A comparative, randomised, two period, multi-center, cross-over 14-week bioequivalence study of VANTOBRA (T100) versus TOBI (Novartis) in cystic fibrosis patients with bronchopulmonary chronic *Pseudomonas aeruginosa* infection

Clinical Study Report

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1 TITLE PAGE

Clinical Phase	Ib
Study Title	A comparative, randomized, two period, multi-center, cross-over 14-week bioequivalence study of VANTOBRA (T100) versus TOBI (Novartis) in cystic fibrosis patients with bronchopulmonary chronic *Pseudomonas aeruginosa* infection
Investigational Products	▪ VANTOBRA (= T100) ▪ TOBI (Novartis)
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Study Duration	May 2011- March 2012
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2 STUDY SYNOPSIS

Name of Sponsor: PARI Pharma GmbH Lochhamer Schlag 21 82166 Graefelfing, Germany	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: VANTOBRA	**Volume:**	
Name of Active Ingredient: Tobramycin	**Page:**	

Title of Study:	A comparative, randomized, two period, multi-center, cross-over 14-week bioequivalence study of VANTOBRA (T100) versus TOBI (Novartis) in cystic fibrosis patients with bronchopulmonary chronic *Pseudomonas aeruginosa* infection	
Study number (Sponsor): **EudraCT number:**	12012.101 2010-023235-41	
Co-ordinating Investigator:	Prof. Dorota Sands**,** Instytut Matki i Dziecka, ul.Kasprzaka 17a, 01-211 Warszawa, Poland	
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Publication:	Planned	
Study Period:	First patient in (FPI): MAY 2011 Last patient out (LPO): MAR 2012	**Phase:** Ib
Objective:	The primary objective of this study was to determine bioequivalence of VANTOBRA / eFlow (hereinafter VANTOBRA or T100) and TOBI (Novartis) / PARI LC PLUS (hereinafter TOBI) in children and adolescents/adults (aged 4 to 13 and > 13 years). In addition, the study should allow assessment of efficacy and safety of the two different drug/device combinations.	

Endpoints:	**Primary endpoint** Plasma $AUC_{0\text{-}12h}$Area under the plasma concentration-time curve of Tobramycin from the first time point [t=0] to the time point of the last measured concentration [$t_{(last)}$] **Secondary endpoints** Efficacy: ▪ C_{max} and trough levels of Tobramycin in plasma and sputum ▪ Change of Colony Forming Units (CFU) of *P. aeruginosa* ▪ Changes in lung function (FEV_1, FVC, $FEF_{25\text{-}75}$, PEF) Safety: ▪ Proportion of treated lung exacerbations until end of treatment ▪ Audiology: voice alterations and signs of tinnitus ▪ Change in vital signs; number of bronchospasms ▪ Proportion of patients reporting ARs, by severity and by action taken ▪ Proportion of patients reporting SARs/SUSARs ▪ Proportion of patients with clinically significant laboratory value abnormalities related to the study drug ▪ Discontinuations due to ARs ▪ Bronchospasms after the end of inhalation ▪ Proportion of resistant *P. aeruginosa* strains with a minimal inhibitory concentration of > 4 µg/ml Others: ▪ Treatment complicance ▪ Inhalation time ▪ CFQ-R
Methodology:	Open, randomized, cross-over, multiple dose bioequivalence study (Treatment Phase 1: 4 weeks; wash-out phase between treatments: 4 weeks; Treatment Phase 2: 4 weeks).
Number of patients:	60 patients planned, 64 patients screened; 58 patients randomized: ▪ Patients analysed for safety: N = 58 ▪ Patients analysed for clinical efficacy: N = 54 ▪ Patients analysed for pharmacokinetics: N = 49
Patient selection criteria:	The population of this study were patients suffering from cystic fibrosis with bronchopulmonary chronic *Pseudomonas aeruginosa* infection.
Study drugs:	VANTOBRA: One blow-fill-seal vial contained 1.7 ml preservative-free nebuliser solution with 170 mg tobramycin (aminoglycoside); eFlow nebuliser, and TOBI: One ampoule contained 5 ml preservative-free nebuliser solution with 300 mg tobramycin (aminoglycoside); PARI LC PLUS, with PARI Boy SX compressor.
Route of administration:	Inhalation
Duration of treatment:	Twice daily for 4 weeks

Criteria for evaluation: **- Efficacy** **- Safety**	See Endpoints
Statistical methods:	Pharmacokinetic parameters and the assessment of bioequivalence were calculated by using WinNonlin (WinNonlin® Software Release 5.2.1, Pharsight Products, USA). Pharmacokinetics was determined using following parameters: <u>Plasma and sputum:</u> ▪ Plasma AUC_{0-12h} Area under the plasma concentration-time curve from the first time point [t=0] to the time point of the last measured concentration [$t_{(last)}$] (calculated using the trapezoidale rule). ▪ C_{max} Maximum plasma and sputum concentrations (directly obtained from measured values). ▪ t_{max} Time of maximum plasma and sputum concentrations (directly obtained from measured values). All other parameters, incl. clinical efficacy and safety variables, were calculated using descriptive statistics and presented in tables and/or graphs. Some explorative statistical tests were performed for lung parameters. The test for normality of the residual distribution was performed on ln-transformed data using the Wilk-Shapiro procedure (5 % level of significance). 90%-confidence intervals for the difference between drug formulations least-squares means (LSM) was calculated for the log-transformed parameters plasma AUC_{0-12h} and plasma C_{max}. The acceptance range for the 90% confidence band for the ratio of the back-transformed LSMEANS of Tobramycin was 80 to 125% for the parameter plasma AUC_{0-12h} and 70 to 133% for plasma C_{max}.
Results: **- Bioequivalence** **- PK parameters**	The arithmetic mean AUC_{0-12h} values (± SD) for VANTOBRA and TOBI in *plasma* (n=49) were 5778.8 ± 3569.15 ng·h/ml and 5809.7 ± 3097.98 ng·h/ml, respectively. The geometric mean AUC_{0-12h} values (90% CI) for VANTOBRA and TOBI in *plasma* (n=49) were 4159.2 ng·h/ml and 4904.9 ng·h/ml, respectively. The median AUC_{0-12h} values (90% CI) for VANTOBRA and TOBI in *plasma* (n=49) were 5731.9 ng·h/ml and 5387.5 ng·h/ml, respectively. The maximum arithmetic mean *plasma* Tobramycin concentrations C_{max} for VANTOBRA and TOBI (n=49) were 1271.2 ± 805.5 ng/ml and 1333.7 ± 757.5 ng/ml, respectively. The maximum geometric mean *plasma* Tobramycin concentrations C_{max} for VANTOBRA and TOBI (n=49) were 911.0 ng/ml and 1101.4 ng/ml, respectively. The median *plasma* Tobramycin concentrations C_{max} for VANTOBRA and TOBI (n=49) were 1105.6 ng/ml and 1226.2

ng/ml, respectively.

The mean t_{max} values for VANTOBRA in *plasma* (n=49) was 0.80 ± 0.39 h and for TOBI0.80 ± 0.31 h, respectively.

The maximum arithmetic mean *sputum* Tobramycin concentrations C_{max} for VANTOBRA and TOBI (n=49) were 1950741.0 ± 2186546.8 ng/g and 1416501.0 ± 1505653.0 ng/g, respectively.

The mean t_{max} values for VANTOBRA in *sputum* (n=49) was 0.38 ± 1.12 h and for TOBI 0.39 ± 1.16 h, respectively.

The calculation of bioequivalence has revealed that the point estimator and upper confidence limit (UCL) for AUC_{0-12h} are within the band width of 80 to 125%, but not the lower confidence limit (LCL):

AUC_{0-12h}	**LCL (%)**	**Ratio (%)**	**UCL (%)**	**CV_{res} (%)**
All	68.32	85.03	105.83	71.87

The calculation of bioequivalence has revealed that the point estimator and upper confidence limit (UCL) for C_{max} are within the band width of 70 to 133 %, but not the lower confidence limit (LCL):

C_{max}	**LCL (%)**	**Ratio (%)**	**UCL (%)**	**CV_{res} (%)**
All	66.30	83.05	104.03	74.50

Therefore, under formal points of view, bioequivalence could not be demonstrated if the calculation was based on geometric means.

