0	2
Bother nocturnal enuresis	20	0,05	0,22	0	0	1
Incontinence Score	**21**	**2,05**	**2,09**	**2**	**0**	**8**

ICIQ-FLUTS Month 6 Week 1

FLUTS completed?	reduced	standard	Total
Yes	19 (86.4%)	21 (84%)	40 (85.1%)
No	3 (13.6%)	4 (16%)	7 (14.9%)
	22 (100%)	25 (100%)	47 (100%)

Total group	n	Mean	SD	median	min	max
Nocturia	40	1,67	1,12	1,5	0	4
Bother nocturia	40	1,73	2,47	1	0	10
Urgency	40	0,97	0,80	1	0	2
Bother urgency	39	2,28	2,92	1	0	10
Bladder pain	40	0,65	1,05	0	0	4
Bother bladder pain	39	1,15	2,29	0	0	10
Frequency	40	0,87	0,82	1	0	3
Bother frequency	39	1,72	2,36	1	0	10
Filling Score	**40**	**4,18**	**2,29**	**4**	**0**	**12**
Hesitancy	40	0,62	0,77	0	0	3
Bother hesitancy	38	1,05	1,85	0	0	10
Straining	40	0,45	0,82	0	0	3
Bother straining	38	0,53	1,18	0	0	6
Intermittency	40	0,53	0,78	0	0	3
Bother intermittency	38	1,05	1,93	0	0	10
Voiding Score	**40**	**1,6**	**1,99**	**1**	**0**	**6**
Urge leakage	40	0,5	0,72	0	0	2
Bother urge leakage	39	1,46	2,79	0	0	10
Leakage frequency	40	0,55	0,82	0	0	3
Bother leakage frequency	39	1,36	2,60	0	0	10
Stress leakage	40	0,6	0,63	1	0	2
Bother stress leakage	39	1,03	1,90	0	0	8
Leakage	40	0,15	0,43	0	0	2
Bother leakage	39	0,38	0,96	0	0	4
Nocturnal enuresis	40	0,08	0,35	0	0	2
Bother nocturnal enuresis	38	0,08	0,27	0	0	1
Incontinence Score	**40**	**1,87**	**2,08**	**1**	**0**	**8**

Reduced frequency group	n	Mean	SD	median	min	max
Nocturia	19	1,53	1,07	1	0	4
Bother nocturia	19	1,42	2,32	0	0	8
Urgency	19	0,95	0,78	1	0	2
Bother urgency	18	2,28	3,05	1	0	9
Bladder pain	19	0,58	0,90	0	0	3
Bother bladder pain	19	1,05	2,12	0	0	7
Frequency	19	0,58	0,69	0	0	2
Bother frequency	18	1,61	2,15	1	0	6
Filling Score	**19**	**3,63**	**1,86**	**3**	**0**	**7**
Hesitancy	19	0,63	0,76	1	0	3
Bother hesitancy	18	1	1,28	0	0	3
Straining	19	0,26	0,56	0	0	2
Bother straining	18	0,33	0,77	0	0	3
Intermittency	19	0,37	0,60	0	0	2
Bother intermittency	18	0,94	1,43	0	0	4
Voiding Score	**19**	**1,26**	**1,59**	**1**	**0**	**6**
Urge leakage	19	0,63	0,68	1	0	2
Bother urge leakage	18	2,17	3,43	0	0	10
Leakage frequency	19	0,63	0,68	1	0	2
Bother leakage frequency	18	2,06	3,46	0	0	10
Stress leakage	19	0,53	0,61	0	0	2
Bother stress leakage	18	1,17	2,46	0	0	8
Leakage	19	0,21	0,42	0	0	1
Bother leakage	18	0,56	1,20	0	0	4
Nocturnal enuresis	19	0	0,00	0	0	0
Bother nocturnal enuresis	18	0	0,00	0	0	0
Incontinence Score	**19**	**2**	**1,67**	**2**	**0**	**5**

