SPONSOR	European Association of Urology Research Foundation (EAU RF) Mr. E.N. van Kleffensstraat 5 NL 6842 CV Arnhem PO Box 30016 6803 AA Arnhem The Netherlands
CLINICAL STUDY REPORT	
STUDY TITLE	Treatment of High Grade Non-Muscle Invasive Bladder Carcinoma by Standard Number and Dose of Intravesical BCG Instillations versus Reduced Number and Dose of Intravesical BCG Instillations. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial
PROTOCOL No.	2008 - 01
NAME OF IMP	Bacillus Calmette-Guérin (BCG)
CLINICAL PHASE	Phase III
INDICATION STUDIED	High Grade Non-Muscle Invasive Bladder Carcinoma
DATE FIRST PATIENT IN	18 December 2013
DATE OF EARLY STUDY TERMINATION	30 June 2020
DATE LAST PATIENT OUT	30 June 2020
PRINCIPAL INVESTIGATOR	Levent N. Türkeri Dept. of Urology, Marmara University Medical School Istanbul, Turkey Marko M. Babjuk Dept. of Urology, Charles University 2nd Faculty of Medicine Praha 5, Czech Republic
SPONSOR's CONTACT PERSON FOR THIS REPORT	Raymond G. Schipper, PhD PO Box 30016, 6803 AA Arnhem, The Netherlands Tel: + 31 26 3890677, Fax: +31 26 3890679
GCP STATEMENT	This study was performed in compliance with the Good Clinical Practice guideline.
REPORT VERSION & DATE	Final, 11/06/2021
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Treatment of High Grade Non-Muscle Invasive Bladder Carcinoma by Standard Number and Dose of Intravesical BCG Instillations versus Reduced Number and Dose of Intravesical BCG Instillations. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial

REPORT WRITER

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2. PRINCIPAL INVESTIGATOR'S SIGNATURE

Treatment of High Grade Non-Muscle Invasive Bladder Carcinoma by Standard Number and Dose of Intravesical BCG Instillations versus Reduced Number and Dose of Intravesical BCG Instillations. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial

Protocol no. EAU RF 2008

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S) (or sponsor's responsible medical officer)	
STUDY TITLE:	Treatment of High Grade Non-Muscle Invasive Bladder Carcinoma by Standard Number and Dose of Intravesical BCG Instillations versus Reduced Number and Dose of Intravesical BCG Instillations. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial
STUDY AUTHOR(S):	*Raymond Schipper, Christien Caris*
I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study	
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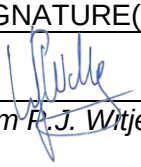
INVESTIGATOR:	
OR SPONSOR(S) RESPONSIBLE MEDICAL OFFICER	*Wim P. J. Witjes,* MD, PhD
AFFILIATION:	*EAU Research Foundation*
DATE:	*13-06-2021*

3. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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.
ASA	American Society of Anaesthesiology
BCG	Bacillus Calmette-Guérin
BMI	Body Mass Index
CA	Competent Authority
CEC	Central Ethics Committee
CFU	Colony Forming Units
CI	Confidence Interval
CIS	Carcinoma In Situ
CRF	Case Report Form
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CUETO	Club Urológico Español de Tratamiento Oncológico
CV	Curriculum Vitae
DNA	DeoxyriboNucleic Acid
EAU RF	European Association of Urology Research Foundation
EC	Ethics Committee
eCRF	electronic Case Report Form
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
FU	Follow-up
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
HCL	Hospices Civils de Lyon
HIV	Human Immunodeficiency Virus
HG	High Grade
HR	Hazard Ratio
IC	Informed Consent
ICIQ	International Consultation on Incontinence Questionnaire
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IFN	Interferon
IL	Interleukin
IMP	Investigational Medical Product
IRB	Institutional Review Board
ITT	Intention-To-Treat
IVU	IntraVenous Urogram
JKS	Zentrum für Klinische Studien Jena
LEC	Local Ethics Committee
LG	Low Grade
LUTS	Lower Urinary Tract Symptoms
M1W1	Month 1 Week 1
mRNA	messenger RiboNucleic Acid
NBI	Narrow-Band Imaging
NMIBC	Non Muscle Invasive Bladder Cancer
QLQ	Quality of Life Questionnaire

QoL	Quality of Life
PCa	Prostate Cancer
PT	Preferred Term
PU	Prostatic Urethra
RF	Reduced Frequency
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.
SD	Standard Deviation
SF	Standard Frequency
SmPC	Summary of Product Characteristics
SOC	System Organ Class
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.
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.
SWOG	South West Oncology Group (US)
TUR	TransUrethral Resection
UCICEC	La Unidad Central de Investigación Clínica y Ensayos Clínicos del Hospital La Paz
UTI	Urinary Tract Infection
UUTI	Upper Urinary Tract Investigation
WBC	White Blood Cells
WHO ISUP	World Health Organisation / International Society of Urological Pathology

4. SYNOPSIS

Name of Sponsor: European Association of Urology Research Foundation (EAU RF)	EudraCT Number: 2010-019181-91 EAU RF number: 2008-01	
Name of finished product: BCG Medac, BCG OncoTICE, BCG Connaught		
Name of active ingredient: BCG (Bacillus-Calmette-Guérin)		

Title of study:	Treatment of High Grade Non-Muscle Invasive Bladder Carcinoma by Standard Number and Dose of Intravesical BCG Instillations versus Reduced Number and Dose of Intravesical BCG Instillations. A European Association of Urology Research Foundation Randomised Phase III Clinical Trial
Investigators:	***EAU Research Foundation NIMBUS Study Group:*** Germany: Dr. Jörg Horstmann, Aachen; Dr. Stefan Machtens; Bergisch Gladbach; Dr. Eberhard Mumperow, Langenfeld; Dr. Andreas Al Ghazal, Ulm; Dr. Thomas Pulte, Würselen; Dr. Michael Stephan-Odenthal, Leverkusen; Dr. Georgios Gakis, Tübingen; Dr. Mario Kramer, Lübeck; Prof. Dr. Marc-Oliver Grimm, Jena; Professor Dirk Zaak, Traunstein; Professor Dr. Bernd Schmitz-Dräger, Nürnberg; Dr. Holger Schreier Braunschweig; Dr. Jan Lehmann, Kiel; Dr. Torsten Werner, Herzberg am Harz; Dr. Jörg Klier, Köln; Dr. Jan Marin, Kempen; Dr. Wolfgang Rulf, Erkrath; Dr. Eva Hellmis, Duisburg; Dr. Andreas Schneider, Salzhausen; Dr. Spiegelhalder, Mettmann; Professor Dr. Manfred Wirth, Dresden; Professor Dr. Theodor Klotz, Weiden; Dr. Henrik Suttmann, Hamburg; Dr. Michael Siebels, München-Pasing; Dr. Gerd Rodemer, Wilhelmshaven; Dr. Robert Rudolph, Kirchheim/Teck; Dipl. med. Roger Zillmann, Berlin-Pankow. The Netherlands: Dr. M. de Bruin, Roermond; Dr. S. Bos, Alkmaar; Professor Dr. R. van Moorselaar, Amsterdam; Professor Dr. T de Reijke, Amsterdam; Dr. J. Boormans, Rotterdam; Dr. B. Wijsman, Tilburg; Dr. H.H.E. van Melick, Nieuwegein; Dr. E van Boven, Beugen; Dr. R.P. Meijer, Utrecht; Dr. A.G. van der Heijden, Nijmegen; Dr. H. Vergunst, Nijmegen; Dr. E. te Slaa, Zwolle/Meppel; Dr. A.M. Leliveld-Kors, Groningen/Winschoten. France: Professor Marc Colombel, Lyon; Professor Alain Ruffion, Pierre-Bénite; Dr. Christian Pfister, Rouen; Professor Morgan Roupret, Paris; Professor Jacques Irani, Le Kremlin-Bicêtre; Dr. Gabriel Stoica, Alençon. Belgium: Dr. Siska Van Bruwaene, Kortrijk; Dr. Filip Ameye, Gent; Dr. Harm Arentsen, Brugge; Professor Dr. Steven Joniau, Leuven. Spain: Pastora Beardo, Vitoria-Gasteiz (Álava)

Study centre(s):	51 sites from 5 European Countries (Germany, The Netherlands, France, Belgium, Spain)
Publication (reference):	Marc-Oliver Grimm, Antoine G. van der Heijden, Marc Colombel, Tim Muilwijk, Luis Martınez-Pineiro, Marko M. Babjuk, Levent N. Turkeri, Joan Palou, Anup Patel, Anders S. Bjartell, Christien Caris, Raymond G. Schipper, Wim P.J. Witjes, for the EAU Research Foundation NIMBUS Study Group. Treatment of High-grade Non–muscle-invasive Bladder Carcinoma by Standard Number and Dose of BCG Instillations Versus Reduced Number and Standard Dose of BCG Instillations: Results of the European Association of Urology Research Foundation Randomised Phase III Clinical Trial "NIMBUS" European Urology, Volume 78, Issue 5, November 2020, Pages 690-698
Studied period (years):	2013-2020
Clinical Phase:	Phase III
Objectives:	The primary objective of this study was to identify if reduced number of BCG instillations is not inferior to standard number and dose intravesical BCG treatment in patients with high grade NMIBC. The primary endpoint for inferiority analysis was time to first recurrence. The secondary objectives were 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 differed between the two study arms.
Methodology:	This study was 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 (weeks 1,2,3); total 15 full dose BCG instillations: standard frequency (reference therapy) 2) Induction cycle BCG-full dose; weeks 1,2, and 6 plus maintenance cycles at months 3, 6 and 12 (weeks 1,3); total 9 full dose BCG instillations: reduced frequency (experimental therapy)
Number of patients: (planned and analysed)	The initial target in this Phase III study was to enrol 1000 patients who were randomly assigned to one of 2 treatment schedules in a 1:1 ratio, BCG standard- or reduced frequency regimen. Owing to BCG shortage, recruitment was delayed and statistical assumptions were redefined and, taking into account prolonged recruitment and follow-up times, patient numbers were reduced to 412 per arm maintaining statistical power. At the time of stopping recruitment (see section "Premature End of Study"), a total of 359 patients from 51 sites were randomised.
Diagnosis and main criteria for inclusion:	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 were eligible for inclusion. The absence of high-grade papillary NMIBC after routine repeated TUR (re-TUR) and/or re-re-TUR had to be confirmed at histopathological examination. As per protocol amendment 5, dated May 2017:

	a) patients with histological detection of T1 tumour in the TUR or re-TUR should have undergone an additional TUR; b) patients having Ta high-grade tumour could be included without re-TUR, in case muscle tissue was provided in a biopsy specimen confirming complete removal of the tumour.
Test products: **Dose and mode of administration:** **Duration of treatment:**	BCG Medac, BCG OncoTICE, BCG Connaught BCG Medac was delivered as a powder and solvent for suspension for intravesical use. After reconstitution, one vial contained BCG (Bacillus-Calmette-Guérin) bacteria seed RIVM derived from seed 1173-P2 2 x 10^8 to 3 x 10^9 viable units. BCG OncoTICE was delivered as a powder and solvent for suspension for intravesical use. After reconstitution, one vial contained a total of 2-8 x 10^8 CFU of OncoTICE BCG. BCG Connaught was delivered as a powder and solvent for suspension for intravesical use. After reconstitution, one vial contained a total 1.8 to 15.9 x 10^8 CFU of BCG Connaught. Standard Dose Instillations took place with 1 vial of BCG. Treatment with the randomised treatment schedule (BCG induction cycle) started 2 weeks after and no later than 6 weeks after the last resection. The first maintenance therapy should have been given at month 3 that is defined as 6-12 weeks after the last instillation of the induction BCG cycle (week 6) and thereafter at months 6 (18-24 weeks) and 12 (42-48 weeks) after the last instillation of the induction BCG cycle.
Reference therapy: **Dose and mode of administration:** **Criteria for evaluation**	Standard Frequency therapy Induction cycle BCG-full dose; weeks 1 through 6 plus maintenance cycles at months 3, 6 and 12 (weeks 1,2,3); total 15 full dose BCG instillations The primary endpoint was time to first recurrence. Secondary objectives were rate of progression to muscle-invasive (≥T2) disease, identification of the number and grade of recurrent tumours, and identification of the incidence and severity of side effects, specifically the occurrence of treatment-related toxicity higher than grade 2 (according to WHO).
Statistical methods:	This was a randomised nonblinded clinical study designed to establish noninferiority of a reduced versus a standard number of BCG instillations. The efficacy analysis was performed including all patients who were randomized (intention-to-treat analysis). Inferiority of the experimental arm was defined as the true hazard ratio (HR; hazard experimental/ hazard standard) for first recurrence being lower than 0.75. The sample size was calculated to be 500 patients per arm at a statistical power of 80%. Owing to BCG shortage, recruitment was delayed and statistical assumptions were redefined in amendment 4 from May 2016. Taking into account prolonged recruitment and follow-up times, patient numbers were reduced to 412 per arm maintaining statistical power. Safety analyses and IDMC evaluations were performed initially at yearly intervals, and as of 2017 at 6 month intervals. According to the protocol, when inferiority was shown at interim analysis, further analyses were requested to check for

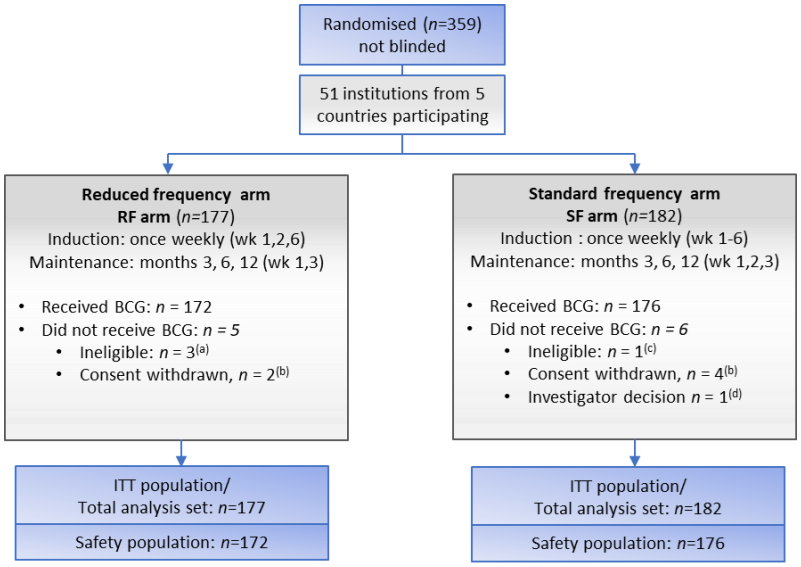
	biases and stopping the study needed to be considered, in case the upper limit of the 95% CI was less than 0.75. The HR for time from randomisation to first recurrence was analysed in the intention-to-treat population, as well as the rate of progression to muscle-invasive disease, occurrence of distant metastasis, and survival. Time to first recurrence was estimated by means of the Kaplan-Meier method. A univariate Cox proportional hazard model was applied to assess treatment effects.
Premature End of Study	After reviewing the safety data analysis based on the cut-off date of July 1, 2019, the IDMC advised stopping the study, as the upper limit of the one-sided 97.5% CI of the HR regarding recurrence fell below 0.75. The steering committee immediately stopped patient recruitment (Oct 2019), patients were informed, and those still treated in the RF arm were given the opportunity to switch to the standard schedule. Study end was set to the time point of completion of the visit at month 6, week 3 for all patients (June 2020).
Summary and conclusions	A total of 359 patients from Germany (152), the Netherlands (111), France (68), Belgium (27) and Spain (1) were randomised between December 2013 and October 2019. See for Trial Diagram Figure 1. **Figure 1.** Consolidated Standard of Reporting Trials diagram.  BCG = bacillus Calmette-Guérin; ITT = intention to treat; RF = reduced frequency; SF = standard frequency. [a] 1xT >T2, 1x history of upper urinary tract tumour, 1x laboratory abnormalities. [b] consent withdrawn prior to start BCG treatment. [c] 1x no re-re-TUR performed because patient opted for cystectomy. [d] no further details available. Baseline characteristics for patients and disease are described in Table 1.