- **Clinical efficacy**

  - Mean number of *P. aeruginosa* colony forming units (CFU) in sputum at Visit 3 compared to Visit 2 and Visit 5 compared to Visit 4, stratified into overall density and planctonic or mucoid for all age groups [n = 54])
  - Lung function (FEV_1, FEF_{25-75},FVC and PEF) at every study visit for all age groups [n = 54]

  (Data stratified for the age groups 4-13 years and > 13 years are provided in the Appendix.)

Treatment with Tobramycin resulted in an overall reduction in CFU density of *P. aeruginosa*, irrespective of the specific drug/device combination. In general, the treatment effect was more pronounced in the first than in the second treatment period. During the first treatment phase a similar log_{10} CFU reduction was achieved with VANTOBRA and TOBI (-1.77 ± 2.74 vs. -1.70 ± 2.93, $p < 0.005$), in the second treatment phase the reduction was -1.30 ± 2.55 and 0.12 ± 1.78, respectively. The calculation over the complete treatment period revealed an overall reduction of PA CFU density of -3.07 ± 5.26 and -1.62 ± 5.14 for VANTOBRA and TOBI, respectively.

The changes in the different lung function parameters under investigation were consistently indicative for an improvement under both therapies with a tendency of better improvement under VANTOBRA therapy.

	The treatment effects of FEV_1 % predicted were very similar for both groups, VANTOBRA and TOBI, in the first treatment period. However, a positive treatment effect was also observed for VANTOBRA in the second treatment phase. During the first treatment phase a similar percentual increase in FEV_1 was achieved with VANTOBRA and TOBI (8.20 ± 9.49 vs. 24.80 ± 9.58), in the second treatment phase the change was 2.40 ± 10.64 and -0.44 ± 8.10, respectively. The calculation over the complete treatment period revealed an overall increase in FEV_1 of 10.59 ± 20.81 and 4.48 ± 18.24 for VANTOBRA and TOBI, respectively. The treatment effects of FEV_{25-75} (predicted) were very similar for both groups, VANTOBRA and TOBI, in the first treatment period. However, a positive treatment effect was also observed for VANTOBRA in the second treatment phase. During the first treatment phase a similar percentual increase in FEV_{25-75} was achieved with VANTOBRA and TOBI (9.15 ± 13.76 vs. 10.28 ± 14.32), in the second treatment phase the change was 2.35 ± 16.08 and -1.54 ± 15.20, respectively. The calculation over the complete treatment period revealed an overall increase in FEV_{25-75} of 11.50 ± 30.43 and 9.01 ± 31.29 for VANTOBRA and TOBI, respectively. The treatment effects on FVC were comparable between VANTOBRA and TOBI. However, a positive treatment effect was also recognized in patients who received T100 in the second treatment phase, whereas in patients who received TOBI during the second treatment period the positive effect could not be preserved. During the first treatment phase a similar percentual increase in FVC was achieved with VANTOBRA and TOBI (6.53 ± 9.78 vs. 4.74 ± 11.45), in the second treatment phase the change was 0.03 ± 9.56 and -0.07 ± 6.99, respectively. The calculation over the complete treatment period revealed an overall increase in FVC of 6.56 ± 20.25 and 4.75 ± 19.40 for VANTOBRA and TOBI, respectively. The treatment effects of PEF are not statistically different between the both groups VANTOBRA and TOBI. However, a positive treatment effect is seen in patients who received VANTOBRA in the second treatment phase. During the first treatment phase a similar percentual increase in PEF was achieved with VANTOBRA and TOBI (3.92 ± 16.60 vs. 5.44 ± 13.41), in the second treatment phase the change was 3.00 ± 12.30 and -0.95 ± 11.23, respectively. The calculation over the complete treatment period revealed an overall increase in PEF of 6.92 ± 28.96 and 4.65 ± 25.19 for VANTOBRA and TOBI, respectively.
- **Safety**	Overall, 76 adverse events were reported in 29 patients (50 % of all patients) of the safety population under investigation (n = 58). 29 patients experienced no AEs. Three AEs were severe in intensity, all others were classified to be mild to moderate. 32 adverse events (approx. 42% of all AEs) were considered to be related to the study drug, i.e. they were defined as ADRs. All of them were classified as mild to moderate in intensity. In no case study medication had to be discontinued temporarily or permanently due to an ADR. There were 5 serious adverse events (SAEs) recorded in 4 patients;

	the reason for seriousness was hospitalisation in all cases. None of the SAEs was drug-related. No fatality was observed. Six events were described as clinically relevant increases in laboratory values (4 in one patient, who discontinued TOBI-treatment and increase of LDH in another two patients, one patient in the VANTOBRA, one patient in the TOBI group, both continued the treatment). All of those abnormal parameters were recorded as AEs, i.e. none of these were drug related. All other changes of laboratory values outside of the normal range were assessed by the investigators as "not clinically significant". There were no clinically relevant pre- vs. end-of-study changes in vital signs. No pre- vs. end-of-study changes in physical examination were observed. Bronchospasms as defined in the protocol occurred only in 2 patients under TOBI (3.4% of the patients) and were considered by the investigator as an ADR. Audiology testing revealed two cases of tinnitus in patients under VANTOBRA treatment (3.4% of all patients). Both cases were mild in severity and transient as resolving shortly after inhalation. One patient in the VANTOBRA group showed pathological signs in pure tone audiometry measured by bone connectivity (highest value for left ear at 2 KHz was 35 dB). Pulmonary exacerbation was observed in one patient (1109) only during the wash-out phase after TOBI treatment. This patient required treatment with antibiotics which were prohibited as per study protocol and thus was withdrawn from further study participation. Investigations on the occurrence of resistant PA revealed only inconclusive results as cultures of sputum samples showed no growth of the pathogen in approx. half of the assays. Analysis of the CFQ-R revealed only inconclusive results. Neither relevant differences nor even trends were found between the treatment groups or age strata. The time per inhalation was impressively reduced in the drug/device combination of VANTOBRA / eFlow (mean: 4.4 min) as compared to the combination TOBI / PARI LC PLUS (mean: 24.3 min). Compliance to therapy of the patients was generally high in both groups with 99% for VANTOBRA patients (as recorded by an electronic Monitoring System of the device) and 99% for TOBI patients (as recorded in patient diaries).

Conclusions:

The study concept followed predominantly a design for bioequivalence (BE). Nonetheless, relevant clinical efficacy and safety parameters were taken into consideration and investigated, thus allowing also statements regarding therapeutic equivalence (TE).

BE could not be demonstrated for the primary endpoint using the formalism as recommended in the guidelines. However, most of the clinical efficacy parameters investigated (CFU/Lung function) were in favour for the VANTOBRA-treated patients.

Not only VANTOBRA was characterised by high coefficients of variation but also the reference product TOBI.

There is a principle dilemma in the investigation of pharmacokinetics (PK) of Tobramycin, originated from a) the route of drug administration via inhalation, and b) the nature of CF which contributes to a marked increase in patient variability:

- The CF disease status exerts a significant impact on the properties of mucus (viscous, aqueous, central/peripheral, surface covering), lung morphology, inflammation/exercerbation, hydration status of the patient, severity of the disease).
- The efficiency of inhalation, and thus the drug deposition in the lung, depends on the breathing pattern of patients
- The different efficiency of the devices
- Tobramycin PK values resulted also in a high coefficient of variation even when administered intravenously, although eliminating one parameter (inhalation) which mainly contributes to an increased variability.