Standard treatment group	n	Mean	SD	median	min	max
Nocturia	21	1,81	1,17	2	0	4
Bother nocturia	21	2	2,63	1	0	10
Urgency	21	1	0,84	1	0	2
Bother urgency	21	2,29	2,88	2	0	10
Bladder pain	21	0,71	1,19	0	0	4
Bother bladder pain	20	1,25	2,49	0	0	10
Frequency	21	1,14	0,85	1	0	3
Bother frequency	21	1,81	2,58	1	0	10
Filling Score	21	4,67	2,56	4	1	12
Hesitancy	21	0,62	0,81	0	0	2
Bother hesitancy	20	1,1	2,27	0	0	10
Straining	21	0,62	0,97	0	0	3
Bother straining	20	0,7	1,46	0	0	6
Intermittency	21	0,67	0,91	0	0	3
Bother intermittency	20	1,15	2,32	0	0	10
Voiding Score	21	1,9	2,28	1	0	6
Urge leakage	21	0,38	0,74	0	0	2
Bother urge leakage	21	0,86	1,98	0	0	8
Leakage frequency	21	0,48	0,93	0	0	3
Bother leakage frequency	21	0,76	1,38	0	0	4
Stress leakage	21	0,67	0,66	1	0	2
Bother stress leakage	21	0,9	1,30	0	0	3
Leakage	21	0,1	0,44	0	0	2
Bother leakage	21	0,24	0,70	0	0	3
Nocturnal enuresis	21	0,14	0,48	0	0	2
Bother nocturnal enuresis	20	0,15	0,37	0	0	1
Incontinence Score	21	1,76	2,43	1	0	8

ICIQ-FLUTS Month 6 Week 3

FLUTS completed?	reduced	standard	Total
Yes	18 (85.7%)	21 (91.3%)	39 (88.6%)
No	3 (14.3%)	2 (8.7%)	5 (11.4%)
	21 (100%)	23 (100%)	44 (100%)

Total group	n	Mean	SD	median	min	max
Nocturia	39	1,9	1,12	2	0	4
Bother nocturia	37	2,22	2,81	1	0	8
Urgency	39	1,18	1,05	1	0	3
Bother urgency	37	2,08	2,97	1	0	10
Bladder pain	39	0,85	0,96	1	0	4
Bother bladder pain	37	1,54	2,52	0	0	10
Frequency	39	1,08	1,04	1	0	4
Bother frequency	37	2,11	2,89	1	0	10
Filling Score	**39**	**5**	**2,93**	**4**	**0**	**15**
Hesitancy	39	0,51	0,72	0	0	3
Bother hesitancy	37	0,95	2,09	0	0	9
Straining	39	0,33	0,70	0	0	3
Bother straining	37	0,81	1,81	0	0	9
Intermittency	39	0,56	0,91	0	0	4
Bother intermittency	37	0,86	1,92	0	0	9
Voiding Score	**39**	**1,41**	**1,92**	**1**	**0**	**9**
Urge leakage	39	0,59	0,72	0	0	2
Bother urge leakage	37	1,49	2,60	0	0	9
Leakage frequency	39	0,82	1,07	1	0	4
Bother leakage frequency	37	1,73	2,93	0	0	10
Stress leakage	39	0,62	0,85	0	0	3
Bother stress leakage	37	1,03	2,05	0	0	10
Leakage	39	0,18	0,51	0	0	2
Bother leakage	37	0,73	2,18	0	0	9
Nocturnal enuresis	39	0,18	0,68	0	0	4
Bother nocturnal enuresis	37	0,46	1,77	0	0	9
Incontinence Score	**39**	**2,38**	**2,69**	**2**	**0**	**12**

Reduced frequency group	n	Mean	SD	median	min	max
Nocturia	18	1,56	1,04	1	0	4
Bother nocturia	16	2,13	3,03	1	0	8
Urgency	18	1,06	0,94	1	0	3
Bother urgency	16	2,31	3,38	1	0	10
Bladder pain	18	0,67	0,91	0	0	3
Bother bladder pain	16	1,44	2,63	0	0	7
Frequency	18	0,67	0,77	0,5	0	2
Bother frequency	16	1,94	2,89	0,5	0	8
Filling Score	**18**	**3,94**	**2,39**	**4**	**0**	**9**
Hesitancy	18	0,56	0,78	0	0	3
Bother hesitancy	16	0,94	2,29	0	0	9
Straining	18	0,28	0,75	0	0	3
Bother straining	16	0,94	2,38	0	0	9
Intermittency	18	0,83	1,15	0,5	0	4
Bother intermittency	16	1,13	2,45	0	0	9
Voiding Score	**18**	**1,67**	**2,33**	**1**	**0**	**9**
Urge leakage	18	0,5	0,71	0	0	2
Bother urge leakage	16	1,38	2,80	0	0	8
Leakage frequency	18	0,56	0,71	0	0	2
Bother leakage frequency	16	1,5	2,97	0	0	8
Stress leakage	18	0,39	0,61	0	0	2
Bother stress leakage	16	0,63	1,54	0	0	6
Leakage	18	0,22	0,55	0	0	2
Bother leakage	16	0,94	2,41	0	0	8
Nocturnal enuresis	18	0,11	0,32	0	0	1
Bother nocturnal enuresis	16	0,38	1,50	0	0	6
Incontinence Score	**18**	**1,78**	**2,21**	**1,5**	**0**	**7**