Table 1. Baseline characteristics for patients and disease

	Randomised treatment		
	Reduced frequency treatment schedule (n = 177)	Standard frequency treatment schedule (n = 182)	**Total** (n = 359)
Gender, n (%)			
Male	144 (81.4)	152 (83.5)	296 (82.5)
Female	33 (18.6)	30 (16.5)	63 (17.5)
Type of cancer, n (%)			
Primary	163 (92.1)	167 (91.8)	330 (91.9)
Recurrent	14 (7.9)	15 (8.2)	29 (8.1)
Number of tumors, n (%)			
Single	95 (53.7)	106 (58.2)	201 (56.0)
Multiple	82 (46.3)	76 (41.8)	158 (44.0)
Highest tumor category, n (%)			
T0#	0 (0)	3 (1.7)	3 (0.8)
Ta	82 (46.3)	77 (42.3)	159 (44.3)
T1	94 (53.1)	102 (56.0)	196 (54.6)
≥T2*	1 (0.6)	0 (0)	1 (0.3
Associated CIS, n (%)			
Yes	49 (27.7)	52 (28.6)	101 (28.1)
No	128 (7.3)	130 (71.4)	258 (71.9)
BCG strain used, n (%)			
BCG Medac	156 (88.1)	164 (90.1)	320 (89.1)
BCG Tice	16 (9.0)	16 (8.8)	32 (8.9)
BCG Connaught	5 (2.8)	2 (1.1)	7 (2.0)

Three patients had CIS only (ineligible)
* Patient did not receive BCG and is not included in follow up (ineligible)

In total,177 patients were randomised to the reduced frequency (*RF*) treatment schedule and 182 to the standard frequency (*SF*) treatment schedule. Thereof, 172 (97.2%) and 176 (96.7%) received at least one BCG instillation in the *RF* arm and *SF* arm, respectively.

The prognostic factors at initial resection were as follows:
RF arm: Ta/T1: 46.3/53.7%; primary/recurrent: 92.1/7.9%; single/multiple tumours: 53.7/46.3%; concomitant carcinoma in situ: 27.7%.
SF arm: Ta/T1: 44/56%; primary/recurrent: 91.8/8.2%; single/multiple tumours: 58.2/41.8%; concomitant carcinoma in situ: 28.6%.

The absence of high-grade (papillary, as per protocol amendment 4) NMIBC after routine re-TUR and/or re-re-TUR had to be confirmed at histopathological examination.
As per protocol amendment 5, dated May 2017:

a) patients with histological detection of T1 tumour in the TUR or re-TUR should have undergone an additional TUR.
b) patients having Ta high-grade tumour could be included without re-TUR, in case muscle tissue was provided in a biopsy specimen allowing to confirm complete removal of the tumour.

The vast majority of patients underwent routine re-TUR: 158 (89%) in the *RF* arm and 165 (91%) in the *SF* arm. Muscle tissue was present in 90.5% and 97% of the re-TUR specimens in the *RF* arm and *SF* arm, respectively.
T-category in re-TUR was T0 (83.5%), Ta (12%) and T1 (4.4% in the *RF* arm and T0 (81.2%), Ta (12.7%) and T1 (6.1%) in the *SF* arm.

	Patients with high grade tumour in the re-TUR and included prior to amendment 5 underwent a re-re-TUR in 2 out of 11 (18.2%) in the *RF* arm and 4 out of 15 (26.7%) in the *SF* arm. In 3 out of 3 patients in the *RF* arm and 1 out of 4 in the *SF* arm with T1 tumor at re-TUR and included according to amendment 5, a re-re-TUR was performed. Five patients underwent a re-re-TUR even though not required by protocol. Forty-six (29 in *RF* arm and 17 in *SF* arm) patients did not undergo a re-(re)-TUR, although this should have been done based on the applicable protocol at the time, or did not have muscle tissue present in the last TUR specimen and were possibly incompletely resected and were considered ineligible. 59 patients were ineligible for other reasons. A total of 286 protocol deviations were reported. Types of deviations were inclusion/exclusion criteria (40.2%), non-compliance with protocol assessments (41.6%), non-compliance with study treatment (10.5%), randomisation error (2.8%) or other (4.9%). Questionnaires (EORTC QLQ C30, ICIQ-LUTS) have been completed prior to the first and last instillation of every cycle.
Efficacy results:	The median follow-up time of this final analysis was 14 months for all patients and 17 months for patients without recurrence. After 14 months of median follow-up, the intention-to-treat analysis showed a difference in recurrences between treatment arms: 55/177 (reduced frequency) versus 30/182 patients (standard frequency) with a hazard ratio of **0.47 [95% CI: 0.30 – 0.74]**. In additional analyses in subpopulations the hazard ratio was: **0.47 [95% CI: 0.30 – 0.74]** for all patients that received at least one BCG instillation (348 patients); **0.48 [95% CI: 0.29 – 0.79]** excluding patients with CIS only, T2 tumour and possible incomplete resection (309 patients). One and seven patients in the *RF* and the *SF* arm, respectively, progressed to muscle-invasive disease (≥T2), and one additional patient treated with the standard therapy developed distant metastases.
Safety results:	For 283 patients a total of 2655 AEs have been reported. A total of 131/177 patients were affected with 858 AEs in the *RF* arm and 152/182 patients were affected with 1797 AEs in the *SF* arm. 9 patients died for the following reasons; car accident (1), Cerebral vascular accident (1), Autoimmune encephalitis or paraneoplastic syndrome (1), Sepsis (1) Pulmonary embolism (1) or reason unknown (4). In all cases there was no reasonable possible relationship to study treatment.

	No SUSARS were reported.
Conclusion:	The NIMBUS RF schedule was inferior to the standard schedule regarding time to first recurrence. Fewer patients were affected with fewer AEs in the reduced treatment arm than in the standard arm. In patients with high-grade NMIBC, this study supports the use of the standard BCG regimen as recommended by the EAU guideline (6 weeks of induction followed by 3 weeks of maintenance at 3, 6, and 12 months) after complete tumour resection.
Date of the report:	11-06-2021

5. ETHICS

5.1 Independent Ethics Committee or Institutional Review Board

The protocol, all amendments and all related informed consent forms have been reviewed by the Competent Authority (CA), Central Ethics Committee (CEC) and/or Local Ethics Committee (LEC) in each participating country. A signed and dated statement that the protocol and informed consent were approved by the IRB/IEC was archived with the other documents of the study. A list of all CAs, CECs and LECS consulted is given in Appendix 1.

5.2 Ethical conduct of the study

The study was carried out in accordance with the Declaration of Helsinki.

5.3 Patient information and consent

The investigator explained to each patient (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it could entail.
Each patient was informed that participation in the clinical study was voluntary and that he/she could withdraw from the study at any time and that withdrawal of consent would not affect his/her subsequent medical treatment or relationship with the treating physician.
The informed consent was given by means of (a) standard written statement(s), written in non-technical language. The patient received a copy of the signed document.
For selected centres which participated in the DNA and/or Cytokine substudy, additional information on the substudies was added to the patient information sheet and a separate informed consent form was signed if the patient agreed to participate in the DNA and/or Cytokine substudy.
A sample of the patient information and consent form is given in Appendix 2.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 International Steering Committee

The following persons were members of the Steering Committee:

Leading investigators:

Prof. Dr. Levent N. Türkeri	Marmara University Medical School, Istanbul, Turkey
Prof. Dr. Marko M. Babjuk	Charles University, Praha, Czech Republic
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

6.2 Scientific Committee

The members of the Steering Committee and the statistician (Rogier Donders, Radboudumc) responsible for the study methodology were members of the Scientific Committee. The Leading Investigators chaired the Scientific Committee.

6.3 Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) was established. The primary responsibility of the IDMC was to review interim safety data (prepared by the study statistical data analyst) 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.

The Committee included a urological oncologist, a urologist and an epidemiologist not involved in the study, based on their experience, reputation for objectivity, absence of conflicts of interest.

The following persons were members of the IDMC:
Prof. Dr. Markus Kuczyk, urologist, Germany
Prof. Dr. Bart Kiemeney, epidemiologist, the Netherlands
Prof. Dr. George Thalmann, urologic oncologist, Switzerland

6.4 Administration

Central study coordination was done by the EAU Research Foundation (Arnhem, The Netherlands).

Subsidiary parties were:
- European Association of Urology (EAU)
- German Cancer Aid (Stiftung Deutsche Krebshilfe)
- Medac: Gesellschaft Für Klinische Spezial Präparate GMBH
- Hospices Civils de Lyon (HCL)

Initiation and monitoring was done by:
- Germany: Zentrum für Klinische Studien Jena (JKS)
- The Netherlands: EAU Research Foundation (EAU RF)
- France: Hospices Civils de Lyon (HCL)
- Belgium: EAU Research Foundation (EAU RF)
- Spain: La Unidad Central de Investigación Clínica y Ensayos Clínicos del Hospital La Paz (UCICEC)

Data management was performed by EAU Research Foundation.

Writing of the clinical study report and study manuscript was done by the employees of EAU Research Foundation in cooperation with the Steering Committee.

An overview of the parties involved is given in Appendix 3
An overview of the participating centres and investigators is given in Appendix 4

7. INTRODUCTION

Introduction according to the original protocol

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 was 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

8. STUDY OBJECTIVES

The primary objective of this study was to identify if reduced number of BCG instillations were not inferior to standard number and dose intravesical BCG treatment in patients with high grade NMIBC. Primary endpoint was time to first recurrence.
Secondary endpoints were: 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 were compared between the two study arms.

9. INVESTIGATIONAL PLAN

9.1 Overall study design and plan

This was 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 (weeks 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 (weeks 1,3).

Initially, the study included a 2-year recruitment phase, followed by a 3-year observation phase (i.e. the first randomised patient would be observed for 5 years in total, the last randomised patient would be observed for 3 years). Owing to BCG shortage, the recruitment period was prolonged from 2 to 6 years (See also section 9.2.1). Due to the Premature End of Study end of follow-up period was set to the time point of completion of the visit at month 6, week 3 for all patients (See also section 9.2.6).

9.2 Discussion of study design

9.2.1 Extension of recruitment period

The persistent worldwide shortage of BCG that started in 2014 hampered the start-up of new sites/countries and accrual of the NIMBUS trial. Therefore, the recruitment period was extended from 2 to 6 years (changed from 2 to 3 years in Amendment 3, changed from 3 to 4 years in Amendment 4, changed from 4 to 6 years in Amendment 5).
The initial target was to recruit 1000 patients. Following the extension of recruitment period from 3 to 4 years (Amendment 4) the total number of patients was adapted accordingly (824).

9.2.2 Transurethral Resection (TUR)

The recommendations to perform a second Transurethral Resection (TUR) of the bladder in the diagnosis of bladder cancer were changed in the 2017 EAU guidelines. It was recommended to perform a second TUR (Re-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 (Amendment 5) it was 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 (Amendment 5).

9.2.3 Pregnancy

The presence of pregnancy was an exclusion criterion. However it was not clearly described in the protocol how to practice adequate contraception and to continue such precautions during the study treatment period. Text was adapted in some sections of the protocol and in the patient information to more clarify the study procedures for female patients of childbearing potential (Amendment 5) .

9.2.4 Data analysis

The IDMC reviewed the data in December 2018 (based on data present in the eCRF on October 1st 2018) and requested some adaptation of the data analysis as described in the study protocol. Because the median time to first recurrence was likely not be reached (life table risk of recurrence remained below 50%), the IDMC proposed to change this criterion into a HR of 0.75. Because the requirement of a 1% one sided significance level was extremely restrictive, the IDMC proposed to test at a 2.5% one sided significance level which was in agreement with the upper limit of the 95% CI around the HR being less than 0.75 (Amendment 6).

9.2.5 BCG (sub)strains

Continued supply availability of BCG was a main challenge in many countries including the countries that participated in the NIMBUS study. In addition to BCG Medac, BCG TICE and BCG Connaught, substrains used for vaccine production were available, e.g., Brazilian (Moreau/Rio de Janeiro), Danish (Copenhagen–1331), Japanese (Tokyo–172-1), Russian (Moscow–368) and Bulgarian (Sofia–SL222). Different strains tended 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 was therefore the result of historical use, production, logistics or other factors. Because of the BCG shortage we therefore allowed 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 (Amendment 6). At the end of the NIMBUS study, no (sub)strains other than BCG Medac, BCG TICE and BCG Connaught were used.

9.2.6 Premature End of Study

After reviewing the safety data analysis based on the cut-off date of July 1, 2019, the IDMC advised stopping the study, as the upper limit of the one-sided 97.5% CI of the HR regarding recurrence fell below 0.75. The steering committee immediately stopped patient recruitment (Oct 2019), patients were informed, and those still treated in the RF arm were given the opportunity to switch to the standard schedule. Study end was set to the time point of completion of the visit at month 6, week 3 for all patients (June 2020). In Germany this corresponded to the date of 15th April 2020. No protocol amendments were needed/ submitted except for France (see section 9.8).

9.3 Selection of study population

Patients with high grade (Pathological Grading according to WHO/ISUP classification, see reference 12) Ta-T1 urothelial carcinoma of the bladder with or without CIS and who had not received any prior BCG intravesical instillation therapy were recruited from urology departments in European hospitals participating in this study. At the time of the recruitment stop on 17 October 2019 (see section 9.2.6), 359 patients from 51 centres were randomised.