In summary, the study showed that CF patients cannot be regarded as a suitable model for plasma PK-assessment and/or comparisons of inhaled antibiotics using rigid and formal rules for calculation, but the results have to be discussed in the context of the clinical outcome.

Regarding clinical efficacy, treatment with VANTOBRA provided a comparable, if not even better, control of *P. aeruginosa* when analyzing CFU at start and end of treatment. As a consequence, lung function parameters, most impressively FEV_1, improved markedly under VANTOBRA treatment.

Regarding drug safety it could be stated that all observed ARs were consistent with the expected and known side effect profile of the drug substance class (Tobramycin) and are mainly concentrated within the SOC “Respiratory, thoracic and mediastinal disorders”.

None of the SAEs were related to the study drugs; all of them occurred during the wash-out period. Three out of four of these affected patients stopped their participation in the study and were not included into the PK calculations and the assessment of clinically efficacy. Reason for withdrawal was the medical requirement for the use of prohibited comedication (i.v. antibiotic therapy).

There were no other relevant safety findings as indicated by physical examination, vital signs measurements, clinical laboratory evaluations, number of bronchospasms, and audiometry.

The study provided no evidence that patients were posed on risk for Tobramycin in neither of the two treatment arms.

Overall conclusion:

Treatment with VANTOBRA demonstrated a comparable pharmacokinetic behaviour as TOBI with a similar, at least not inferior, clinical benefit regarding efficacy and safety with a significantly reduced inhalation duration (4 min versus 24 min) and a simultaneously reduced drug burden.

The investigated drug and device combination VANTOBRA / eFlow can be regarded as therapeutically equivalent to the comparator system TOBI / PARI LC PLUS.

Date of Report: **10 JUL 2012**

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ABPA	Allergic Bronchopulmonary Aspergillosis
ACT	Anatomical, Chemical, Therapeutical (WHO Code for Drugs)
ADR(s)	Adverse Drug Reaction(s)
AE(s)	Adverse Event(s)
AR	Adverse Reaction
AUC	Area Under the Curve
BE	Bioequivalence
BID/b.i.d.	bis in die=Twice a Day
BFS	Blow-Fill-Seal
bpm	beats per minute (measurement of heart rate)
CA	Competent authority
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CI	Confidence Interval
CIOMS	Council of International Organisations of Medical Sciences
C_0	Trough Level
C_{max}	Maximal Concentration
C_{min}	Minimal (trough plasma) Concentration
CV	Coefficient of Variation [in %]
CV	Curriculum Vitae
CRF	Case Report Form
CRO	Contract Research Organization
dB	Dezibel
DB	Database
DD	Delivered Dose
DQF	Data Query Form
e.g.	Exempli Gratia (for example)
ED	Early Discontinuation
EoW	End of Week
EoS	End of Study
EudraCT	European Clinical Trials Database
FAS	Full Analysis Set
FEV_1	Forced Expiratory Volume in 1 second
$FEV_{25/75}$	Forced Expiratory Flow at the Midportion (25-75%) of Vital Capacity
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
i.e.	Id est (that is)
i.v.	Intravenous (injection; infusion)
ICH	International Conference on Harmonisationof Technical Requirements for Registration of Pharmaceuticals for Human Use (USA, Europe, Japan)
(I)EC	(Independent) Ethics Committee
IMP(D)	Investigational Medicinal Product (Dossier)
ITT	Intent-To-Treat (population)
kHz	Kilo Hertz
LC	Liquid Chromoatography
LCL	Lower Confidence Limit
LLOQ	Lower Limit of Quantitation
LLT	Low Level Term
LSM	Least-Squares Mean
MedDRA	Medical Dictionary for Regulatory Activities
MIC	Minimal Inhibitory Concentrations
mmHg	Millimetre Hydrargyrum = Mercury (SI unit of Blood Pressure)
MS	Mass Spectrometry
N/n	Number/Frequency
NCR	No Carbon Required (paper sheets)
n.a. or N/A	Not Applicable

OLS	Ordinary Least Squares
PA	*Pseudomonas Aeruginosa*
PEF	Peak Expiratory Flow
PK	Pharmacokinetics
PP	Per Protocol (population)
QA	Quality Assurance
QC	Quality Control
QPIT	Quantitative Pilocarpine Ionophoreses Test
RBC	Red Blood Cell
RD	Respirable Dose
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan / Safety Analysis Population
SAR(s)	Serious Adverse Reaction(s)
SDV	Source Data Verification
SP	Safety Population
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR(s)	Suspected Unexpected Serious Adverse Reaction(s)
TE	Therapeutic Equivalence
t_{max}	Time to Maximal Concentration
TOBI	TOBI® (Novartis), Tobramycin 300 mg/5 ml nebuliser solution
UCL	Upper Confidence Limit
VANTOBRA	T100, Tobramycin 170 mg/1.7 ml nebuliser solution
WHO	World Health Organisation

5 ETHICS

5.1 Independent Ethics Committee (IEC)

Independent Ethics Committee (IEC) approval was obtained prior to start of the study and consequently before any study drug was admitted. The name of the IEC competent for Center 1 was as follows:

Committee of Bioethics of the Institute of Mother&Child,
Komisja Bioetyczna przy Instytucie Matki i Dziecka
ul. Kasprzaka 17 a
01-211 Warszawa

The other ECs related to the other three study centers were the following institutions:

Center 2 Dr Sapiejka
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ul. Śniadeckich 33
80-204 Gdańsk, Poland
Center 3 Doc. Mazurek
Komisja Bioetyczna przy Okręgowej Izbie Lekarskiej w Krakowie
ul. Krupnicza 11a
31-123 Kraków, Poland
Center 4 Dr Gąszczyk
Komisja Bioetyczna przy Akademii Medycznej
ul. Pasteura 1
50-367 WROCŁAW, Poland

5.2 Ethical Conduct of the Study

This trial was conducted under the sponsorship of PARI Pharma, Graefelfing, Germany, in accordance with the protocol, the Declaration of Helsinki (1996) and with Good Clinical Practice (GCP) issued by the International Conference on Harmonisation (ICH) and in compliance with local laws as well as the European Directive 2001/20/EC.

All patient identities were kept confidential. Each patient was assigned a unique randomisation number, which in turn was used in the case report form (CRF) replacing the patient's name.

This study was approved by the Office of the Registration of Medical Products, Ministry of Health, Warsaw, Poland (CA).

5.3 Patient Information and Consent

Written informed consent was obtained for every patient prior to screening for the study. Each patient was advised of the nature and the risk of the study by the investigator. Each patient was given sufficient opportunity to read the patient information, to ask any questions and to consider whether to participate. Patient Information and the signed Informed Consent Form were provided to the study patient and/or their parents; the original was retained with the patient's source documents. Different Forms were used for different age groups: for parents of children 4 – 11 years, for adolescents (12 – 18 years) additionally to that for their parents, and for adult patients (> 18 years). (Sample Forms are presented in the **Appendix 16.1.3**).

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Coordinating Investigator

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A fifth center, Prof. Dr. hab. Piotr Gutkowski, TRIAL S.C. ul. Czecha 5, 04-555 Warszawa, Poland, was cancelled because no patients could be recruited.

Clinical Laboratory Facilities

The laboratory safety parameters were determined in the local clinical laboratories of the trial hospital centers.

Laboratory Performing Plasma and Sputum Assays

ACC GmbH Analytical Clinical Concepts
Dr. Bernd Scheidel
Schöntalweg 9
63849 Leidersbach, Germany

Packaging and Labeling of Clinical Trial Supplies

The study drugs were manufactured and/or packed and labeled by PARI Pharma according to their GMP-SOPs:

- TOBI was manufactured by Novartis (purchased from the market) and study specific labeling was performed by PARI Pharma according SOP VA 70036 (Packing and Labeling of medicinal products) and work instruction AV 70273. After labeling the IMP release was performed per study center.
- VANTOBRA was manufactured and packed by Fresenius Kabi Norway, labeling performed by PARI Pharma according to SOP VA 70036 (Packing and Labeling of medicinal products) and Work Instruction AV 70273.