Standard treatment group	n	Mean	SD	median	min	max
Nocturia	21	2,19	1,1	2	1	4
Bother nocturia	21	2,29	2,7	1	0	8
Urgency	21	1,29	1,1	1	0	3
Bother urgency	21	1,9	2,7	0	0	8
Bladder pain	21	1	1,0	1	0	4
Bother bladder pain	21	1,62	2,5	1	0	10
Frequency	21	1,43	1,1	1	0	4
Bother frequency	21	2,24	3,0	1	0	10
Filling Score	**21**	**5,9**	**3,1**	**6**	**1**	**15**
Hesitancy	21	0,48	0,7	0	0	2
Bother hesitancy	21	0,95	2,0	0	0	8
Straining	21	0,38	0,7	0	0	2
Bother straining	21	0,71	1,3	0	0	4
Intermittency	21	0,33	0,6	0	0	2
Bother intermittency	21	0,67	1,4	0	0	5
Voiding Score	**21**	**1,19**	**1,5**	**0**	**0**	**4**
Urge leakage	21	0,67	0,7	1	0	2
Bother urge leakage	21	1,57	2,5	0	0	9
Leakage frequency	21	1,05	1,3	1	0	4
Bother leakage frequency	21	1,9	3,0	0	0	10
Stress leakage	21	0,81	1,0	1	0	3
Bother stress leakage	21	1,33	2,4	0	0	10
Leakage	21	0,14	0,5	0	0	2
Bother leakage	21	0,57	2,0	0	0	9
Nocturnal enuresis	21	0,24	0,9	0	0	4
Bother nocturnal enuresis	21	0,52	2,0	0	0	9
Incontinence Score	**21**	**2,9**	**3,0**	**2**	**0**	**12**

ICIQ-FLUTS Month 12 Week 1

FLUTS completed?	reduced	standard	Total
Yes	17 (100%)	19 (86.4%)	36 (92.3%)
No	0 (0%)	3 (13.6%)	3 (7.7%)
	17 (100%)	22 (100%)	39 (100%)

Total group	n	Mean	SD	median	min	max
Nocturia	36	1,69	1,04	2	0	4
Bother nocturia	35	1,86	2,33	1	0	8
Urgency	36	1,17	1,11	1	0	4
Bother urgency	34	1,91	2,48	1	0	10
Bladder pain	36	0,39	0,55	0	0	2
Bother bladder pain	31	0,97	1,70	0	0	6
Frequency	36	1	1,07	1	0	4
Bother frequency	35	1,71	2,44	1	0	10
Filling Score	**36**	**4,25**	**2,23**	**4,5**	**0**	**8**
Hesitancy	36	0,58	0,84	0	0	3
Bother hesitancy	33	0,82	1,29	0	0	3
Straining	36	0,39	0,69	0	0	2
Bother straining	33	0,48	0,94	0	0	3
Intermittency	36	0,69	0,89	0	0	3
Bother intermittency	32	0,88	1,48	0	0	5
Voiding Score	**36**	**1,67**	**2,11**	**1**	**0**	**7**
Urge leakage	36	0,56	0,65	0	0	2
Bother urge leakage	33	0,91	2,02	0	0	10
Leakage frequency	36	0,5	0,88	0	0	4
Bother leakage frequency	32	0,91	2,32	0	0	10
Stress leakage	36	0,64	0,68	1	0	2
Bother stress leakage	33	1,03	2,14	0	0	10
Leakage	36	0,14	0,42	0	0	2
Bother leakage	32	0,25	0,62	0	0	2
Nocturnal enuresis	36	0,14	0,54	0	0	3
Bother nocturnal enuresis	32	0,31	1,12	0	0	6
Incontinence Score	**36**	**1,97**	**2,05**	**1**	**0**	**8**