9.3.1 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 *Added in Amendment 4*
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 ~~2. R~~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 tissue) of the initial tumor site(s) *Deleted/Added in Amendment 2 Deleted/Added in Amendment 5*
3. Re-re-TUR should be performed in case of histological detection of T1 low/high grade tumor ~~*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). Added in Amendment 4 Deleted/Added in Amendment 5*
4. Histopathologically confirmed absence of ~~*high-grade papillary NMIBC*~~ *T1 low/high grade in the re-TUR specimen and/or re-re-TUR specimen. Added in Amendment 4 Deleted/Added in Amendment 5*
5. 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)~~
Deleted in Amendment 2

~~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~~ *Deleted in Amendment 5*
~~6. Prior multi-instillation intravesical chemotherapy is allowed, provided that the last instillation was completed 3 months prior to randomisation in this study.~~ *Deleted in Amendment 5*
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 Added in Amendment 6
7. Signed and dated informed consent form.
12. Patients is clinically fit enough to receive BCG treatment.
Added in Amendment 4

Eligibility patients with CIS only, Ta and T1 tumors in TUR:

After the first transurethral resection (TUR), patient underwent a re-TUR ~~at weeks 4-6 after initial resection.~~ *6 weeks (between 4-8 weeks) after the macroscopic complete resection. Deleted/Added in Amendment 2 Added in Amendment 4*

- *Patients without tumor in the re-TUR specimen are eligible for the study. Added in Amendment 4*

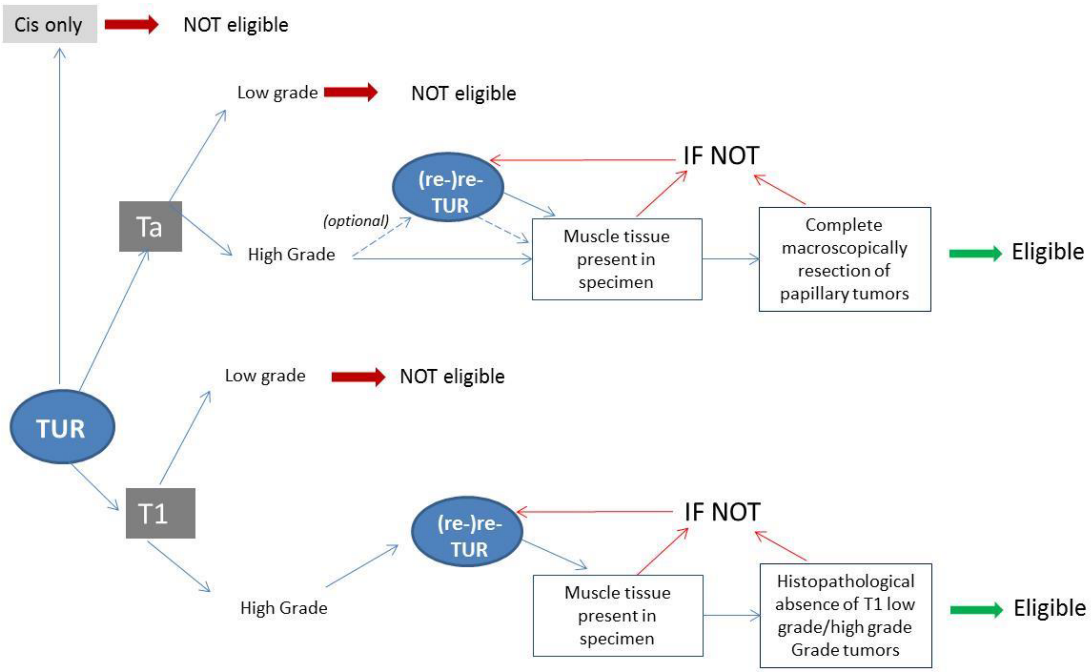
Patients with histological detection of high grade papillary NMBIC in the re-TUR ~~who~~ should underwent a second re-TUR and were eligible for the study if they fulfilled all ~~inclusion~~ selection criteria i.e. patients should have been, macroscopically and histologically confirmed, ~~tumor~~free of high-grade papillary tumors in the re-re-TUR specimen. If so, first re-TUR was considered as TUR as defined by the protocol.
Deleted/Added in Amendment 2 Deleted/Added in Amendment 4

- *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. Added in Amendment 4*

The section between the dotted lines was removed in Amendment 5 and the following text and figure was added:

- *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 provided muscle is present and reported in the specimen and 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).



Flow chart for eligibility patients with CIS only, Ta and T1 tumors in TUR

9.3.2 Exclusion criteria

Patients with any of the following exclusion criteria were not 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-*(re)*-TUR surgical specimens *Added in Amendment 5*
~~4. Patients with incomplete resection of visible tumors~~ *Deleted in Amendment 5*
~~5. Absence of muscle tissue in the re-TUR specimen(s)~~ *Deleted in Amendment 5*
4. Presence of any upper urinary tract tumors 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 ~~other than the~~ basal cell carcinoma of the skin *or localised prostate cancer in active surveillance Added in Amendment 4 Deleted/Added in Amendment 5*
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* within 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~~ *Deleted/Added in Amendment 5*
~~11. Patients with a WHO performance score of > 2 or ASA grade 4-5 (Appendix 9)~~
~~13. Patients older than 80 years of age~~
~~14. Patients with uncontrollable UTI~~
~~15. Patients with White Blood Count (WBC) below 3.0 x 109/l or platelet count below 100 x 109/l at baseline~~

~~16. Renal and hepatic function values exceeding two times the upper normal value of the local laboratory~~
Deleted in Amendment 4
10. Patients with uncontrollable UTI

9.3.3 Removal of patients from therapy or assessment

In the patient informed consent form the patients were informed that they had the right to withdraw from the study at any time without affecting their subsequent care and could be withdrawn at the investigator's discretion at any time. In the event that the patient dropped out, the investigator, if possible, indicated the reason for withdrawal. Reasonable effort was 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 were not replaced.

Off study criteria:

- When the investigator considered it in the best interest of the patient that he/she was withdrawn
- First recurrence ~~after completion of the 6 weeks induction course of BCG.~~ *Deleted in Amendment 6*
- 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
- Occurrence of a new malignancy requiring the use of systemic chemotherapy.

9.4 Treatments

9.4.1 Treatments administered

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 was used: BCG Tice, BCG Medac or BCG Connaught. *In case of a BCG shortage of one of these three strains, it was allowed to use another locally approved BCG strain, e.g., Moreau/Rio de Janeiro, Copenhagen–1331, Tokyo–172-1, Moscow–368, Sofia–SL222. Added in Protocol Amendment 6*
BCG was prescribed by the investigator according to usual daily practice. Added in Protocol Amendment 5

Treatment with the randomised treatment schedule started 2 weeks after and no later than 6 weeks after the last resection (*initial resection,* re-TUR or re-re-TUR). *Added in Amendment 5*
The first maintenance therapy was given *at month 3 that was defined as* ~~3 months (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. Standard Dose Instillations took place with 1 vial of BCG. *Deleted/Added in Amendment 3*

The weekly BCG instillations during induction and maintenance cycles were conducted within 7 ± 2 days. Added in Amendment 2

In case of side effects the instillation schedule could be modified. The rules for modification of the treatment in different side effects were mentioned in Appendix 6 of the study protocol.

Any deviation from the required dose or schedule as well as the reason for the deviation was documented in the eCRF by the investigator.
In case of cessation of BCG treatment, if possible, follow up cytology and cystoscopy was 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 took place. Patients with fluid restriction will be compared with patients without fluid restriction and patients with rotation during the instillation procedure were compared with patients without rotation with respect to side effects and efficacy. A limited number of extra questions in the CRF were completed in case the investigator decided to participate in this substudy.

9.4.2 Identity of investigational product(s)

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 was used: BCG OncoTICE, BCG Medac or BCG Connaught.
BCG Medac is marketed in Germany, the Netherlands and France. BCG OncoTICE is marketed in the Netherlands and Belgium. BCG Connaught is marketed in France, Spain and Italy. Suppliers of the investigational products were Medac GmbH (BCG Medac) , Merck Sharp & Dohme Limited (BCG OncoTICE) and Sanofi Pasteur Limited (BCG Connaught). Available safety findings can be derived from the reference safety documents, i.e. the SmPC's of BCG Medac, BCG OncoTICE and BCG Connaught.

9.4.3 Method of assigning patients to treatment groups

Randomisation was done via *a web-based data management system* ~~the EAU-RF website~~.
When a patient was eligible to participate in the study and written informed consent was obtained, the patient was randomised via the web-based data management system.
Treatment allocation was ~~communicated by e-mail~~ *displayed immediately on the screen after entry of* ~~For treatment allocation~~ the following ~~information will be needed~~: *Deleted/Added in Amendment 5*

- Institutions name
- Name of investigator
- Patient identification / Patients date of birth
- Date of *informed consent*~~last TUR~~ *Deleted/Added in Amendment 5*
- 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~~). *Deleted in Amendment 5*
- CIS present: Y/N.

In this study, there were 5 stratification factors in which the marginal treatment totals were balanced. These stratification factors 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 or BCG Medac and 5) single or multiple tumors. The validated randomisation program used the minimisation method with a random element as described by Pocock for treatment assignment [15].
At randomisation, a number was allocated to the patient (patient sequential identification number). This number identified the patient and was reported on all eCRF's and other relevant documents. This patient sequential identification number identified the patient for the Sponsor. The local investigator and his personnel maintained a list which identifies the patients' sequential identification number with the patients source data. This list was safeguarded by the local investigator and his personnel.

9.4.4 Selection of doses in the study

BCG Medac was delivered as a powder and solvent for suspension for intravesical use. After reconstitution, one vial contained BCG (Bacillus-Calmette-Guérin) bacteria seed RIVM derived from seed 1173-P2 2 x 10^8 to 3 x 10^9 viable units.
BCG OncoTICE was delivered as a powder and solvent for suspension for intravesical use. After reconstitution, one vial contained a total of 2-8 x 10^8 CFU of OncoTICE BCG.
BCG Connaught was delivered as a powder and solvent for suspension for intravesical use. After reconstitution, one vial contained a total 1.8 to 15.9 x 10^8 CFU of BCG Connaught.

Instillations took place with standard BCG-full dose, i.e. 1 vial of BCG.

9.4.5 Selection and timing of dose for each patient

Patients were in a 1:1 ratio randomly assigned to one of 2 treatment schedules:
1) Induction cycle BCG-full dose; weeks 1 through 6 plus maintenance cycles at months 3, 6 and 12 (weeks 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 (weeks 1,3); total 9 full dose BCG instillations

As of October 17th 2019, patients in the Reduced frequency treatment schedule were offered the possibility to switch to the Standard frequency treatment schedule (see section 9.2.6 Premature End of Study).

9.4.6 Blinding

The NIMBUS was a multicentre prospective, randomized, parallel group, not blinded, trial.

9.4.7 Prior and concomitant therapy

Prior NMIBC therapy had to be documented, as well as concomitant medication up to the visit at month 15 (3 months after last BCG instillation of the maintenance cycles = end of treatment). During the study, other treatments or the administration of other drugs for the prevention/treatment of NMIBC were not permitted. Any other non-experimental drug(s) in treatment for other indications were permitted, provided they are recorded in the eCRF.

9.4.8 Treatment compliance

BCG was prescribed by the investigator according to usual daily practice. Transport, storage, usage and disposal of the BCG was performed according to local standard procedures. Wherever possible, primary and/or secondary packaging material of BCG used for study patients were extra labelled and information (e.g. charge number) of the BCG designated to a study patient was recorded in a drug accountability log.
The treatment time schedule was performed according to treatment arm (Standard Frequency or Reduced Frequency) for which the patient was randomised, as described in the Study Protocol.
Detailed information on the BCG instillations (e.g. date/time, type of BCG strain, dose) were recorded in the eCRF. For selected centres that participated in the substudies, information on date and time of urine and/or blood collection was recorded. Any deviation of study treatment was recorded in the eCRF by completing a Protocol Deviation form. (see for CRF Appendix 5)

9.5 Efficacy and safety variables

9.5.1 Efficacy measurements assessed

The primary efficacy variable was time to first recurrence defined as the time between date of randomisation and date of first recurrence.
Secondary efficacy variables were:

- number and grade of recurrent tumors
- rate of progression to a higher stage (T2 or higher) of the disease.

All patients were followed-up by 3 monthly control cystoscopies and voided urine cytology. Any lesions with high suspicion for malignancy on follow-up cystoscopies were resected completely with additional biopsies of the tumor bed to provide samples of muscle tissue for appropriate pathological examination. No random biopsies were required during the control cystoscopies. However, any suspicious lesion(s) was biopsied to rule out the presence of any type of tumor(s). When a recurrence was suggested by positive cytology, a biopsy was performed because a recurrence can only be established on histological examination.
If the cytology was positive in case of tumor-free cystoscopy, upper urinary tract imaging was performed according to local standards (e.g. IVU, CT-Urography).
In case suspect lesions were pathologically confirmed bladder cancer, the time of first recurrence, number and grade of recurrent tumors and progression to a higher stage was determined.

9.5.2 Safety measurements assessed

Safety assessments consisted of regular monitoring and recording of the following parameters:

Adverse events

Information about all adverse events (AEs), whether volunteered by the patient, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, were collected and recorded on the Adverse Event Case Report Form (according to the International Common Terminology Criteria for Adverse Events (CTCAE) and followed as appropriate. An AE was any untoward medical occurrence in a clinical investigation patient, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE could therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. Adverse event information was collected from the first instillation up to the visit at month 15.

Serious adverse events

Information about all serious adverse events was collected and recorded on the Serious Adverse Event Report Form. To ensure patient safety the local delegate of the Sponsor was informed of each serious adverse event within 24 hours of learning of its occurrence through the process described in section 6.3 of the Study Protocol. A serious adverse event (SAE) was defined in general as an untoward (unfavorable) event which:

- resulted in death.
- was life-threatening.
- required hospitalization or prolongation of existing hospitalization.
- resulted in disability/incapacity,
- was a congenital anomaly/birth defect in the offspring of a study patient.
- was a Grade 4 adverse event according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.

An event which was part of the natural course of the disease under study (i.e., disease progression, recurrence) was captured as an efficacy measure; therefore it did not needed to be reported as a SAE.
Any new cancer (non-related to the cancer under study) needed to be reported as an SAE.

All serious adverse events which occurred from the first instillation up to the visit at month 15 whether or not considered related to the treatment, were reported immediately. Serious adverse events **related to either study participation or related to study treatment** were reported throughout the entire study period.

Pregnancy
Presence of pregnancy was an exclusion criterion in the protocol. Following Amendment 5 it was clearly described in the protocol how to practice adequate contraception and to continue such precautions during the study treatment period. The investigator, or his/her designee, had to record pregnancy information in the Pregnancy Report Form and to submit it to the Sponsor within 24 hours of learning of a patient's pregnancy.

9.5.3 Flow charts

Standard Frequency Arm

			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.

Reduced Frequency Arm

			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.

9.6 Data quality assurance

For this multicentre study, an initiating investigators meeting at a central location was held to standardize data management procedures and resolve questions regarding protocol conduct. At the initiation meeting, the investigator and other site study personnel were instructed how to conduct the study- and data management procedures.

Monitoring visits to sites were conducted by EAU RF (The Netherlands and Belgium) or a designee, i.e. JKS (Germany), HCL (France), UCICEC (Spain), on a regular basis to verify adherence to the protocol and the completeness, accuracy and consistency of the data by performing source document review of specific types of information in all patients enrolled.

All relevant patient data were entered by the investigator or a qualified employee into an electronic CRF in accordance with the instructions provided. The eCRF was designed by EAU RF using MARVIN. During database set up conditional visibility of screens, sections and data items were programmed. Also data consistency checks were programmed which were performed online at time of eCRF data entry. Also listings were generated by EAU RF. In case of discrepancies, queries were issued to the investigator to clarify for instance missing data, inconsistencies, illegible data, illegal values and items that were not clearly corrected. For a sample of the case report form (unique pages only) see Appendix 5.

When all patient and visit data were entered, all data problems were resolved, all data checks and quality control checks had been performed and the data had been signed by the Investigator, the study database was considered to be clean and was locked.