For VANTOBRA an intermediate release for manufacturing, testing and transport was performed by PARI Pharma. After labeling both IMPs were released per labeling campaign (Form see **Appendix 16.1.6**).

GMP Certificate, Certificates of Analysis (CoA), Certificate of Conformity (CoC) etc. are attached in **Appendix 16.1.6**.

Study Monitoring

This study was managed on behalf of PARI Pharma by the following contract research organization (CRO):

Associated Medical Clinical Science Services Sp. z o.o. (hereinafter AMCSS)
ul. Kaczmarka 5
Ruda Śląska, Poland

The study manager was:

Wojciech Wojtyczka, AMCSS

The study monitors were Wojciech Wojtyczka for centers 1, 2 and 3; Ewa Góźdź for center 4 and Dagmara Kącik as back-up monitor.

Study Biostatistician

The Biostatistician responsible for this study was:

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7 INTRODUCTION

7.1 Background Information

The inability to eliminate *Pseudomonas aeruginosa* (PA) from the respiratory tract in most patients with cystic fibrosis (CF) coupled with the growing concern about lung damage secondary to the inflammatory response (Berger 2002; Cantin 1995; Dakin et al. 2002; Konstan et al. 1994) has led to therapeutic attempts following the aim of chronically suppressing PA. Oral systemic administration of antibiotics active against PA is limited by poor absorption of aminoglycosides in the gastrointestinal (GI) tract and the relatively rapid development of bacterial resistance to ciprofloxacin. Parenteral administration of antibiotics requires specialized health services, either hospitalisation or a "home care service" for home i.v. administration. Alternatively, a number of studies have reported positive results with inhaled antibiotics, usually an aminoglycoside or colistin. Initial reports with inhaled tobramycin used 80 mg of the i.v. preparation and relatively inefficient delivery systems (Steinkamp et al. 1989; Weisemann et al. 1998; MacLusky et al. 1989). Nevertheless compared to historical controls, MacLusky et al. demonstrated a significantly lower annual rate of decline in FEV_1, in the treatment group compared to historical controls (MacLusky et al. 1989). A short-term randomized controlled trial using 600 mg three times a day versus placebo using an ultrasonic nebulizer demonstrated improved pulmonary function (Ramsey et al. 1993).

Minimal problems are encountered with the development of bacterial resistance to tobramycin over a three month period (Smith et al. 1989; MacLeod 2000). This led to the development of a formulation of tobramycin specifically for inhalation. A subsequent larger randomized, double-blind controlled trial demonstrated that 28-day cycles on 300 mg in a 5 ml fill volume nebulized by a PARI LC Jet breath enhanced nebulizer led to a 10% increase in forced expired volume in one second (FEV_1), compared to a 2% fall in the placebo control group. These encouraging results led to inhaled tobramycin becoming the standard of care for CF patients infected with PA whose FEV_1 are 75% predicted or lower (Ramsey et al. 1999).

The purpose of this study was to determine the bioequivalence of a novel inhalation system comprising the Tobramycin formulation T100 (170 mg/1.7 ml = VANTOBRA) / eFlow with the registered TOBI / PARI LC PLUS standard treatment. PARI eFlow is more efficient in terms of Delivered Dose (DD) at the mouthpiece and the RD (aerosol particles <5 µm); therefore the loaded dose can be reduced significantly. The percentage of the RD is about 50% compared to 24% for the TOBI / PARI LC PLUS treatment.

7.2 Customized eFlow Nebulizer for VANTOBRA

The eFlow utilises a new technology of nebulising liquid drugs with a perforated vibrating membrane resulting in an aerosol with a low ballistic momentum and a high percentage of droplets in a respirable size range, usually below 5 µm. The eFlow is designed for a more rapid and efficient nebulisation of medication due to a lower drug wastage and a higher percentage of drug available as delivered dose (DD) and respirable dose (RD) compared to conventional jet nebulisers.

The eFlow device has been tested in several nonclinical and clinical trials and the eFlow *rapid* version is available on the European market since May 2005 for approved inhalation drugs such as tobramycin or colistin in cystic fibrosis. The eFlow nebuliser used in the present study is a modified version of the eFlow *rapid* device for an optimised delivery of the investigational drug for the designated patient group. The configuration of the eFlow for VANTOBRA has a high DD, short nebulisation time and inhibits contamination of the surroundings. The eFlow *rapid* is CE-marked in Europe since 2005. The specific eFlow for VANTOBRA for this clinical study also features a Monitoring System that allows to record nebulisation time and duration on a chip card and enables to check patient compliance at the end of the clinical trial.

7.3 Investigational and Reference Medicinal Products (IMP)

The investigational formulation VANTOBRA contains 170 mg Tobramycin in 1.7 ml in single dose units. The formulation was designed for inhalational use. The product is a sterile, preservative-free solution. Osmolality and pH are adjusted to be physiologically tolerable.

VANTOBRA formulation was to be nebulised utilising the eFlow device.

The comparator medication TOBI (300 mg Tobramycin/5 ml) is registered for inhalation therapy for the management of CF patients with PA in USA and EU. The product is commercially available. In USA the pivotal clinical trials were performed with PARI LC PLUS / PulmoAide compressor (Balcke 2004).

7.4 Non-clinical Studies

7.4.1 *In vitro* Aerosol Characterization

In vitro investigations utilising breath simulation and cascade impaction measurements have been performed to obtain information on aerosol characteristics for VANTOBRA nebulised with the eFlow nebuliser and TOBI nebulised with the PARI LC PLUS. **Table 1** summarises the relevant data regarding the nebulisation performance of the two drug delivery regimes. It is apparent from the data set that the drug can be delivered more rapidly and in higher aerosol densities to the lungs using the eFlow device, offering the benefit of shorter inhalation times (15 vs. 4 min).

It is also apparent from the results in **Table 1** that the DD is higher when TOBI (300 mg / 5 ml) is nebulised by the PARI LC PLUS compared to VANTOBRA (170 mg / 1.70 ml) nebulized by eFlow. However, not the dose exiting the mouthpiece (= DD), but the amount of drug reaching the lungs (= RD) is important for efficacy and safety. Therapeutically important is the quantity of nebulised drug in the respirable aerosol droplets (< about 5 µm), which can reach the lungs of patients and the site of infection.

Table 1 **Comparison** of aerosol characteristics of TOBI compared to VANTOBRA

Brand Name **Strength**	**TOBI** **300 mg/5 ml**		**Tobramycin PARI** **150 mg/1.50 ml**		**VANTOBRA** **170 mg/1.70 ml**	
Nebuliser:	**PARI LC PLUS®**		**eFlow®**		**Tolero® eFlow**	
	Mean	**± SD**	**Mean**	**± SD**	**Mean**	**± SD**
Delivered Dose DD [mg]	101	3.4	89	4.4	98	5.4
Respirable Fraction RF [% < 5 µm]	54.7	1.2	79.3	1.8	73.5	7.4
Respirable Dose RD [mg<5µm] (calculated value : RD = RF x DD)	55	1.6	70	3.8	72	8.3
Nebulisation time [min]	15.3	0.6	3.7	0.2	3.9	0.6
MMAD [µm] (NGI @ 15 l/min)	4.5	0.1	3.6	0.1	3.8	0.4

DD = Delivered Dose; RF = Respirable Fraction; RD = Respirable Dose; MMAD = mass-related median aerodynamic diameter; NGI = Next Generation Impactor

The VANTOBRA / eFlow drug/device combination provides a respirable dose (RD) of 72 ± 8.3 mg in comparison to 55 ± 1.6 mg for the TOBI / PARI LC PLUS combination (**Table 1**). The much higher drug delivery rate of 25 mg/min for the VANTOBRA / eFlow versus 6.6 mg/min for the TOBI / PARI LC PLUS enables a significant reduction in nebulisation time from 15 min to 4 min while increasing the respirable dose (RD) at the same time.