Reduced frequency group	n	Mean	SD	median	min	max
Nocturia	17	1,59	1,06	1	0	4
Bother nocturia	16	1,88	2,66	1	0	8
Urgency	17	1,18	1,19	1	0	3
Bother urgency	15	1,87	2,92	1	0	10
Bladder pain	17	0,53	0,62	0	0	2
Bother bladder pain	14	1,14	1,79	0	0	6
Frequency	17	0,88	1,22	0	0	4
Bother frequency	16	1,81	2,99	0,5	0	10
Filling Score	**17**	**4,18**	**2,60**	**4**	**0**	**8**
Hesitancy	17	0,65	0,93	0	0	3
Bother hesitancy	15	0,8	1,21	0	0	3
Straining	17	0,47	0,80	0	0	2
Bother straining	15	0,67	1,05	0	0	3
Intermittency	17	0,71	0,85	1	0	3
Bother intermittency	14	1,14	1,70	0	0	5
Voiding Score	**17**	**1,82**	**2,30**	**1**	**0**	**7**
Urge leakage	17	0,53	0,72	0	0	2
Bother urge leakage	15	1,4	2,80	0	0	10
Leakage frequency	17	0,47	0,72	0	0	2
Bother leakage frequency	15	1,2	2,70	0	0	10
Stress leakage	17	0,47	0,62	0	0	2
Bother stress leakage	15	1	2,59	0	0	10
Leakage	17	0,24	0,56	0	0	2
Bother leakage	15	0,33	0,72	0	0	2
Nocturnal enuresis	17	0	0,00	0	0	0
Bother nocturnal enuresis	15	0,2	0,56	0	0	2
Incontinence Score	**17**	**1,71**	**2,14**	**1**	**0**	**6**

Standard treatment group	n	Mean	SD	median	min	max
Nocturia	19	1,79	1,03	2	0	4
Bother nocturia	19	1,84	2,09	1	0	7
Urgency	19	1,16	1,07	1	0	4
Bother urgency	19	1,95	2,15	1	0	7
Bladder pain	19	0,26	0,45	0	0	1
Bother bladder pain	17	0,82	1,67	0	0	6
Frequency	19	1,11	0,94	1	0	3
Bother frequency	19	1,63	1,95	1	0	5
Filling Score	**19**	**4,32**	**1,92**	**5**	**1**	**8**
Hesitancy	19	0,53	0,77	0	0	2
Bother hesitancy	18	0,83	1,38	0	0	3
Straining	19	0,32	0,58	0	0	2
Bother straining	18	0,33	0,84	0	0	3
Intermittency	19	0,68	0,95	0	0	3
Bother intermittency	18	0,67	1,28	0	0	4
Voiding Score	**19**	**1,53**	**1,98**	**1**	**0**	**7**
Urge leakage	19	0,58	0,61	1	0	2
Bother urge leakage	18	0,5	0,92	0	0	3
Leakage frequency	19	0,53	1,02	0	0	4
Bother leakage frequency	17	0,65	1,97	0	0	8
Stress leakage	19	0,79	0,71	1	0	2
Bother stress leakage	18	1,06	1,77	0	0	6
Leakage	19	0,05	0,23	0	0	1
Bother leakage	17	0,18	0,53	0	0	2
Nocturnal enuresis	19	0,26	0,73	0	0	3
Bother nocturnal enuresis	17	0,41	1,46	0	0	6
Incontinence Score	**19**	**2,21**	**1,99**	**2**	**0**	**8**

ICIQ-FLUTS Month 12 Week 3

FLUTS completed?	reduced	standard	Total
Yes	16 (94.1%)	20 (100%)	36 (97.3%)
No	1 (5.9%)	0 (0%)	1 (2.7%)
	17 (100%)	20 (100%)	37 (100%)