Risk assessment:

The following issues/events were identified as a risk for the documentation, governance, GCP Compliance, or reliability of the trial results:

- *Study procedures not according to standard practice*

After first experience with the protocol, the investigators indicated that some of the study procedures were not according to their daily urological practices. Therefore, the protocol was finetuned in a way that study assessment /timelines were adapted according to routine procedures. (Amendment 2, Amendment 3)

- *Extension of recruitment period*

The persistent worldwide shortage of BCG that started in 2014 hampered the start-up of new sites/countries and accrual of the NIMBUS trial. Therefore, the recruitment period was extended from 2 to 6 years. The initial target was to recruit 1000 patients. Following the extension of recruitment period from 3 to 4 years (Amendment 4) the total number of patients was adapted accordingly (824). Following Amendment 6 the data analysis as described in the study protocol was adapted as the median time to first recurrence was likely not be reached (see for more details section 9.2.4).

- *Impact of COVID-19 on the NIMBUS study:*

Since March 2020, the COVID-19 crisis has affected the conduct of the NIMBUS Study. At the time that rigorous containment measures like quarantine and complete lockdown were taken in most European countries, some study visits that were planned for March/May 2020 (BCG treatment, cytology and cystoscopy) were postponed or cancelled. This has led to additional protocol deviations, however, the overall effect on study results was minimal as it was only applicable for a few patients (5 out of 345) that were still in treatment and a low number of patients (24 out of 345) in Follow-up with only few visits that were cancelled/-postponed. It was expected that (S)AE reporting may have been delayed due to staff

shortage/availability at the sites. However, final monitoring of the (S)AEs recorded showed no evidence of any delay of (S)AE reporting.
Due to travel ban monitors and restriction of visits to health care facilities it was not possible to conduct on-site monitoring or close out visits. These visits (including the close-out visits), if allowed, were (partly) replaced by remote monitoring or if not allowed/possible were postponed until physical access to hospitals was allowed again.

- Premature End of Study

In Oct 2019 patient recruitment was immediately stopped (see section 9.2.6), patients were informed, and those still treated in the RF arm were given the opportunity to switch to the standard schedule. Study end was set to the time point of completion of the visit at month 6, week 3 for all patients.
Due to the premature ending of the trial (359 out of the 824 initially planned patients were randomised), the primary and secondary objectives of the NIMBUS study were not assessed as planned in the protocol.

9.7 Statistical methods planned in the protocol and determination of sample size

Determination of sample size

The initial assumptions for the power calculations were the following:
- Primary endpoint on which sample size was based is median time to first recurrence.
- The median time to first recurrence for the study population is 60 months
- Recruitment period was 2 years
- Follow up after recruitment was 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 was 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 (texperimental/tstandard) 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 was 500 patients per arm resulting in the total number of patients to be randomized at 1000 patients at an acceptable power of between 80 and 85%.
Recruitment period was 2 years and all patients were to be followed for an additional 3 years or until recurrence or progression, if occurred before this period.

The worldwide shortage of BCG hampered accrual of the NIMBUS trial. Therefore, the recruitment period was extended from 2 to 6 years (changed from 2 to 3 years in Amendment 3, changed from 3 to 4 years in Amendment 4, changed from 4 to 6 years in Amendment 5). Therefore, in Amendment 4, N per arm and % power were adjusted accordingly:

N per arm	Number of events needed	power *
324	298	70
365	335	75
412	379	80
472	434	85
552	508	90

From this table, the sample size needed per arm was *412.*

Interim Analysis

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

The reason for performing the interim analysis was based on ethical safety considerations. In the presence of evidence of inferiority of the reduced frequency arm, the study was to be stopped.

The interim analysis was planned to be performed using a significance level of 2,5 % (one sided). Inferiority was defined as a true hazard ratio for first recurrence ($hazard_{experimental}/hazard_{standard}$) lower than 0.75. If there were doubts on the efficacy of the reduced frequency arm, further in depth analyses were to be performed to investigate a possible imbalance in prognostic factors. The IDMC would advise to stop the study when the upper limit of the 95% CI was less than 0.75. No changes in the sample size were required because of the interim analysis.

The interim analysis on the hazard ratio for first recurrence was also to be performed between the different BCG strains used (Statistical tests at the 5% level of significance, two-sided)

Results of the interim analysis were to be evaluated by an Independent Data Monitoring Committee (IDMC). After evaluation of the data, the IDMC would communicate an advice to the Steering Committee members to continue or stop the trial. In order to maintain data integrity, the Steering Committee was blinded to the analysis results and remained blinded if the IDMC would suggest to continue the study.

Regular safety analyses were done in preparation of IDMC meetings.

Final Statistical Analyses

Due to the premature ending of the trial, the final statistical analyses were not assessed as planned in the protocol (See section 9.2.6 Premature End of Study).

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

The incidence and severity of all adverse events were tabulated per treatment group.

The efficacy analysis was performed including all patients who were randomized (intention-to-treat analysis).
Inferiority of the experimental arm was defined as the true hazard ratio (HR; hazard experimental/ hazard standard) for first recurrence being lower than 0.75.
According to the protocol, when inferiority was shown at interim analysis, further analyses were requested to check for biases and stopping the study needed to be considered, in case the upper limit of the 95% CI was less than 0.75. The HR for time from randomisation to first recurrence was analysed in the intention-to-treat population, as well as the rate of progression to muscle-invasive disease, occurrence of distant metastasis, and survival. Time to first recurrence was estimated by means of the Kaplan-Meier method. A univariate Cox proportional hazard model was applied to assess treatment effects.

For each patient entering, the reason for discontinuation (e.g. patient decision, urologists decision, lack of efficacy, adverse events) was clarified.

9.8 Changes in conduct of the study or planned analyses

- **Initial protocol, dated June 2nd 2013**

The initial protocol is provided in Appendix 6.

- ***Amendment 2, dated May 19th 2014***

This substantial amendment was created for the following reasons:

After first experience with the protocol from the German investigators, the protocol was finetuned in a way that study timelines were adapted according to daily urological practices. Also the safety reporting process was updated according to the newest obligations. Two scientific interesting substudies for selected centres only were added and the patient information sheet and informed consent form were updated accordingly.

Amendment 2 is provided in Appendix 7.

- ***Amendment 3, dated July 9th 2015***

This substantial amendment was created for the following reasons:

After first experience of the Dutch investigators with the protocol, the protocol was fine-tuned in a way that study timelines and study procedures were adapted according to daily urological practices.
These included:

- 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 was collected between 4-8 hours after each installation.

The worldwide shortage of BCG 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

Amendment 3 is provided in Appendix 8.

➢ ***Amendment 4, dated May 2nd 2016***

This substantial amendment was created for the following reasons:

After the first period of experience of the investigators with the protocol, the protocol was fine-tuned in a way that study timelines and study procedures were 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 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 was adapted accordingly.

Text has been adapted in some sections of the protocol to more clarify the study procedures.

Amendment 4 is provided in Appendix 9.

➢ ***Amendment 5, dated May 15th 2017***

This substantial amendment was created for the following reasons:

The recommendations to perform a second Transurethral Resection (TUR) of the bladder in the diagnosis of bladder cancer were 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 was 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 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 was an exclusion criterion in the protocol. It was 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 was 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 was adapted in some sections of the protocol to more clarify the study procedures.

Amendment 5 is provided in Appendix 10.

- ***Amendment 6, dated January 7th 2019***

This substantial amendment was created for the following reasons:

The IDMC reviewed the data (based on data present in the eCRF on October 1st 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 would not be reached (life table risk of recurrence remains below 50%), the IDMC proposed to change this criterion into a HR of 0.75. Because the requirement of a 1% one sided significance level was extremely restrictive, the IDMC proposed to test at a 2.5% one sided significance level which was in agreement with the upper limit of the 95% CI around the HR being less than 0.75.

Continued supply availability of BCG was a main challenge in many countries including the countries that participated in the NIMBUS study. As a result, NIMBUS sites were forced to (temporary) switch to another BCG (sub)strain.
All the BCG vaccines used in the study were derived 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 were Brazilian (Moreau/Rio de Janeiro), Danish (Copenhagen–1331), Japanese (Tokyo–172-1), Russian (Moscow–368) and Bulgarian (Sofia–SL222). Different strains tended 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 was therefore the result of historical use, production, logistics or other factors.
In case of BCG shortage we therefore allowed 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.

Some text was changed/added to update information or more clarify study procedures.

Amendment 6 is provided in Appendix 11.

- ***Premature End of Study***

In August 2019, the Independent Data Monitoring Committee (IDMC) 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 non inferiority of the reduced frequency arm which was defined as the true HR (hazardexperimental/-hazardstandard) for first recurrence being higher than or equal to 0.75. Inferiority was defined as a true HR for first recurrence lower than 0.75. The stopping criterion as defined in the protocol was the upper limit of the 95% CI being less than 0.75. In this safety analysis this stopping criterion was met.

Therefore, on 17 October 2019, all sites that participated 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 was shortened until all patients had at least 6 months of follow-up (i.e. performed visit Month 6 Week 3).
On 7 November 2019, the NIMBUS sites were informed that the follow-up period ended at 17 November 2019 with the exception of;
- patients that had not yet completed the 6 months follow-up period; for these patients follow-up was ended after the Month 6 Week 3 visit.
- patients that, on 17 November 2019, were in the middle of the treatment cycle of Month 12 (M12 W1-W3); follow-up ended after the Month 12 Week 3 visit (even if visits took place after 17 November 2019).
On 7 November 2019, the NIMBUS sites were provided with a Letter for the Patient, 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.

Following the premature End of Study, only for France an Amendment of the Protocol was needed (See Appendix 12).

10. STUDY PATIENTS

10.1 Disposition of patients

A total of 359 patients from Germany (152), the Netherlands (111), France (68), Belgium (27) and Spain (1) were randomised between December 2013 and October 2019.
Randomisation was initially done in the Curadoc database system. On May 7th 2015 a switch was made to another database system called Marvin. There was a slight unbalance between the treatment groups caused by the initial system (Curadoc: 19 reduced frequency, 25 standard frequency). This has levelled off when the number of randomisations increased. Randomisation in Marvin was perfectly balanced.

CuraDOC randomisations

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Country	Germany	15	20	35
	The Netherlands	4	5	9
Total		19	25	44

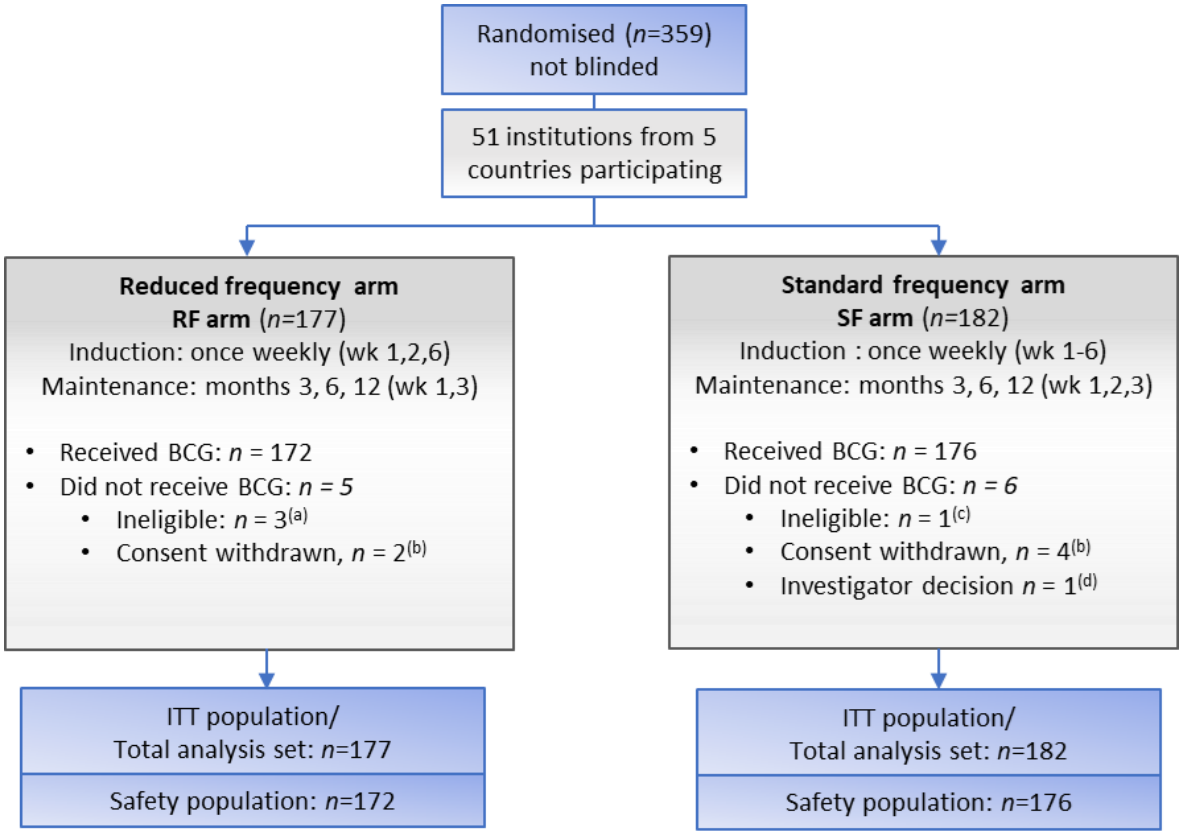
Randomisation Data (all randomised patients included)

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Country	Germany	72 (40.7%)	80 (44.0%)	152 (42.3%)
	The Netherlands	57 (32.2%)	54 (29.7%)	111 (30.9%)
	France	34 (19.2%)	34 (18.7%)	68 (18.9%)
	Belgium	14 (7.9%)	13 (7.1%)	27 (7.5%)
	Spain	0 (0%)	1 (0.5%)	1 (0.3%)
Total		177 (100%)	182 (100%)	359 (100%)

Two sided Chi-square test: p=0.832

See for Consolidated Standard of Reporting Trials diagram Figure 1.

Figure 1. Consolidated Standard of Reporting Trials diagram.



BCG = bacillus Calmette-Guérin; ITT = intention to treat; RF = reduced frequency; SF = standard frequency.

[a] 1xT >T2, 1x history of upper urinary tract tumour, 1x laboratory abnormalities.

[b] consent withdrawn prior to start BCG treatment.

[c] 1x no re-re-TUR performed because patient opted for cystectomy.

[d] no further details available.

10.2 Protocol deviations

Tables below show the number of protocol deviations (1 patient can have multiple deviations).