7.4.2 Non-clinical Pharmacology

VANTOBRA is specially formulated for inhalation use. When inhaled, Tobramycin is concentrated in the airways.

Tobramycin is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. It acts primarily by disrupting protein synthesis, leading to altered cell membrane permeability, progressive disruption of the cell envelope, and eventual cell death.

Tobramycin has *in vitro* activity against a wide range of Gram-negative organisms including *Pseudomonas aeruginosa*. It is bactericidal at concentrations equal or slightly higher than inhibitory concentrations.

7.5 Toxicology

7.5.1 Tobramycin

Toxicological data for Tobramycin sulphate were generated during the development of Nebcin® by Lilly in 2000.

The published toxicological data for the acute exposure of the active ingredient Tobramycin sulphate are summarized in **Tables 2** and **3**.

Table 2 Data for the acute toxicity of Tobramycin sulphate [Lilly 2000]

Route	Species	Dosage	Findings
Oral	Rat	7000 mg/kg	No deaths, reduced activity, watery faeces
Skin	Rabbit	500 mg/kg	Mortality, diarrhoea
Inhalation	Rat	6800 mg/m^3 for 1 hour	No deaths or toxicity
Intravenous	Rat	Median letal dose 133 mg/kg	Convulsions, reduced activity
Intravenous	Dog	100 mg/kg	No deaths, vomiting
Skin contact	Rabbit	N/A	Slightly irritant
Eye contact	Rabbit	N/A	Slightly irritant

The published toxicological data for chronic exposure of the active substance Tobramycin sulphate are listed in **Table 3**:

Table 3 Data for subacute toxicity of Tobramycin sulphate [Lilly 2000]

Target organ effects	Kidney effects (increased blood urea nitrogen, increased creatinine, kidney tissue changes)
Reproduction	No effect identified in animal studies
Sensitisation	No applicable information found
Mutagenicity	Not mutagenic in bacterial cells

7.5.2 Supportive Data on aerosolized Tobramycin

Three inhalation toxicology studies of preservative-free aerosolized Tobramycin were conducted in rats and guinea pigs at 3 to 109 times the estimated human dose, for as long as two years, to evaluate the local effects on the respiratory tract.

The following non-clinical studies were performed and filed to the FDA by Pathogenesis Corp. for the NDA 50,753 in 1997 for TOBI:

14-Day Inhalation Toxicity Study of Tobramycin in the Rat and Guinea Pig (SC950011) (IND)

14-Day Inhalation Toxicity Study of Tobramycin in the Rat (N001328A) (IND)

6-Month Inhalation Toxicity Study of Tobramycin in the Rat (N001328B)

Mutagenicity Tests with Tobramycin in the *Salmonella typhymurium-Escherichia coli* Mammalian Microsome Reverse Mutation Assay with Confirmatory Assay (17452-0-409R)

Mutagenicity Tests on Tobramycin in the L5178Y TK+/- Mouse Lymphoma Forward Mutation Assay with Confirmatory Assay (17452-0-431R)

Mutagenicity Tests on Tobramycin: Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells With and Without Metabolic Activation with an Assay with Multiple Harvests (17452-0-437R)

Mutagenicity Tests on Tobramycin: Chromosomal Aberrations in Chinese Hamster Ovary (CHO) Cells With and Without Metabolic Activation with an Assay with Multiple Harvests (18080-0-437R)

Mutagenicity Tests on Tobramycin in an *in vivo* Mouse Micronucleus Assay (17452-0-455CO)

Tobramycin was toxicologically characterized for the registration of Nebcin®. In addition during the development of TOBI a toxicological program of Tobramycin for inhalation was performed that was considered sufficient for registration purpose from the FDA and the EMA. The 100 mg/ml

concentration was tested in the 14-day rat toxicology study with minimal differences in incidence and severity of lesions between the 60 mg and 100 mg/ml group.

Additional inhalation toxicological studies are of limited value, since a different nebulisation system and droplet size pattern (Garcia-Contreras and Hickey 2002) must be used to meet with the anatomical requirements of the test species being usually nose and not oral breathers. The resulting lung deposition pattern in these species most likely will not be comparable with those in humans.

7.6 Pharmacokinetics and Bioavailability of Aerosolized Tobramycin in Cystic Fibrosis

The pharmacokinetic properties of inhaled Tobramycin in CF patients is well characterized: Geller et al. (2002) published the results of a pharmacokinetic study performed with TOBI /PARI LC PLUS: Study objectives: To describe the pharmacokinetics and bioavailability of inhaled tobramycin (TOBI; Chiron Corporation; Seattle, WA), 300 mg dose, delivered by a nebuliser (PARI LC PLUS; Pari Respiratory; Richmond, VA) and a compressor (Pulmo-Aide, model 5650D; DeVilbiss Health Care; Somerset, PA) in CF patients during the pivotal phase III trials. Design: Data from two identical, 24-week, randomised, double-blind, placebo-controlled, parallel-group studies.

Setting: US sites randomised 258 patients with CF to receive tobramycin, 300 mg twice daily, in three 28-day on-/28-day off-treatment cycles. Measurement: Tobramycin sputum concentrations were assessed 10 min after the first and last doses administered in the 20-week study. Plasma tobramycin concentrations were assessed before and 1 h after the first and last doses had been administered. The population estimate of the apparent clearance was used to estimate the bioavailability fraction. Results: The mean peak sputum concentration was 1.237 µg/g. About 95% of the patients achieved sputum concentrations > 25 times the minimum inhibitory concentration of the PA isolates. One hour after the dose, the mean plasma concentration was 0.95 µg/ml. Tobramycin did not accumulate in the sputum or plasma over the course of the study. Pharmacokinetic data were best represented by a two-compartment model with biexponential decay and slope estimates comparable to those following parenteral administration. The estimated systemic bioavailability after aerosol administration was 11.7% of the nominal dose.

Conclusion: Administration of Tobramycin, 300 mg b.i.d., in a 28-day off-/28-day on-regimen produced low plasma tobramycin concentrations, reducing the potential for systemic toxicity. High sputum concentrations ensure efficacious antibiotic levels at the site of the infection. Inhaled tobramycin significantly improved the therapeutic ratio over that of parenteral administered aminoglycosides.

A study published in 2009 by Hubert et al. compared pharmacokinetics of TOBI administered by the PARI LC PLUS or eFlow *rapid*. The study included 25 patients with cystic fibrosis and TOBI was inhaled for 15 days either by the PARI LC PLUS or eFlow *rapid* in a cross-over design. The mean plasma concentration for TOBI / PARI LC PLUS based on blood sampling 1h post inhalation and commonly regarded as being equivalent to C_{max} was 1.3 µg/ml versus 1.2 µg/ml for the combinations TOBI /eFlow *rapid*.

At the present time, one clinical phase Ib trial to investigate the comparison of PK of Tobramycin PARI 150 mg / eFlow and TOBI / PARI LC PLUS has been performed [Internal Clinical Trial Report G007.05].

This PK study fulfilled its primary objective and confirmed that Tobramycin PARI 150 mg / eFlow did not increase systemic exposure to Tobramycin compared to the reference product TOBI / PARI LC PLUS. This was important for safety aspects, because aminoglycosides possess various systemic toxicities, the most relevant being irreversible ototoxicity.

Despite the reduced Tobramycin filling dose (-50%) and nebulisation time (approx. -65%) with Tobramycin PARI 150 mg / eFlow, tobramycin sputum concentrations were similar to those of the reference product. Though the antibiotic levels in sputum may be of limited value as a surrogate endpoint for efficacy, this result supplements previous evidence in the deposition clinical trial

G007.03 that Tobramycin PARI 150 mg / eFlow possesses an equivalent lung deposition in CF patients.