Total group	n	Mean	SD	median	min	max
Nocturia	36	2,08	1,32	2	0	4
Bother nocturia	35	2,51	3,03	1	0	10
Urgency	36	1,08	1,05	1	0	3
Bother urgency	35	2,34	3,05	1	0	9
Bladder pain	36	0,86	1,10	0,5	0	4
Bother bladder pain	34	2,15	3,26	0	0	9
Frequency	36	1,14	0,99	1	0	4
Bother frequency	35	2,4	3,09	1	0	10
Filling Score	**36**	**5,17**	**3,02**	**5,5**	**0**	**13**
Hesitancy	36	0,64	0,72	1	0	3
Bother hesitancy	34	0,97	1,99	0	0	8
Straining	36	0,28	0,45	0	0	1
Bother straining	34	0,47	1,19	0	0	6
Intermittency	36	0,56	0,84	0	0	4
Bother intermittency	34	0,76	1,62	0	0	6
Voiding Score	**36**	**1,47**	**1,68**	**1**	**0**	**6**
Urge leakage	36	0,72	0,78	1	0	3
Bother urge leakage	35	2,11	3,15	0	0	10
Leakage frequency	36	0,72	1,03	0	0	4
Bother leakage frequency	34	1,91	3,09	0	0	10
Stress leakage	36	0,58	0,73	0	0	3
Bother stress leakage	35	1,17	2,15	0	0	10
Leakage	36	0,11	0,32	0	0	1
Bother leakage	34	0,35	1,43	0	0	8
Nocturnal enuresis	36	0,11	0,52	0	0	3
Bother nocturnal enuresis	34	0,26	1,38	0	0	8
Incontinence Score	**36**	**2,25**	**2,36**	**2**	**0**	**10**

Reduced frequency group	n	Mean	SD	median	min	max
Nocturia	16	1,62	1,09	1,5	0	4
Bother nocturia	15	1,93	2,66	1	0	8
Urgency	16	1,06	1,06	1	0	3
Bother urgency	15	1,73	2,74	1	0	9
Bladder pain	16	0,69	0,95	0	0	3
Bother bladder pain	15	1,73	3,13	0	0	8
Frequency	16	0,81	1,05	0,5	0	3
Bother frequency	15	2	3,07	1	0	10
Filling Score	**16**	**4,19**	**2,76**	**4**	**0**	**8**
Hesitancy	16	0,94	0,85	1	0	3
Bother hesitancy	15	1,6	2,77	0	0	8
Straining	16	0,25	0,45	0	0	1
Bother straining	15	0,67	1,63	0	0	6
Intermittency	16	0,81	1,05	1	0	4
Bother intermittency	15	1,13	1,96	0	0	6
Voiding Score	**16**	**2**	**1,90**	**2**	**0**	**6**
Urge leakage	16	0,56	0,73	0	0	2
Bother urge leakage	15	1,8	3,28	0	0	10
Leakage frequency	16	0,69	0,79	0,5	0	2
Bother leakage frequency	15	1,73	3,13	0	0	10
Stress leakage	16	0,38	0,62	0	0	2
Bother stress leakage	15	0,87	2,59	0	0	10
Leakage	16	0,19	0,40	0	0	1
Bother leakage	15	0,67	2,09	0	0	8
Nocturnal enuresis	16	0	0,00	0	0	0
Bother nocturnal enuresis	15	0	0,00	0	0	0
Incontinence Score	**16**	**1,81**	**2,07**	**1**	**0**	**5**

Standard treatment group	n	Mean	SD	median	min	max
Nocturia	20	2,45	1,40	2	1	4
Bother nocturia	20	2,95	3,28	2	0	10
Urgency	20	1,1	1,07	1	0	3
Bother urgency	20	2,8	3,25	1,5	0	9
Bladder pain	20	1	1,21	1	0	4
Bother bladder pain	19	2,47	3,41	0	0	9
Frequency	20	1,4	0,88	1	0	4
Bother frequency	20	2,7	3,15	1,5	0	9
Filling Score	**20**	**5,95**	**3,05**	**6**	**2**	**13**
Hesitancy	20	0,4	0,50	0	0	1
Bother hesitancy	19	0,47	0,84	0	0	2
Straining	20	0,3	0,47	0	0	1
Bother straining	19	0,32	0,67	0	0	2
Intermittency	20	0,35	0,59	0	0	2
Bother intermittency	19	0,47	1,26	0	0	5
Voiding Score	**20**	**1,05**	**1,40**	**0**	**0**	**4**
Urge leakage	20	0,85	0,81	1	0	3
Bother urge leakage	20	2,35	3,12	1	0	9
Leakage frequency	20	0,75	1,21	0	0	4
Bother leakage frequency	19	2,05	3,14	0	0	9
Stress leakage	20	0,75	0,79	1	0	3
Bother stress leakage	20	1,4	1,79	1	0	6
Leakage	20	0,05	0,22	0	0	1
Bother leakage	19	0,11	0,46	0	0	2
Nocturnal enuresis	20	0,2	0,70	0	0	3
Bother nocturnal enuresis	19	0,47	1,84	0	0	8
Incontinence Score	**20**	**2,6**	**2,56**	**2,5**	**0**	**10**