Type of deviations

		Reduced frequency treatment schedule	Standard treatment schedule	
Recorded Type of deviation	Inclusion / exclusion criteria	60 (39.7%)	55 (40.7%)	115 (40.2%)
	Non-compliance with protocol assessments	62 (41.1%)	57 (42.2%)	119 (41.6%)
	Non-compliance with study treatment	12 (7.9%)	18 (13.3%)	30 (10.5%)
	Other, specify	14 (9.3%)	0 (0.0%)	14 (4.9%)
	Randomisation Error	3 (2.0%)	5 (3.7%)	8 (2.8%)
Total		151 (100%)	135 (100%)	286 (100%)

Inclusion / exclusion criteria

		Reduced frequency treatment schedule	Standard treatment schedule	Total
Reason	Abnormal lab values	2	0	2
	CIS only	0	3	3
	Early postoperative chemotherapy (Mitomycin) was administered after re-TUR.	0	3	3
	Exclusion Criterion #1 (previous intravesical BCG therapy)	1	1	2
	Exclusion Criterion #8 (immunodeficiency)	1	0	1
	High grade tumor at last TUR and no additional TUR	1	0	1
	High grade tumor at re-TUR and no re-re-TUR (Amendment 3/4)	9	9	18
	High grade tumor at re-TUR and no re-re-TUR (original protocol)	0	1	1
	Highest grade T1 LG in TUR	0	1	1
	Incorrect time window between TUR and re-TUR	23	24	47
	Low grade tumor at TUR at study entry	0	1	1
	Muscle invasive tumor	1	0	1
	No detrusor at TUR and no re-TUR done	1	0	1
	No detrusor in re-re-TUR	2	0	2
	No detrusor in re-TUR (Amendment 3/4)	10	2	12
	No detrusor in TUR nor re-TUR	2	1	3
	No-re-TUR performed (Amendment 3/4)	1	0	1
	T1 at re-TUR, no re-re-TUR done	0	4	4
	T1 tumor at re-re-TUR	1	0	1
	T1 tumor at TUR, no re-TUR	2	0	2
	Tumor in prostatic urethra	1	2	3
	Tumor(s) in upper urinary tract	2	3	5
Total		60	55	115

Non-compliance with protocol assessments

		Reduced frequency treatment schedule	Standard treatment schedule	
Reason	Cystoscopy and/or cytology done after treatment visit	8	4	12
	Cystoscopy suspicious, but no TUR performed	1	0	1
	Cystoscopy and/or cytology not done	18	12	30
	FU visit not done	22	21	43
	M3W1 BCG after suspected Cystoscopy and/or cytology (prior to Unscheduled TUR)	0	1	1
	M9 not done	2	5	7
	No pregnancy test done	2	0	2
	Screening UUTI not done	4	9	13
	Suspected lesions coagulated	2	1	3
	Treatment visit not done	3	3	6
	Unscheduled TUR done instead of M3 Cystoscopy	0	1	1
Total		62	57	119

Non-compliance with study treatment

		Reduced frequency treatment schedule	Standard treatment schedule	
Reason	Additional BCG instillation(s)	12	18	30
Total		12	18	30

Other, specify

		Reduced frequency treatment schedule	
Reason	Switch treatment arm after premature study end	14	14
Total		14	14

Randomisation Error

		Reduced frequency treatment schedule	Standard treatment schedule	
Reason	BCG Treatment start < Randomisation.	3	3	6
	IC signed on M1W1 (after Randomisation)	0	1	1
	Re-TUR after Randomisation (before M1W1)	0	1	1
Total		3	5	8

11. EFFICACY EVALUATION

11.1 Data sets analysed

For data sets analysed (Intention-To-Treat population, safety population) see 10.1 Figure 1.
The intention to treat population included all randomised patients.
The safety population included all patients who had received at least one BCG instillation.

Ineligible patients

Ineligible (all criteria)				
		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Ineligible (all criteria)	yes	55 (31.1%)	50 (27.5%)	105 (29.2%)
	no	122 (68.9%)	132 (72.5%)	254 (70.8%)
Total		177 (100%)	182 (100%)	359 (100%)

Reason ineligible				
		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Reason ineligible	Abnormal lab values	2	0	2
	CIS only[1]	0	3	3
	Early postoperative chemotherapy (Mitomycin) was administered after re-TUR	0	3	3

	Exclusion Criterion #1 (previous intravesical BCG therapy)	1	0	1
	Exclusion Criterion #1 (previous intravesical BCG therapy and tumor in upper urinary tract)	0	1	1
	Exclusion Criterion #8 (immunodeficiency)	1	0	1
	High grade or T1 tumor at re TUR and no re-re-TUR[2]	9	14	23
	High grade tumor at last TUR and no additional TUR[2]	1	0	1
	Incorrect time window between TUR and re-TUR	18	20	38
	Low grade tumor at TUR at study entry	0	2	2
	Muscle invasive tumor[3]	1	0	1
	No detrusor in last TUR specimen[2]	15	3	18
	No-re-TUR performed[2]	3	0	3
	T1 tumor at re-re-TUR[2]	1	0	1
	Tumor in upper urinary tract	3	4	7
Total		55	50	105

[3] No BCG received
Note: Most of these patients received BCG anyway (only 8 have not been treated).

Patients with CIS only [1], patients who were possibly not tumor free when starting BCG treatment [2] and the patient with a T2 tumour [3] were excluded in the analysis displaying time to recurrence as shown in section 11.4.6.2, Figure 4 (eligible population).

11.2 Demographic and other baseline characteristics

Table 2. Baseline characteristics for patients and disease

	Randomised treatment		
	Reduced frequency treatment schedule (n = 177)	Standard frequency treatment schedule (n = 182)	**Total** (n = 359)
Gender, n (%)			
Male	144 (81.4)	152 (83.5)	296 (82.5)
Female	33 (18.6)	30 (16.5)	63 (17.5)
Type of cancer, n (%)			
Primary	163 (92.1)	167 (91.8)	330 (91.9)
Recurrent	14 (7.9)	15 (8.2)	29 (8.1)
Number of tumors, n (%)			
Single	95 (53.7)	106 (58.2)	201 (56.0)
Multiple	82 (46.3)	76 (41.8)	158 (44.0)
Highest tumor category, n (%)			
T0[#]	0 (0)	3 (1.7)	3 (0.8)
Ta	82 (46.3)	77 (42.3)	159 (44.3)
T1	94 (53.1)	102 (56.0)	196 (54.6)
≥T2*	1 (0.6)	0 (0)	1 (0.3)
Associated CIS, n (%)			
Yes	49 (27.7)	52 (28.6)	101 (28.1)
No	128 (72.3)	130 (71.4)	258 (71.9)
BCG strain used, n (%)			
BCG Medac	156 (88.1)	164 (90.1)	320 (89.1)
BCG Tice	16 (9.0)	16 (8.8)	32 (8.9)
BCG Connaught	5 (2.8)	2 (1.1)	7 (2.0)

[#] Three patients had CIS only (ineligible)
* Patient did not receive BCG and is not included in follow up (ineligible)

Mean age, SD and range (min-max)

		Randomisation		
		Reduced frequency treatment schedule	Standard treatment schedule	Total (n=359)
Age at randomisation	Mean (yr) (SD)	68.77 (8.98)	68.77 (9.33)	68.77 (9.15)
	Range (yr)	35 – 88	39 - 86	35 - 88

Two sided t-test: p=0.999

Mean height, SD and range (min-max)

		Randomisation		
		Reduced frequency treatment schedule (n=168)	Standard treatment schedule (n=167)	Total (n=335)
Height	Mean (cm) (SD)	173 (8.3)	175 (8.6)	174 (8.5)
	Range (cm)	150 - 196	154 -- 199	150 - 199

Two sided t-test: p=0.078

Mean weight, SD and range (min-max)

		Randomisation		
		Reduced frequency treatment schedule (n=167)	Standard treatment schedule (n=167)	Total (n=334)
Weight	Mean (kg) (SD)	81.5 (16.9)	84.4 (16.9)	82.9 (16.9)
	Range (kg)	43 - 148	50 - 138	43 - 148

Two sided t-test: p=0.116

Mean BMI, SD and range (min-max)

		Randomisation		
		Reduced frequency treatment schedule (n=167)	Standard treatment schedule (n=167)	Total (n=334)
BMI	Mean (SD)	26.9 (4.6)	27.4 (4.3)	27.1 (4.5)
	Range	16.9 – 44.6	18.1 – 43.6	16.9 – 44.6

Two sided t-test: p=0.373

WHO Performance status

		Randomisation		
WHOPS		Reduced frequency treatment schedule	Standard treatment schedule	Total
	0. Asymptomatic	121 (68.4%)	131 (72.0%)	252 (70.2%)
	1. Symptomatic but completely ambulatory	55 (31.1%)	50 (27.5%)	105 (29.2%)
	2. Symptomatic, < 50% in bed during day	1 (0.6%)	1 (0.5%)	2 (0.6%)
Total		177 (100%)	182 (100%)	359 (100%)

Two sided Chi-square test: p=0.754

Childbearing status

		Randomisation		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Childbearing status	Childbearing potential	1 (3.0%)	0 (0%)	1 (1.6%)
	Post-menopausal	30 (90.9%)	28 (93.3%)	58 (92.1%)
	Surgically sterile	2 (6.1%)	2 (6.7%)	4 (6.3%)
Total		33 (100%)	30 (100%)	63 (100%)

ASA Performance status

ASA Performance Status	Randomisation		Total
	Reduced frequency treatment schedule	Standard treatment schedule	
1. A normal healthy patient	83 (46.9%)	91 (50.0%)	174 (48.5%)
2. A patient with mild systemic disease	72 (40.7%)	73 (40.1%)	145 (40.4%)
3. A patient with severe systemic disease	22 (12.4%)	17 (9.3%)	39 (10.9%)
4. A patient with severe systemic disease that is a constant threat to life	0 (0.0%)	1 (0.5%)	1 (0.3%)
Total	177 (100%)	182 (100%)	359 (100%)

Two sided Chi-square test: p=0.584

TUR Data

Advanced imaging at cystoscopy prior to TUR

		Randomised treatment		Total
		Reduced frequency treatment schedule	Standard treatment schedule	
Advance imaging at cystoscopy prior to TUR	Yes	34 (19.2%)	28 (15.4%)	62 (17.3%)
	No	140 (79.1%)	151 (83.0%)	291 (81.1%)
	Unknown	3 (1.7%)	3 (1.6%)	6 (1.7%)
Total		177 (100%)	182 (100%)	359 (100%)

Two sided Chi-square test: p=0.629

Type of advanced imaging at cystoscopy prior to TUR

		Randomised treatment		Total
		Reduced frequency treatment schedule	Standard treatment schedule	
Type of advanced imaging at cystoscopy prior to TUR	Blue light cystoscopy	29 (85.3%)	23 (82.1%)	52 (83.9%)
	NBI	3 (8.8%)	1 (3.6%)	4 (6.5%)
	Other, specify	2 (5.9%)	4 (14.3%)	6 (9.6%)
Total		34 (100%)	28 (100%)	62 (100%)

Muscle present in TUR specimen?

		Randomisation		Total
		Reduced frequency treatment schedule	Standard treatment schedule	
Muscle present?	yes	151 (85.3%)	149 (81.9%)	300 (83.6%)
	no	26 (14.7%)	33 (18.1%)	59 (16.4%)
Total		177 (100%)	182 (100%)	359 (100%)

Was immediate post TUR intravesical instillation administered?

		Randomisation		Total
		Reduced frequency treatment schedule	Standard treatment schedule	
Post TUR instillation?	yes	52 (29.4%)	59 (32.4%)	111 (30.9%)
	no	125 (70.6%)	123 (67.6%)	248 (69.1%)
Total		177 (100%)	182 (100%)	359 (100%)

Two sided Chi-square test: p=0.533

Post TUR instillation agent

		Randomisation		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Post TUR instillation agent	BCG	1 (1.9%)	0 (0.0%)	1 (0.9%)
	Mitomycin	43 (82.7%)	51 (86.4%)	94 (84.7%)
	Epirubicin	1 (1.9%)	2 (3.4%)	3 (2.7%)
	Doxorubicin	7 (13.5%)	6 (10.2%)	13 (11.7%)
Total		52 (100%)	59 (100%)	111 (100%)

Total number of tumors at TUR

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
TUR total number of tumors	0	0	3	3
	1	97	105	202
	2	36	32	68
	3	23	11	34
	4	7	12	19
	5	6	4	10
	6	2	4	6
	7	4	3	7
	8	0	1	1
	9	0	1	1
	10	0	1	1
	12	1	0	1
	14	0	1	1
	16	0	1	1
Total		176	179	355

Re-TUR Data

Re-TUR performed?

		Randomisation		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Re-TUR performed?	yes	158 (89.3%)	165 (90.7%)	323 (90.0%)
	no	19 (10.7%)	17 (9.3%)	36 (10.0%)
Total		177 (100%)	182 (100%)	359 (100%)

Following amendment 5 re TUR was no longer needed in case of pTa HG (completely resected, muscle tissue present). This applies to 31 patients in above table.
5 patients did not undergo a re-TUR even though they should have based on the protocol applicable at the time of randomisation.

Cystoscopy prior to Re-TUR

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Cystoscopy prior to Re-TUR done?	yes	56 (35.4%)	61 (37%)	117 (36.2%)
	no	102 (64.6%)	104 (63%)	206 (63.8%)
Total		158 (100%)	165 (100%)	323 (100%)

Advanced imaging at cystoscopy prior to Re-TUR		
	Randomised treatment	Total

		Reduced frequency treatment schedule	Standard treatment schedule	
Advance imaging at cystoscopy prior to Re-TUR?	yes	14 (25.0%)	17 (27.9%)	31 (26.5%)
	no	42 (75.0%)	44 (72.1%)	86 (73.5%)
Total		56 (100%)	61 (100%)	117 (100%)

Two sided Chi-square test: p=0.725

Type of advanced imaging at cystoscopy prior to Re-TUR

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Type of advanced imaging at cystoscopy prior to Re-TUR	Blue light cystoscopy	14 (100%)	15 (88.2%)	29 (93.6%)
	NBI	0 (0%)	1 (5.9%)	1 (3.2%)
	Unknown	0 (0%)	1 (5.9%)	1 (3.2%)
Total		14 (100%)	17 (100%)	31(100%)

Muscle tissue present in Re-TUR specimen?

		Randomisation		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Muscle present?	yes	143 (90.5%)	160 (97.0%)	303 (93.8%)
	no	15 (9.5%)	5 (3.07%)	20 (6.2%)
Total		158 (100%)	165 (100%)	323 (100%)

Was immediate post Re-TUR intravesical instillation administered?

Post Re-TUR instillation?

		Randomisation		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Post Re-TUR instillation?	yes	1 (0.6%)	3 (1.8%)	4 (1.2%)
	no	157 (99.4%)	162 (98.1%)	319 (98.8%)
Total		158 (100%)	165 (100%)	323 (100%)

Two sided Chi-square test: p=0.336

Post Re-TUR instillation agent

		Randomisation		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Post Re-TUR instillation agent	Mitomycin	0 (0%)	3 (100%)	3 (75%)
	Doxorubicin	1 (100%)	0 (0%)	1 (25%)
Total		1 (100%)	3 (100%)	4 (100%)

Total number of tumors at Re-TUR

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Re-TUR total number of tumors	0	132	134	266
	1	16	17	33
	2	5	4	9
	3	4	3	7
	4	0	3	3
	5	0	3	3
	6	1	1	2
Total		158	165	323

Re-re-TUR Data

In 33 patients a re-re-TUR should have been performed according to the protocol applicable at the time of randomisation (26 patients with high grade in the re-TUR and included prior to amendment 5 and 7 patients with T1 tumor at re-TUR and included according to amendment 5).

Re-re-TUR performed?

		Randomisation		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Re-re-TUR performed?	yes	5 (%)	5 (%)	10 (%)
	no	9 (%)	14 (%)	23 (%)
Total		14 (100%)	19 (100%)	33 (100%)

11.3 Measurements of treatments compliance

All BCG instillations have been recorded in the eCRF, including any deviations from the required dose or schedule.

11.4 Efficacy results and tabulations of individual patient data

11.4.1 Analysis of Efficacy

The median follow-up time of this final analysis was 14 months for all patients and 17 months for patients without recurrence.