Tobramycin PARI 150 mg / eFlow furthermore showed a favorable safety and tolerability profile compared to the reference product, with fewer and less severe adverse reactions. Especially respiratory adverse reactions were less frequent, which may indicate that the investigational therapy controlled signs and symptoms of CF at least as well as the reference therapy.

Though a proof of efficacy was out of scope of this study, evidence in this direction originated from an analysis of respiratory infections. This was performed post-hoc and revealed a comparable frequency in both groups. Thus the reduced nominal tobramycin dose and nebulisation time of Tobramycin PARI 150 mg / eFlow compared to the reference combination (TOBI / PARI LC PLUS) did not appear to jeopardize antibiotic efficacy. In addition, there were no relevant differences across both treatment arms in terms of lung function parameters during treatment phase.

7.7 Benefit / Risk Assessment

The benefit for patients participating in this study was to have access to an inhalation system and drug which allowed short inhalation times and might include improved microbiological status and improved pulmonary function in comparison to non-treated patients.

The risk of participation in this study included tobramycin related adverse reactions (AR): these can be voice alterations, tinnitus, increased serum creatinine levels, bronchospasm. For parenteral aminoglycosides ototoxicity, manifested as both auditory and vestibular toxicity (manifested as vertigo, ataxia or dizziness) and nephrotoxicity are reported.

Participants in the study were treated with tobramycin doses which were either registered (TOBI) or had an equivalent delivered dose (VANTOBRA). VANTOBRA was expected to provide identical effects as TOBI. Therefore, the treatment periods in the study were exactly adapted to the corresponding regular treatment schedules for routine patients.

7.8 Subsequent Treatment and Medical Attendance after Study Termination

Cystic fibrosis patients included in this study were allowed to be treated after completion with a Tobramycin formulation of a marketed product and a nebulising device that has market authorisation.

8 STUDY OBJECTIVES

The primary objective of study 12012.101 was to determine bioequivalence of VANTOBRA and TOBI in children and adolescents/adults (aged 4 to 13 and > 13 years) using eFlow or PARI LC PLUS devices, respectively. In addition, the study should allow assessments of efficacy and safety of the two different drug/device combinations.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study was a multicentre open label, randomized, 2-period, 2-sequence, crossover study following administration of Tobramycin with different inhalation systems and different doses in 2x30 patients treated either with VANTOBRA (170 mg) / eFlow or TOBI (300 mg) / PARI LC PLUS. There was a washout-phase of 4 weeks between dosing and Treatment Periods 1 and 2 (see Flow Chart **Table 4** and **Figure 1** Study Design).

After informed consent was obtained, all screening tests establishing patient eligibility, were performed before first dose administration. Screening procedures included demographics, medical history, current medications, physical examination, vital signs (blood pressure, pulse rate and oral temperature), height and weight measurements, blood sampling and urine collection for laboratory safety tests (hematology, clinical chemistry, and urinalysis; for detailed parameters see **Appendix, 16.2**).

Randomization was performed immediately pre-dose on Day 1 of Period 1. Patients were randomized to one of the two treatment sequences (TOBI followed by VANTOBRA or VANTOBRA followed by TOBI) according to the randomization list, which was provided to the treatment centers (see **Appendix 16.1.7**).

At the end of each treatment phase blood samples (3-4 ml) for the assessment of Tobramycin concentrations were collected in lithium-heparin tubes, pre-dose (30 - 15 min prior to inhalation), and at 30 min, 1, 1.5, 2, 4, 6, 8 and 12 h after end of inhalation.

At the end of each treatment phase sputum PK samples for the assessment of Tobramycin concentrations were collected in sterile culture dishes, pre-dose (30 - 15 min prior to inhalation), and at 10 min, 30 min, 1.5, 2 and 8 h after end of inhalation.

The date and actual blood and sputum sampling times were recorded in the CRF.

Patients returned for a post-study Visit 7 ± 2 days after receiving the final dose of study medication. Post study visit procedures included spirometry, audiometry, vital signs, physical examination, urinalysis, and blood samples for hematology and clinical chemistry. If there was a clinically significant clinical or laboratory abnormality in need of monitoring, patients were followed until resolution of the abnormality or until it was considered stable.

Figure 1 Study Design

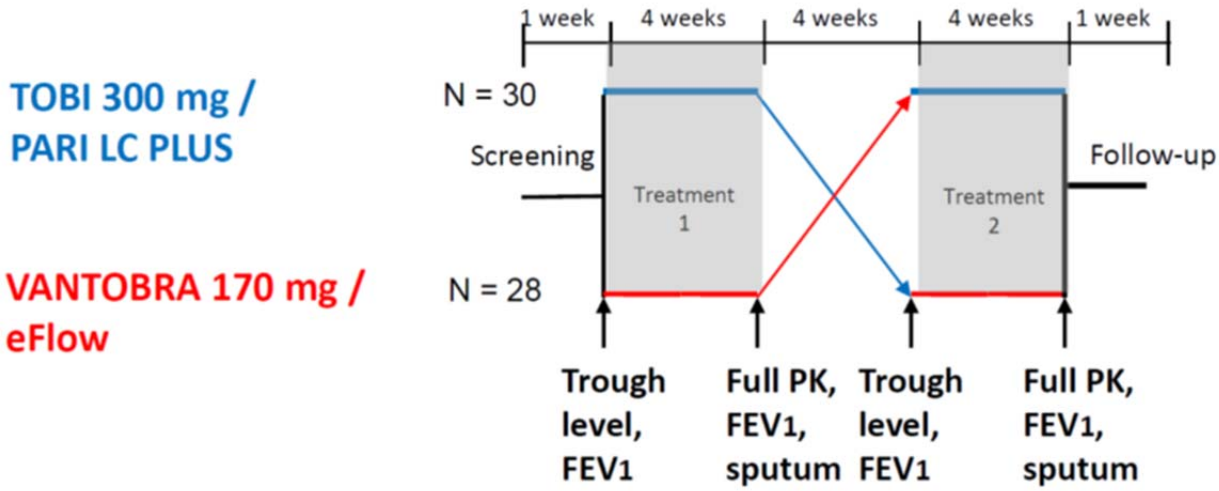


Table 4 Flow Chart

Procedures at study site	**Study start**	**Treatment Phase 1**		**Wash-out**	**Treatment Phase 2**		**EoS/ Follow-up**	**ED[1]**
Week	**-1**	**0**	**4**	**5-8**	**8**	**12**	**13**	NA
Day	**-7**	**0**	**28(-2)**	**28-56**	**56 (±2)**	**84(-2)**	**90 (±2)**	NA
Visit	**1**	**2**	**3**	**–**	**4**	**5**	**6**	NA
Informed Consent	X							
Medical History[2]	X							
X-ray within the last 12 months[3]	X							
Physical Examination	X						X	X
Vital signs	X	X	X		X	X	X	X
Concomitant Medication	X	X	X		X	X	X	X
Patient's Diary		X[4]	X[5]		X[6]	X[7]		
Patient Compliance			X			X		
Adverse Events		X	X		X	X	X	X
Eligibility Criteria	X	X			X[8]			
Device Handling training		X			X			
Safety labs testing[9]	X	X	X		X	X	X	X
Audiometry	X	X	X		X	X	X	X
Inhalation (morning dose) at the site		X	X	–	X	X		
Spirometry - routine - pre dose - 30 min post dose	X	 X[10] X	 X X		 X X	 X X	X	X
Sputum Specimen-microbiology	X[11]	X	X		X	X		
PK • blood specimen (pre inhalation, 0.5, 1, 1.5, 2, 4, 6, 8 and 12 hours after inhalation) • sputum specimen (pre inhalation, 10 min, 0.5, 1.5, 2 and 8 hours after inhalation)			 X X		 X X			
Trough level in blood and sputum (pre inhalation only)		X			X			
Dispense Study Drug and Device		X			X			
Drug/Device Accountability			X			X		X
CF questionnaire-revised (CFQ-R)	X	X	X		X	X	X	X
Return device and remaining study drug			X			X		X
Urine pregnancy test	X				X		X	X

[1]ED: Early Discontinuation Visit is required for patients who early terminate the study. This visit is to be performed within 14 days of the discontinuation date to evaluate AEs and final lab test results.
[2]Medical history includes demographics, history of medication, especially history of antibiotics. Investigational site must request copies of medical records from patient's most recent previous care giver to confirm verbal history.
[3] If the examination was not performed within last 12 months please make it at the screening.
[4]Dispense.
[5] Return.
[6]Dispense.
[7] Return.
[8]Check inclusion criteria no 4 before entering into Treatment Phase 2
[9]Laboratory testing includes:
Haematology: haemoglobin, haematocrit, WBC and differential, RBC, platelet count
Blood Chemistry: AST/SGOT, ALT/SGPT, LDH, AP, total bilirubin, GGT, glucose, albumin, creatinine, BUN, urinalysis: pH, specific gravity, protein, blood, glucose.
[10]If patient has a drop of >20% FEV_1 from Screening Visit, enrollment will be delayed.
[11]If patient has no PA isolated from sputum within 2 months prior to screening, sputum microbiology must be performed.

9.2 Discussion of Study Design

Usually the drug serum concentration is a regulatory accepted surrogate parameter to evaluate lung deposition of drugs administered via the inhalable route to allow the assessment of comparability and thus, indirectly, to allow estimations regarding efficacy.

The Bioequivalence design was primarily chosen for practical reasons (limited number of patients available in an orphan indication, hybrid application) to perform the study within a reasonable time frame. The effort to conduct a fully powered non-inferiority study addressing the efficacy of a well-known drug was agreed not to be rectified from ethical, administrative and technical points of view.

Serum AUC instead of serum C_{max} was selected as the primary endpoint because it reflects a continuous situation and therefore reveals a more robust statement than a single time point assessment of C_{max}. In addition, the different inhalation times of the two devices were expected to impact C_{max}.

From a medical point of view drug serum concentrations may also be considered as a surrogate safety parameter for systemic drug toxicity.

To achieve approval the study should, however, not only demonstrate that the safety profile of the tested drug/device system (VANTOBRA / eFlow) is not worse than the reference combination but also that the efficacy is similar, if not better, than the existing TOBI / PARI LC PLUS system. Therefore, clinical efficacy parameters like CFU of *P. aeruginosa* and lung function parameters (FEV_1, FEF_{25-75}, etc.) were planned prospectively to be investigated in order to allow a statement regarding Therapeutic Equivalence.

Regarding the absolute amount of Tobramycin contained in TOBI (300 mg) it was derived from previous clinical studies with the more intensive and effective inhalation procedure using the PARI eFlow system that an absolute amount of 170 mg Tobramycin should be sufficient to achieve similar or even identical pharmacokinetics and clinical efficiacy as TOBI. Beyond that, the drug safety of Tobramycin should be improved by this lower dose and the shorter time which is needed to inhale the substance completely.

The selection of a 4-week on-treatment/off-treatment schedule was driven by the adaptation of the study treatment to routine practice.

The cross-over design was considered as a methodology to allow limitation of expected intra- and interindividual variations.

9.3 Selection of Study Population

A sufficient number of patients with clinically diagnosed cystic fibrosis (CF) and chronic pulmonary infection by *P. aeruginosa* had to be screened, to facilitate that a total of 50 evaluable patients could be enrolled into the study.

9.3.1 Inclusion Criteria

Patients were included in the study if they met all of the following criteria:

1. Patient (or appropriate legal representative) signed the written informed consent including data protection agreement after the nature of the study had been fully explained prior to any screening procedure.
2. Patient was a male or female and at least 4 years of age at the time of screening.
3. Patient's diagnosis of cystic fibrosis (CF) was confirmed by
   - one or more specific clinical features consistent with CF
     and

- elevated chloride concentration in the sweat ≥ 60 mEq/l (by quantitative pilocarpine iontophoresis test - QPIT)
  and/or
- presence of disease-associated CF transmembrane conductance regulator (CFTR) mutations in both alleles.

4. Patient had adequate pulmonary function at screening defined as a
   - FEV_1 between at least 25% and less or equal to 85% of normal predicted values for age, sex and height based on Knudson criteria
     and
   - peripheral artery haemoglobin oxygen saturation (SaO_2) of at least 88% at rest measured by pulse oximetry on room air.
5. Patient had a positive culture for PA at screening (Visit 1): PA isolated from sputum only if patient did not have a known history of positive PA culture within the last 2 months.
6. Patient is clinically stable at screening (no change in FEV_1 > 25% within one month prior to Screening Visit).
7. Patient was able to comply with all protocol requirements (e.g. able to produce sputum and perform pulmonary function tests).
8. Sexually active women of childbearing potential and sexually active men had to use a highly effective method of contraception throughout the IMP treatment period.
9. Females of childbearing potential had to have a negative serum pregnancy test within 7 days before Visit 2/randomisation.

9.3.2 Exclusion Criteria

Patients were not admitted to the study if they met one or more of the following criteria:

1. Use of investigational medications within 30 days before study entry or during the trial.
2. Inability to handle the study inhalers to inhale the test preparations.
3. Patient had a known local or systemic hypersensitivity or adverse reaction to inhaled aminoglycosides or systemic aminoglycosides.
4. Administration of anti-pseudomonal aminoglycoside antibiotics were not allowed within 30 days before first administration of IMP. Macrolides were permitted, provided that they were taken as a maintenance therapy for at least 6 weeks before entering the trial. Other antibiotics were not allowed within 7 days before first administration of IMP.
5. Patient with haemoptysis at any time within 4 weeks prior to screening (Visit 1)
6. FEV_1 < 25% predicted.
7. Patient had a positive sputum or deep throat cough culture (or BAL) with *Burkholderia cepacia* (*B. cepacia*) at screening (Visit 1) and/or a history of positive culture yielding *B. cepacia* within 1 year prior to screening.
8. Presence of allergic bronchopulmonary aspergillosis (ABPA).
9. Patient experienced severe respiratory infection within one month prior to screening (Visit 1) which required hospitalisation or treatment with i.v. antibiotics.
10. Elevated serum creatinine > 1.2 mg/dl or BUN > 20 mg/dl or proteinuria of grade 2+ or greater,
11. Significant liver disease (> 2x upper standard limits of liver enzyme activity and no thrombocytopenia or clinical active disease).
12. Patients with auditory or/and vestibular dysfunctions.
13. Patient had a history of lung transplantation.
14. Patient had a co-existing medical condition or abnormality that would compromise the participant's safety or the quality of the study data, in the opinion of the investigator.
15. Active drug and alcohol abuse or psychiatric disease.

9.3.3 Removal of Patients from the Study

Patients had the right to withdraw from the study at any time for any reason. The investigator had the right to remove patients from the study due to non-compliance with visits and for administrative or other reasons. It was understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of patients was to be avoided.

Patients were considered for withdrawal from the study and appropriate therapy initiated if, in the opinion of the investigator, any of the following occured:

- Development of toxicity or adverse reactions, which warrants drug discontinuation.
- Continuation of study drug(s) was medically contraindicated.
- Patient was significantly noncompliant.

Temporary interruptions of study drug(s) administration were discouraged. The patients were counselled regarding the importance of not missing doses of study drugs.

Any patient being prematurely discontinued from the study performed the Early Discontinuation (ED) visit, equal to End-of-Study visit (Visit 6), performed within 2 weeks of drug withdrawal.

A final evaluation was completed at the time of the patient withdrawal and the reason for withdrawal from the study explained. If the reason for removal of a patient from the study was an adverse reaction, incl. a clinically significant abnormal laboratory test result, the patient had to be followed until complete resolution or stabilization of the event or laboratory abnormality or as deemed reasonable by the investigator in consultation with PARI Pharma.