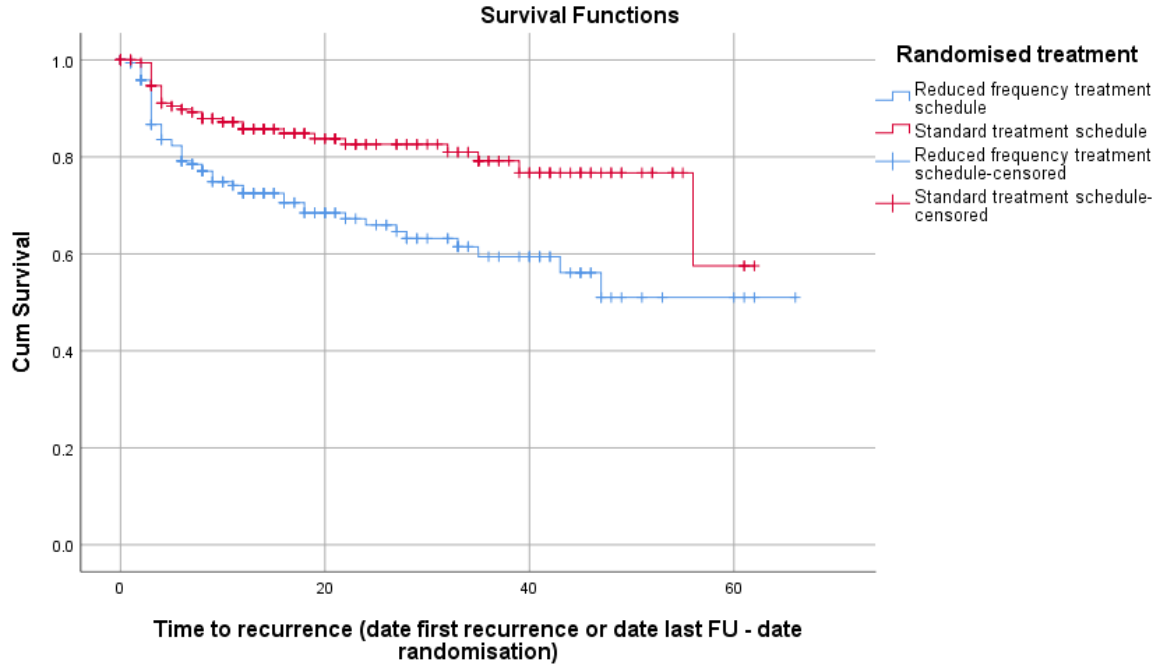
After 14 months of median follow-up, the intention-to-treat analysis showed a difference in recurrences between treatment arms: 55/177 (reduced frequency) versus 30/182 patients (standard frequency) with a hazard ratio of **0.47 [95% CI: 0.30 – 0.74]**, see Figure 2.

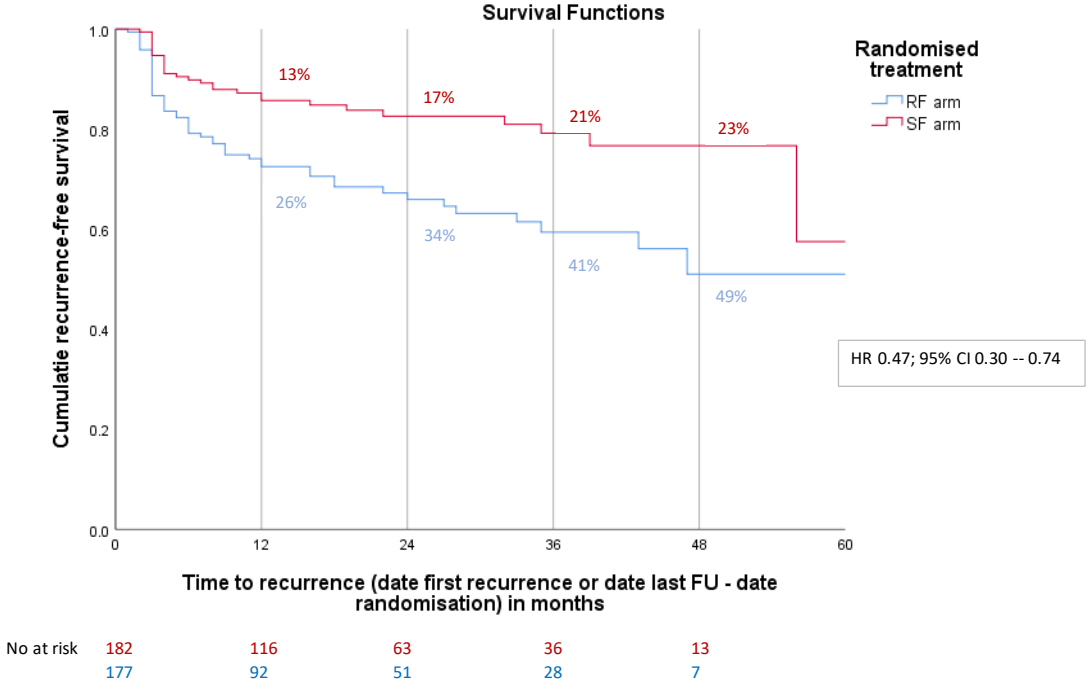
Figure 2. Kaplan-Meier survival analysis displaying time to recurrence (time between randomisation and date of first recurrence or last follow-up) in all patients (intention-to-treat analysis)
CI = confidence interval; HR = hazard ratio; RF = reduced frequency arm; SF = standard frequency.

Total population: 359 patients

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Recurrence?	yes	55 (31.1%)	30 (16.5%)	85 (23.7%)
	no	122 (68.9%)	152 (83.5%)	274 (76.3%)
Total		177 (100%)	182 (100%)	359 (100%)

Two sided Chi-square test: p=0.001





No at risk	182	116	63	36	13
	177	92	51	28	7

pT category of recurrence

		Randomisation		Total
		Reduced frequency treatment schedule	Standard treatment schedule	
pT category	Ta	32 (58%)	10 (33%)	42 (49%)
	T1	9 (16%)	8 (27%)	17 (20%)
	>=T2	1 (2%)	7 (23%)	8 (9%)
	Biopsy, Tcat unknown (cystectomy performed)	1 (2%)	0 (0%)	1 (1%)
	No papillary tumor (CIS only)	10 (18%)	3 (10%)	13 (15%)

	T category unknown, lesion coagulated	2 (4%)	2 (7%)	4 (5%)
Total		55 (100%)	30 (100%)	85 (100%)

Questionnaires (EORTC QLQ C30, ICIQ-LUTS) have been completed prior to the first and last instillation of every cycle. For results see Appendix 13.

End of Study

Premature discontinuation

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Premature discontinuation?	yes	173 (97.7%)	178 (97.8%)	351 (97.8%)
	no	4 (2.3%)	4 (2.2%)	8 (2.2%)
Total		177 (100%)	182 (100%)	359 (100%)

Reason premature discontinuation

Reason premature discontinuation	Randomised treatment		Total
	Reduced frequency treatment schedule	Standard treatment schedule	
Ineligible	3 (1.7%)	1 (0.6%)	4 (1.1%)
Consent withdrawn	6 (3.5%)	17 (9.6%)	23 (6.6%)
Adverse Event	2 (1.2%)	3 (1.7%)	5 (1.4%)
Investigator decision	0 (0%)	2 (1.1%)	2 (0.6%)
First recurrence which has been identified any time after the completion of induction course BCG	36 (20.8%)	18 (10.1%)	54 (15.4%)
Occurrence of new CIS	10 (5.8%)	3 (1.7%)	13 (3.7%)
Occurrence of urothelial carcinoma in the upper tract, or in the prostatic urethra	2 (1.2%)	3 (1.7%)	5 (1.4%)
Occurrence of distant metastases	0 (0%)	1 (0.6%)	1 (0.3%)
Occurrence of a new malignancy requiring use of systemic chemotherapy	0 (0%)	3 (1.7%)	3 (0.9%)
Lost to follow up	8 (4.6%)	4 (2.2%)	12 (3.4%)
Death	7 (4.0%)	4 (2.2%)	11 (3.1%)
Other, specify	99 (57.2%)	119 (66.9%)	218 (62.1%)
Total	173 (100%)	178 (100%)	351 (100%)

Specification other reason premature discontinuation

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Specification other reason premature discontinuation	BGG allergic	1	0	1
	Coagulation of lesions	2	2	4
	Decision of the patient	3	1	4
	Discontinued by mistake	1	0	1
	Discontinued in error, no recurrence	1	0	1
	First recurrence and a tumor in PU	1	2	3
	No BCG given by incontinence	1	0	1
	Pat decided cystectomy	1	0	1
	Patient has dementia	1	0	1
	Patient received cystectomy in Aug-2014	0	1	1
	Patient refused further treatment and FU	0	1	1
	Patient refuses further BCG-treatment	0	1	1
	Premature stop study	81	107	188
	Recurrence after 2 BCG installations	1	0	1
	Recurrence of papillary tumor with CIS	4	4	8
	Unknown death	1	0	1
Total		99	119	218

11.4.2 Statistical/Analytical Issues

11.4.2.1 Adjustment for covariates

Adjustment for covariates was not performed as stratification was done at randomization.

11.4.2.2 Handling of dropouts or missing data

In addition to the total study population (the intention-to-treat) analyses, additional analyses in subpopulations (at least 1 BCG installation, eligible population) were performed. Additional data subgroup analysis and imputation of missing data may be performed in future.

11.4.2.3 Interim analyses and data monitoring

In august 2019, the IDMC reviewed the trial's progress and conducted a safety analysis of the interim data (cut-off date July 1, 2019).
After 12 months of median follow-up, the analysis in the intention-to-treat population showed a safety-relevant difference in recurrences between treatment arms: 46/170 (reduced frequency arm) vs. 21/175 patients (standard frequency arm). Additional safety analyses showed an HR of 0.40 with the upper part of the one-sided 97.5% CI of 0.68, meeting a pre-defined stopping criterion for inferiority.
The study's primary objective was to show non inferiority of the reduced frequency arm which was defined as the true HR (hazardexperimental/-hazardstandard) for first recurrence being higher than or equal to 0.75. Inferiority was defined as a true HR for first recurrence lower than 0.75. The stopping criterion as defined in the protocol was the upper limit of the 95% CI being less than 0.75. In this safety analysis this stopping criterion was met.

11.4.2.4 Multicentre studies

In this study, study centre was one of stratification factors in which the marginal treatment totals was balanced. Therefore, results of individual centres were not analysed/presented.

11.4.2.5 Multiple Comparisons/Multiplicity

Following Amendment 5, interim and final analyses were performed at the 2.5% significance level one sided instead of the 5% level of significance level two-sided as planned in the original protocol. No adjustments were made to nominal significance levels to account for multiple comparisons made on the same data.

11.4.2.6 Use of an "efficacy subset" of patients

The following efficacy subpopulations were analysed:

- Treated population that received at least one BCG instillation (348 patients)
  See Figure 3 for the Kaplan-Meier survival analysis
- Eligible population excluding patient with CIS only, T2 tumour and possible incomplete resection (309 patients)
  See Figure 4 for the Kaplan-Meier survival analysis

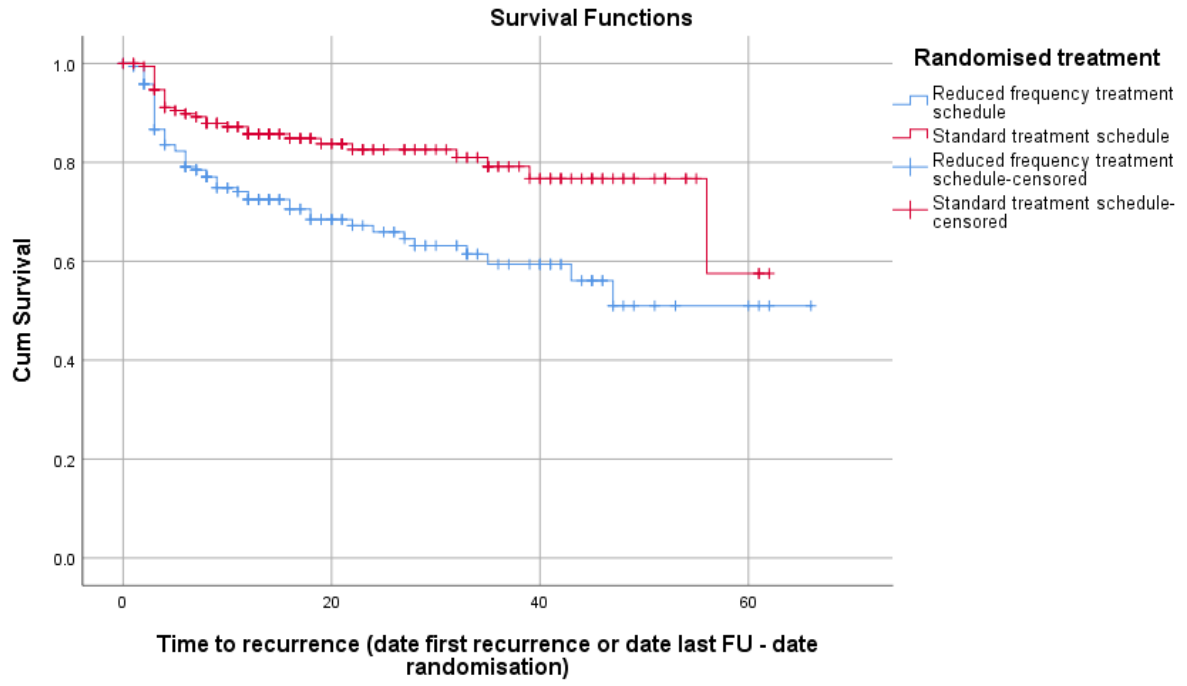
Figure 3. Kaplan-Meier survival analysis displaying time to recurrence (time between randomisation and date of first recurrence or last follow-up) in all patients that received at least one BCG instillation (treated population).

Treated population: 348 patients received at least one BCG instillation

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Recurrence	Yes	55 (32.0%)	30 (17.0%)	85 (24.4%)
	No	117 (68.0%)	146 (83.0%)	263 (75.6%)
Total		172 (100%)	176 (100%)	348 (100%)

Two sided Chi-square test: p=0.001

Kaplan Meier survival analysis, comparing only the treatment groups.



Log rank test: p=0.001

Cox regression analysis for treatment only, hazard ratio for first recurrence (hazardexperimental/hazardstandard) and the corresponding 95% CI .

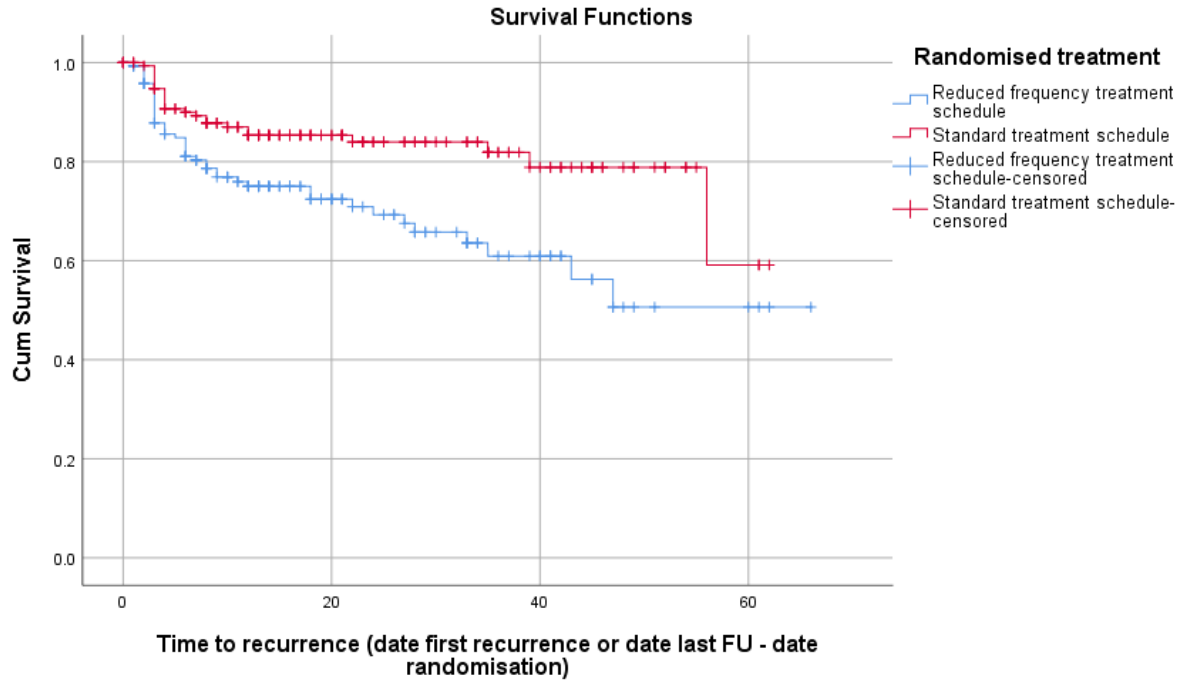
This hazard ratio is **0.473 [95% CI: 0.303 – 0.738]**.

Figure 4. Kaplan-Meier survival analysis displaying time to recurrence (time between randomisation and date of first recurrence or last follow-up) excluding patients with CIS only, T2 tumour and possible incomplete resection (eligible population, see also 11.1)

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Recurrence	yes	43 (29.3%)	25 (15.4%)	68 (22.0%)
	no	104 (70.7%)	137 (84.6%)	241 (78.0%)
Total		147 (100%)	162 (100%)	309 (100%)

Two sided Chi-square test: p=0.003

Kaplan Meier survival analysis, comparing only the treatment groups.



Log rank test: p=0.003

Cox regression analysis for treatment only, hazard ratio for first recurrence (hazardexperimental/hazardstandard) and the corresponding 95% CI .

This hazard ratio is **0.482 [95% CI: 0.294 – 0.789]**.

11.4.3 Efficacy conclusions

The results clearly reveal an increased recurrence rate in the RF arm. After 14 months of median follow-up, the intention-to-treat analysis showed a difference in recurrences between treatment arms: 55/177 (reduced frequency) versus 30/182 patients (standard frequency) with a hazard ratio of 0.47 [95% CI: 0.30 – 0.74]. In additional analyses in subpopulations the hazard ratio was: 0.47 [95% CI: 0.30 – 0.74] for all patients that received at least one BCG instillation (348 patients); 0.48 [95% CI: 0.29 – 0.79] excluding patients with CIS only, T2 tumour and possible incomplete resection (309 patients).
In conclusion, the NIMBUS reduced frequency schedule was inferior to the standard frequency schedule regarding time to first recurrence.

12. SAFETY EVALUATION

12.1 Extent of exposure

Treatment information/ BCG instillations

At least one dose of BCG received

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
At least one dose of BCG received	Yes	172 (97.2%)	176 (96.7%)	348 (96.9%)
	No	5 (2.8%)	6 (3.3%)	11 (3.1%)
Total		177 (100%)	182 (100%)	359 (100%)

Two sided Chi-square test: p=0.795

Number of per protocol BCG instillations

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Number of BCG instillations	0	5	6	11
	1	1	0	1
	2	6	2	8
	3	33	2	35
	4	3	0	3
	5	11	2	13
	6	4	19	23
	7	33	4	37
	8	2	5	7
	9	79	8	87
	10	0	2	2
	11	0	5	5
	12	0	25	25
	13	0	2	2
	14	0	6	6
	15	0	94	94
Total		177	182	359

Treatment modification overall (all visits combined)

Treatment modified				
		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Treatment modified	Yes	278 (21.3%)	359 (16.1%)	637 (18.0%)
	No	1028 (78.7%)	1868 (83.9%)	2896 (82.0%)
Total		1306 (100%)	2227 (100%)	3533 (100%)

Two sided Chi-square test: p=0.000

Treatment modification			
	Randomised treatment		
	Reduced frequency treatment schedule	Standard treatment schedule	Total
Instillation administered too early	40 (14.4%)	17 (4.7%)	57 (8.9%)
BCG dose has been reduced	4 (1.4%)	9 (2.5%)	13 (2.0%)
Instillation was delayed without reducing the BCG dose	180 (64.7%)	274 (76.3%)	454 (71.3%)
Instillation was delayed with reducing the BCG dose	7 (2.5%)	1 (0.3%)	8 (1.3%)
Instillation had to be stopped	47 (16.9%)	58 (16.2%)	105 (16.5%)
Total	278 (100%)	359 (100%)	637 (100%)

Two sided Chi-square test: p=0.000

Reason treatment modified			
	Randomised treatment		
	Reduced frequency treatment schedule	Standard treatment schedule	Total
Side effects (after previous instillation)	73 (26.3%)	137 (38.2%)	210 (33.0%)
Recurrence	24 (8.6%)	14 (3.9%)	38 (6.0%)
Logistic reasons, miscalculated visit date, forgotten	162 (58.3%)	176 (49.0%)	338 (53.1%)
Unscheduled TUR, biopsies	14 (5.0%)	25 (7.0%)	39 (6.1%)
Unknown	5 (1.8%)	7 (1.9%)	12 (1.9%)
Total	278 (100%)	359 (100%)	637 (100%)

Two sided Chi-square test: p=0.003

Instillation administered too early (n=57)

Reason treatment modified			
	Randomised treatment		
	Reduced frequency treatment schedule	Standard treatment schedule	Total
Logistic reasons, miscalculated visit date, forgotten	39 (97.5%)	15 (88.2%)	54 (94.7%)
Unscheduled TUR, biopsies	0 (0.0%)	1 (5.9%)	1 (1.8%)
Unknown	1 (2.5%)	1 (5.9%)	2 (3.5%)
Total	40 (100%)	17 (100%)	57 (100%)

Two sided Chi-square test: p=0.241

BCG dose has been reduced (n=13)

Reason treatment modified			
	Randomised treatment		
	Reduced frequency treatment schedule	Standard treatment schedule	Total
Side effects (after previous instillation)	0 (0.0%)	4 (44.4%)	4 (30.8%)
Logistic reasons, miscalculated visit date, forgotten	4 (100.0%)	5 (55.6%)	9 (69.2%)
Total	4 (100%)	9 (100%)	13 (100%)

Two sided Chi-square test: p=0.109

Instillation was delayed without reducing the BCG dose (n=454)

Reason treatment modified			
	Randomised treatment		
	Reduced frequency treatment schedule	Standard treatment schedule	Total
Side effects (after previous instillation)	63 (35.0%)	106 (38.7%)	169 (37.2%)
Recurrence	0 (0%)	1 (0.4%)	1 (0.2%)
Logistic, miscalculated visit date, forgotten	104 (57.8%)	141 (51.5%)	245 (54.0%)
Unscheduled TUR, biopsies	9 (5.0%)	20 (7.3%)	29 (6.4%)
Unknown	4 (2.2%)	6 (2.2%)	10 (2.2%)
Total	180 (100%)	274 (100%)	454 (100%)

Two sided Chi-square test: p=0.599

Instillation was delayed with reducing the BCG dose (n=8)

Reason treatment modified			
	Randomised treatment		
	Reduced frequency treatment schedule	Standard treatment schedule	Total
Side effects (after previous instillation)	1 (14.3%)	0 (0.0%)	1 (12.5%)
Logistic, miscalculated visit date, forgotten	6 (85.7%)	1 (100.0%)	7 (87.5%)
Total	7 (100%)	1 (100%)	8 (100%)

Two sided Chi-square test: p=0.686

Instillation had to be stopped (n=105)

Reason treatment modified			
	Randomised treatment		
	Reduced frequency treatment schedule	Standard treatment schedule	Total
Side effects (after previous instillation)	9 (19.1%)	27 (46.6%)	36 (34.3%)
Recurrence	24 (51.1%)	13 (22.4%)	37 (35.2%)
Logistic, miscalculated visit date, forgotten	9 (19.1%)	14 (24.1%)	23 (21.9%)
Unscheduled TUR, biopsies	5 (10.6%)	4 (6.9%)	9 (8.6%)
Total	47 (100%)	58 (100%)	105 00%)

Note: In some patients 'stop' only refers to the BCG treatment at a specific timepoint and treatment is continued at a later timepoint. So in these cases treatment is interrupted instead of stopped.

Some patients have received additional BCG instillations not according to protocol and some patients have switched treatment arm (reduced to standard) after premature study stop.

Additional BCG instillations

Additional BCG instillations?		Randomised treatment		Total
		Reduced frequency treatment schedule	Standard treatment schedule	
	Yes, extra instillation(s) given	2	7	9
	Yes, switch treatment	12	0	12
	No	163	175	338
Total		177	182	359

Number of additional BCG instillations

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Number of additional BCG instillations	0	163	175	338
	1	9	1	10
	2	2	0	2

	3	1	3	4
	4	1	0	1
	6	0	1	1
	11	1	0	1
	12	0	2	2
Total		177	182	359

Total number of BCG instillations

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Total number of BCG instillations	0	5	6	11
	1	1	0	1
	2	6	2	8
	3	31	2	33
	4	4	0	4
	5	10	2	12
	6	4	19	23
	7	26	4	30
	8	8	5	13
	9	80	8	88
	10	1	2	3
	11	0	5	5
	12	0	24	24
	13	0	2	2
	14	0	6	6
	15	0	88	88
	16	0	1	1
	18	0	4	4
	20	1	0	1
	27	0	2	2
Total		177	182	359

12.2 Adverse events (AEs)

12.2.1 Brief Summary of Adverse Events

For 283 patients a total of 2655 AEs have been reported. A total of 131/177 patients were affected with 858 AEs in the *RF* arm and 152/182 patients were affected with 1797 AEs in the *SF* arm.

12.2.2 Display of Adverse Events

For 283 patients 2655 adverse events have been reported.

		Randomised treatment		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Indicator of each last matching case as Primary	Duplicate Case	727	1645	2372
	Primary Case	131	152	283
Total		858	1797	2655

A. Type of adverse events (SOC)

SOC				
		Randomised treatment		
System Organ Class (SOC)		Reduced frequency treatment schedule	Standard treatment schedule	Total
	Main type of AE (≥ 5% occurrence)			
	General disorders and administration site conditions	**150 (17.5%)**	**363 (20.2%)**	**513 (19.3%)**
	Preferred term (PT)			
	Asthenia	2 (1.3%)	25 (6.9%)	27 (5.3%)
	Fatigue	56 (37.3%)	140 (38.6%)	196 (38.2%)
	Malaise	13 (8.7%)	37 (10.2%)	50 (9.7%)
	Pyrexia	35 (23.3%)	78 (21.5%)	113 (22.0%)
	Suprapubic pain	17 (11.3%)	43 (11.8%)	60 (11.7%)
	Other (< 5% occurrence)	27 (18.1%)	40 (11%)	67 (13.1%)
	Infections and infestations	**121 (14.1%)**	**172 (9.6%)**	**293 (11.0%)**
	Preferred term (PT)			
	Cystitis	17 (14.0%)	51 (29.7%)	68 (23.2%)
	Influenza	9 (7.4%)	14 (8.1%)	23 (7.8%)
	Nasopharyngitis	7 (5.8%)	11 (6.4%)	18 (6.1%)
	Urinary tract infection	69 (57.0%)	70 (40.7%)	139 (47.4%)
	Other (< 5% occurrence)	19 (15.8%)	26 (15.1%)	45 (15.5%)
	Musculoskeletal and connective tissue disorders	**61 (7.1%)**	**195 (10.9%)**	**256 (9.6%)**
	Preferred term (PT)			
	Arthralgia	16 (26.2%)	74 (37.9%)	90 (35.2%)
	Back pain	4 (6.6%)	5 (2.6%)	9 (3.5%)
	Myalgia	25 (41.0%)	94 (48.2%)	119 (46.5%)
	Other (< 5% occurrence)	16 (26.2%)	22 (11.3%)	38 (14.8%)
	Renal and urinary disorders	**395 (46.0%)**	**855 (47.6%)**	**1250 (47.1%)**
	Preferred term (PT)			
	Dysuria	85 (21.5%)	214 (25.0%)	299 (23.9%)
	Haematuria	75 (19.0%)	171 (20.0%)	246 (19.7%)
	Micturition urgency	93 (23.5%)	163 (19.1%)	256 (20.5%)
	Nocturia	21 (5.3%)	36 (4.2%)	57 (4.6%)
	Pollakiuria	43 (10.9%)	82 (9.6%)	125 (10.0%)

	Post micturition dribble	20 (5.1%)	43 (5.0%)	63 (5.0%)
	Other (< 5% occurrence)	58 (14.7%)	146 (17.1%)	204 (16.3%)
	Other (< 5% occurrence)	**131 (15.3%)**	**212 (11.7%)**	**343 (13%)**
Total		**858 (100%)**	**1797 (100%)**	**2655 (100%)**

B. Adverse event grading

Grade

		Randomisation		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Grade	Mild	463 (54.0%)	1001 (55.7%)	1464 (55.1%)
	Moderate	276 (32.2%)	572 (31.8%)	848 (31.9%)
	Severe	111 (12.9%)	222 (12.41%)	333 (12.5%)
	Life-threatening	3 (0.3%)	0 (0%)	3 (0.1%)
	Death	5 (0.6%)	2 (0.1%)	7 (0.3%)
Total		858 (100%)	1797 (100%)	2655 (100%)

C. Relationship to study treatment

Relationship				
		Randomisation		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Relationship	No reasonable possibility	235 (27.4%)	321 (17.9%)	556 (20.9%)
	Reasonable possibility	623 (72.6%)	1476 (82.1%)	2099 (79.1%)
Total		858 (100%)	1797 (100%)	2655 (100%)

Adverse event grading per relationship category

Relationship to study treatment = **No reasonable possibility**

		Randomisation		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Grade	Mild	116 (49.4%)	175 (54.5%)	291 (52.3%)
	Moderate	84 (35.7%)	102 (31.8%)	186 (33.5%)
	Severe	27 (11.5%)	42 (13.1%)	69 (12.4%)
	Life-threatening	3 (1.3%)	0 (0%)	3 (0.5%)
	Death	5 (2.1%)	2 (0.6%)	7 (1.3%)
Total		235 (100%)	321 (100%)	556 (100%)

Relationship to study treatment = **Reasonable possibility**

		Randomisation		
		Reduced frequency treatment schedule	Standard treatment schedule	Total
Grade	Mild	347 (55.7%)	826 (56.0%)	1173 (55.9%)
	Moderate	192 (30.8%)	470 (31.8%)	662 (31.5%)
	Severe	84 (13.5%)	180 (12.2%)	264 (12.6%)
Total		623 (100%)	1476 (100%)	2099 (100%)

12.3 Deaths, other serious adverse events, and other significant adverse events

12.3.1 Listing of deaths, other serious adverse events, and other significant adverse events

Serious Adverse events

Serious?

		Randomisation		Total
		Reduced frequency treatment schedule	Standard treatment schedule	
Serious?	yes	44 (5.1%)	44 (2.4%)	88 (3.3%)
	no	814 (94.9%)	1753 (97.6%)	2567 (96.7%)
Total		858 (100%)	1797 (100%)	2655 (100%)

Summary Tabulation of Serious Adverse Events

➢ Number of SAEs and number of subjects reporting the occurrence of SAEs classified by MedDRA Primary System Organ Class and Preferred Term during the entire study period (Total Treated Population)

		N= 348		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n+**	**n**	**%**
At least one symptom		88	69	19,9
Cardiac disorders (110007541)	Atrial fibrillation (10003658)	1	1	0,3
	Dyspnoea (10013968)	2	2	0,6
	Cardiac death (10049993)	1	1	0,3
	Chest pain (10008479)	1	1	0,3
	Myocardial infarction (10028596)	1	1	0,3
	Cardiac failure (10007554)	2	2	0,3
Gastrointestinal disorders (10017947)	Abdominal pain lower (10000084)	1	1	0,3
	Inguinal hernia (10022016)	1	1	0,3
General disorders and administration site conditions (10018065)	Sudden death (10042434)	3	3	0,9
	Death (10011906)	1	1	0,3
	Accidental death (10063746)	1	1	0,3
	Chest pain (10008479)	1	1	0,3
Hepatobiliary disorders (10019805)	Cholecystitis (10008612)	1	1	0,3
Infections and infestations (10021881)	Urinary tract infections(10046571)	3	3	0,9
	Sepsis (10040047)	1	1	0,3
	Urosepsis (10048709)	5	5	1,5
	Septic Shock (10040070)	1	1	0,3
	Appendicitis (10003011)	2	1	0,3
	Pneumonia pneumococcal (10035728)	1	1	0,3
	Cystitis (10011781)	1	1	0,3
	Orchitis (10031064)	1	1	0,3
	Disseminated Bacillus Calmette-Guerin infection (10076666)	1	1	0,3
	Diverticulitis (10013538)	1	1	0,3
	Pneumonia (10035664)	1	1	0,3
	Osteomyelitis chronic (10031256)	1	1	0,3
Injury, poisoning and procedural complications (10022117)	Bladder perforation (10063575)	1	1	0,3
	Post procedural haematuria (10066225)	1	1	0,3
	Rib fracture (10039117)	1	1	0,3
	Postoperative wound infection (10036410)	1	1	0,3
	Haematuria traumatic (10018871)	1	1	0,3
	Fall (10016173)	1	1	0,3
Investigations (10022891)	Diagnostic procedure (10061816)	1	1	0,3
	Emergency care examination (10053069)	1	1	0,3
	Biopsy bone (1000473)	1	1	0,3
Metabolism and nutrition disorders (10027433)	Diabetic neuropathy (10012680)	1	1	0,3

		N= 348		
Primary System Organ Class (CODE)	**Preferred Term (CODE)**	**n+**	**n**	**%**
Musculoskeletal and connective tissue disorders (10028395)	Spinal fracture (10041569)	1	1	0,3
	Arthritis (10003246)	1	1	0,3
	Polyarthritis (10036030)	1	1	0,3
	Intervertebral disc disorder (10061521)	1	1	0,3
Neoplasms benign, malignant and unspecified (incl. cysts and polyps) (10029104)	Large intestine polyp (10051589)	2	1	0,3
	Central nervous system neoplasm (10007958)	1	1	0,3
	Thyroid cancer (10066474)	1	1	0,3
	Bladder transitional cell carcinoma stage III (10066754)	1	1	0,3
	Gastric cancer recurrent (10017761)	1	1	0,3
	Prostate cancer (10060862)	1	1	0,3
	Prostate cancer stage III (10036919)	1	1	0,3
	Lung adenocarcinoma (10025031)	1	1	0,3
	Colon cancer (10009944)	1	1	0,3
Nervous system disorders (10029205)	Encephalitis autoimmune (10072378)	1	1	0,3
	Cerebral infarction (10008118)	2	1	0,3
	Cerebrovascular accident (10008190)	1	1	0,3
Psychiatric disorders (10037175)	Depression (10012378)	1	1	0,3
Renal and urinary disorders (10038359)	Hydronephrosis ((10020524)	4	2	0,6
	Pyelocaliectasis (10061927)	1	1	0,3
	Postrenal failure (10059345)	1	1	0,3
	Urethral stenosis (10065584)	2	2	0,6
	Haematuria (10018867)	1	1	0,3
	Acute kidney injury (10069339)	1	1	0,3
Reproductive system and breast disorders (10038604)	Epididymitis (10015000)	1	1	0,3
Respiratory, thoracic and mediastinal disorders (10038738)	Pneumonia aspiration (10003525)	1	1	0,3
	Chronic obstructive pulmonary disease (10009033)	1	1	0,3
	Dyspnoea (10013968)	1	1	0,3
Surgical and medical procedures (10042613)	Anal fistula excision (10002157)	1	1	0,3
	Transurethral prostatectomy (10044445)	1	1	0,3
	Coronary angioplasty (10050329)	1	1	0,3
	Diabetes mellitus management (10051599)	1	1	0,3
Vascular disorders (10047065)	Pulmonary embolism (10037377)	2	2	0,6
	Gastrointestinal vascular malformation haemorrhagic (10080561)	1	1	0,3
	Peripheral arterial occlusive disease (10062585)	1	1	0,3
	Intermittent claudication (10022562)	1	1	0,3

At least one symptom = at least one symptom experienced (regardless of the MedDRA Preferred Term)
N = number of subjects with at least one administered dose
n+ = number of AEs

For three SAE's in the RF group and four SAE's in the SF group it was considered that there was a reasonable possibility that the event was related to the study treatment. All other SAE's were considered to be not related.

12.3.2 Narratives of deaths, SUSARS

12 patients died during the study period. Three deaths occurred after Month 15, were not related to study treatment or study participation, and therefore did not have to be reported as SAE. Cause of death in these patients was not related to bladder cancer.

9 patients died for the following reasons:
In the RF group:
- Car accident (1)
- Sepsis (1)
- Autoimmune encephalitis or paraneoplastic syndrome (1)
- Pulmonary embolism (1)
- Unknown (3)

In the SF group:
- Acute heart failure (1)
- Unknown (1)

These deaths occurred prior to Month 15 and were reported as SAE.
In all cases there was no reasonable possible relationship to study treatment.

No pregnancies were reported.

No SUSARS were reported.

12.4 Safety conclusions

The number of AEs reported in the RF arm was lower than in the SF arm (858 vs. 1797). With respect to grading of the reported AEs, relationship to study treatment, and seriousness, there was no clear difference between the two treatment groups.

13. DISCUSSION AND OVERALL CONCLUSIONS

Patients with high-grade non–muscle-invasive carcinoma of the bladder (NMIBC) show an increased risk of recurrence, progression, and metastases (1). Intravesical instillation of BCG is the standard of care in patients with high-grade NMIBC (26). BCG was shown to be superior to intravesical chemotherapy in reducing the risk of recurrence and, possibly, progression (32,33). The current state-of-the-art comprises an induction phase followed by further BCG instillations during a maintenance schedule for 1–3 years (2,29,31,34). Various doses, induction and maintenance schedules, and durations of BCG have been investigated, trying to decrease the severity and frequency of side effects while maintaining efficacy. However, dose reduction to one-third revealed to be less effective without reducing toxicity (28). Furthermore, a maintenance phase comprising only one instillation of BCG every 3 months was not sufficient to significantly decrease recurrence and progression rates over induction alone (29).
NIMBUS investigated whether an RF of instillations during induction and maintenance would result in clinical efficacy similar to standard BCG therapy. Ideally, this was expected to be accompanied by fewer side effects and inconvenience. Our approach was based on a recent animal study showing that BCG instillations at weeks 1 and 6 induce only a predominately Th1-mediated cytokine response being equivalent to 6-weekly BCG instillations (7). One extra instillation at week 2 or 5 increased the Th2 cytokine response, being noteworthy, as BCG-induced Th1/Th2 cytokine ratio is associated with effective antitumour activity (11). Therefore, the NIMBUS induction cycle with BCG instillations was scheduled at weeks 1, 2, and 6. In line with CUETO 98013 showing that one maintenance instillation is insufficient, BCG instillations were applied at weeks 1 and 3 for maintenance in our study. One year of maintenance was applied, as this is considered the minimally required time span (4,27) and as 3 years of maintenance has only a slight impact on recurrence but not on progression (28). However, the results clearly reveal an increased recurrence rate in the RF arm. After 14 months of median follow-up, the intention-to-treat analysis showed a difference in

recurrences between treatment arms: 55/177 (reduced frequency) versus 30/182 patients (standard frequency) with a hazard ratio of 0.47 [95% CI: 0.30 – 0.74]. In additional analyses in subpopulations the hazard ratio was: 0.47 [95% CI: 0.30 – 0.74] for all patients that received at least one BCG instillation (348 patients); 0.48 [95% CI: 0.29 – 0.79] excluding patients with CIS only, T2 tumour and possible incomplete resection (309 patients).
Urine samples were collected from 44 patients to evaluate cytokine response following BCG instillations. Their analyses are on-going and will enable investigation of cytokines induced by Th1- and Th2-mediated immune response.
NIMBUS is the first prospective trial using routine re-TUR prior to BCG induction in line with the current EAU guideline recommendation, which is, however, mainly based on retrospective analyses (35,36). While re-TUR was initially required in all patients, it was later abandoned.
The NIMBUS RF schedule was inferior to the standard schedule regarding time to first recurrence. In patients with high-grade NMIBC, this study supports the use of the standard BCG regimen as recommended by the EAU guideline (6 weeks of induction followed by 3 weeks of maintenance at 3, 6, and 12 months) after complete tumour resection.

14. REFERENCE LIST

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 meta-analysis 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. De Boer, 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.
25. Sylvester RJ, van der Meijden AP, Oosterlinck W, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: a combined analysis of 2596 patients from seven EORTC trials. Eur Urol 2006;49, 466–5; discussion 75–77.
26. Babjuk M, Burger M, Comperat EM, et al. European Association of Urology guidelines on non-muscle-invasive bladder cancer (TaT1 and carcinoma in situ)—2019 Update. Eur Urol 2019;76:639–57.
27. Bohle A, Bock PR. Intravesical bacille Calmette-Guerin versus mito-mycin C in superficial bladder cancer: formal meta-analysis of comparative studies on tumor progression. Urology 2004;63: 682–6, discussion 686–687.
28. Oddens J, Brausi M, Sylvester R, et al. Final results of an EORTC-GU cancers group randomized study of maintenance bacillus Calmette- Guerin in intermediate- and high-risk Ta, T1 papillary carcinoma of the urinary bladder: one-third dose versus full dose and 1 year versus 3 years of maintenance. Eur Urol 2013;63:462–72.
29. Martinez-Pineiro L, Portillo JA, Fernandez JM, et al. Maintenance therapy with 3-monthly bacillus Calmette-Guerin for 3 years is not superior to standard induction therapy in high-risk non-muscle-invasive urothelial bladder carcinoma: final results of randomised CUETO study 98013. Eur Urol 2015;68:256–62.

30. Alhunaidi O, Zlotta AR. The use of intravesical BCG in urothelial carcinoma of the bladder. Ecancermedicalscience 2019;13:905.
31. Babjuk M, Burger M, Compérat E, et al. EAU guidelines on non-muscle-invasive bladder cancer (Ta, T1 and CIS).March https:// uroweb.org/guideline/non-muscle-invasive-bladder-cancer/2019
32. Sylvester RJ, Brausi MA, Kirkels WJ, et al. Long-term efficacy results of EORTC genito-urinary group randomized phase 3 study 30911 comparing intravesical instillations of epirubicin, bacillus Calmette-Guerin, and bacillus Calmette-Guerin plus isoniazid in patients with intermediate- and high-risk stage Ta T1 urothelial carcinoma of the bladder. Eur Urol 2010;57:766–73.
33. 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.
34. Malmstrom Pu, Sylvester Rj, Crawford De, et al. An individual patient data meta-analysis of the long-term outcome of randomised studies comparing intravesical mitomycin C versus bacillus Calmette-Guerin for non-muscle-invasive bladder cancer. Eur Urol 2009;56:247–56.
35. Gontero P, Sylvester R, Pisano F, et al. The impact of re-transurethral resection on clinical outcomes in a large multicentre cohort of patients with T1 high-grade/Grade 3 bladder cancer treated with bacille Calmette-Guerin. BJU Int 2016;118:44–52.
36. Sfakianos JP, Kim PH, Hakimi AA, Herr HW. The effect of restaging transurethral resection on recurrence and progression rates in patients with nonmuscle invasive bladder cancer treated with intravesical bacillus Calmette-Guerin. J Urol 2014;191:341–5.

15. PUBLICATIONS BASED ON THE STUDY

1. Grimm M-O, Van der Heijden A, Colombel M, Muilwijk, Martínez-Piñeiro L., Bjartell A, Caris C, Schipper R, Witjes W, Babjuk M, Türkeri L: Treatment of high grade non-muscle invasive bladder carcinoma by standard number and dose of intravesical BCG instillations versus reduced number and dose of intravesical BCG instillations. An initial report of the phase III clinical trial 'NIMBUS'. Accepted as Poster EAU 2019 Barcelona. European Urology Supplements, Vol. 18, Issue 1, e950, March 2019.
2. Grimm M-O, Heijden Van Der A, Colombel M, Muilwijk T, Martínez-Piñeiro L, Babjuk M , Türkeri L, Patel A, Palou J, Bjartell A, Caris C, Schipper R, Witjes W.P.J, EAU Research Foundation NIMBUS Study Group: Recurrence Risk in patients with High Grade Non-Muscle Invasive Bladder Carcinoma in the Randomised Phase III Clinical Trial 'NIMBUS' stratified for EORTC and CUETO risk categories. A contemporary trend to less recurrences? Accepted for Presentation EAU Annual Congress 2020.
3. Marc-Oliver Grimm, Christien Caris, Wim P.J. Witjes for the NIMBUS Study Group: Reply to Emre Karabay and Ilker Tinay's Letter to the Editor. Re: Non–muscle-invasive Bladder Carcinoma by Standard Number and Dose of BCG Instillations Versus Reduced Number and Standard Dose of BCG Instillations: Results of the European Association of Urology Research Foundation Randomised Phase III Clinical Trial "NIMBUS". Eur. Urol. 78 (4) E163-E164, Oct, 2020. https://doi.org/10.1016/j.eururo.2020.07.004.
4. Marc-Oliver Grimm, Antoine G. van der Heijden, Marc Colombel, Tim Muilwijk, Luis Martınez-Pineiro, Marko M. Babjuk, Levent N. Turkeri, Joan Palou, Anup Patel, Anders S. Bjartell, Christien Caris, Raymond G. Schipper, Wim P.J. Witjes, for the EAU Research Foundation NIMBUS Study Group. Treatment of High-grade Non–muscle-invasive Bladder Carcinoma by Standard Number and Dose of BCG Instillations Versus Reduced Number and Standard Dose of BCG Instillations:

Results of the European Association of Urology Research Foundation Randomised Phase III Clinical Trial “NIMBUS” European Urology, Volume 78, Issue 5, November 2020, Pages 690-698.

16. APPENDICES

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