Patients who drop out following randomization were not replaced.

Early Discontinuation (ED) Visit

Patients who withdraw voluntary, or who were discontinued from the study prior to Visit 5 (end of treatment period 2) performed all final study visit procedures. Those patients were be scheduled for an Early Discontinuation visit (ED Visit) to occur 2 weeks at the latest after stopping the study medication.

All patients withdrawn from the study underwent an ED termination visit like Visit 6. All ongoing AEs and SAEs at the time of the Termination visit were followed up for a further 2 weeks or 4 weeks, respectively. Any patient with ongoing SAEs was to be followed up until recovery or stabilisation of the SAE.

9.4 Treatments

9.4.1 Treatments Administered

Test preparation:

VANTOBRA (= T100). One blow-fill-seal (BFS) vial contained 1.7 ml sterile and preservative-free nebuliser solution with 170 mg Tobramycin; eFlow nebuliser.

Comparator:

TOBI (Novartis). One ampoule contained 5 ml preservative-free nebliser solution with 300 mg Tobramycin; PARI LC PLUS, with PARI Boy SX® compressor.

Patients were randomized to one of two open treatment regimens and stratified according to age groups as follows:

Group	N	Preparation
Group A1 (age 4-13 a)	15	VANTOBRA (= T100) 170 mg / 1.7 ml; eFlow
Group A2 (age > 13 a)	15	VANTOBRA (= T100) 170 mg / 1.7 ml; eFlow
Group B1 (age 4-13 a)	15	TOBI (300 mg / 5 ml); PARI LC PLUS
Group B2 (age > 13 a)	15	TOBI (300 mg / 5 ml); PARI LC PLUS

Study drug and device for Groups A and B were supplied in numbered patient kits supplied by PARI Pharma. The first dose in each treatment phase (at Visits 2 and 4) was administered at site under control of an investigator. Drug supply for the next 4 weeks was then dispensed by responsible site staff.

The study drugs had to be inhaled twice daily, in the morning between 6 and 9 a.m. and in the evening between 6 and 9 p.m. until dryness of the nebulizer. 5 minutes before inhaling the study drug, salbutamol inhalation was allowed. If patients inhaled DNAse, they were instructed, not to mix it with the study medication, but to inhale DNAse separately.

9.4.2 Identity of Investigational Medicinal Products

Investigational medicinal product and test product were provided for a monthly treatment period accompanied with the corresponding device.

Description of patient's kits:

1. VANTOBRA (170 mg / 1.7 ml); eFlow.

   The package contained 56 ampoules with each 1.7 ml VANTOBRA (170 mg Tobramycin / 1.7 ml) in 28 aluminum laminate overpouches (2 ampoules each). The eFlow nebulizer was packed in a separate box together with handling/cleaning instructions.

2. TOBI (300 mg / 5 ml); PARI LC PLUS.

   TOBI was supplied as single unit low-density polyethylene BFS vials containing 300 mg Tobramycin in 5 ml and was dispensed in packages containing 56 vials.

   PARI LC PLUS nebulizer with PARI Boy SX compressor was packed in a separate box together with handling/ cleaning instructions.

All drugs and devices for the test and comparator combinations were supplied and delivered directly to the sites by PARI Pharma. There were four different batches of TOBI but no patient changed the batch during his treatment period (for details see **Appendix 16.1.6**).

9.4.3 Method of Assigning Patients to Treatment Groups

Assigned treatments were administered, with the treatment order defined by the randomization code prepared by the responsible statistician, Volker Guth, ACC GmbH, Leidersbach, Germany, for each center (see Randomization List, **Appendix 16.1.7**).

Patients who met all the inclusion/exclusion criteria were sequentially allocated a randomization number in sequential, chronological order immediately prior to first dose administration.

From the Screening Visit until the allocation of a randomization number, the patients were identified by their initials (the first letter(s) of the forename followed by the first letter(s) of the surname) and date of birth. If two patients had the same initials, letters could be inserted as the middle initial (e.g. X), provided that it was clearly documented.

9.4.4 Selection of Doses in the Study

Not applicable.

9.4.5 Timing of Dose for each Patient

According to the approved recommendations of the reference product TOBI the timing of doses was determined as twice daily with a 12 h interval.

9.4.6 Blinding

No blinding of the treatments was necessary for this BE study phase Ib which had an open-label design.

9.4.7 Prior and Concomitant Therapy

No other antipseudomonal antibiotics than the study medication were allowed during the study period. Beyond that, antipseudomonal antibiotics by any route were not allowed within 7 days before the first administration of study drug (Visit 2) and during the trial. Exception was aminoglycosides which were not allowed within 30 days before the first administration of study drug (Visit 2) and during the trial. However, the use of macrolides was not prohibited during the study ifthey were taken as maintenance therapy within 6 weeks prior to study initiation.

DNAse was allowed but it had to be inhaled separately from the study medication.

The use of salbutamol and saline before test or reference product inhalation was required to be equal at Visits 3 and 5.

The patient was instructed to contact the investigator if any additional medication, which was not recorded at the Screening Visit, was going to be used.

The following classes of antipseudomonal antibiotics were not allowed within 30 days before the first administration of the investigational drug (washout phase), neither during the whole trial:

Aminoglycosides (like the study drug, Tobramycin; also topical preparations), antibiotics of the penicillin type, cephalosporins of all generations, carbapenems, monobactam, macrolides (but were permitted provided that they were taken as a maintenance therapy for at least 6 weeks before entering the trial), fluorochinolones, nephrotoxic diaminopyridines/ sulfonamides, glycopeptides, polypeptides, and fosfomycin. (For a complete list of prohibited antibiotics see **Section 14**, **Table 31**).

9.4.8 Treatment Compliance

The study drugs were supplied to the patient at the study site by site personnel. Details regarding dispensing of the study drugs to each participating patient, including patient identification, the amount of study drug dispensed, the date the drug was dispensed, and the quantity of returned drugs were recorded. A drug-dispensing log was to be maintained and kept up-to-date at all times by the sites.

Patient were instructed to be compliant and to adhere to the following rules:

If a scheduled dose was missed

- five hours or more after the scheduled dose time - error had to be recorded and the *next* scheduled dose taken.
- less than 5 h after the scheduled dose time – error had to be recorded and the *missed* dose taken. All the remaining doses had to be taken at the scheduled time.

Non-compliance was defined as lack of compliance/adherence if there was

- missing of both daily inhalation dose one day a week, and / or
- missing of one of the two daily inhalation doses at least two days a week.

For patients exhibiting non-compliance with administration of study medication, dismissal from the study was at the discretion of PARI Pharma, following documented review with the investigator.

The eFlow for the VANTOBRA inhalation featured a monitoring System. This system required a chip card be inserted into the control unit for operation. Further, the chip card records each treatment's date and start/stop times, as well as the reason for termination. The information was recorded on the chip card, which then was used by clinical sites to ascertain patient adherence to the prescribed treatment. Validated software was incorporated into the control unit to accommodate this function.

The compliance in % over the one month VANTOBRA cycle was captured in the CRF.

The compliance for the TOBI cycle was captured in patient's diary.

9.5 Study Variables

9.5.1 Safety and Pharmacokinetic Measurements

The procedures conducted during the study are summarized in **Figure 1** and **Table 4** (see above).

9.5.1.1 Physical Examination and Clinical Laboratory Parameters

Complete physical examination, including vital sign measurements, was performed at screening (Visit 1) and at the end of the study (Visit 6); targeted physical examination was conducted at Visits 2, 3, 4 and 5. A targeted physical examination included vital signs and evaluation of organ systems associated with adverse event(s), symptoms or opportunistic infections, as needed.

Clinical laboratory evaluations were performed at every visit. **Table 5** lists the parameters to be investigated.

Table 5 Clinical laboratory evaluations

Clinical chemistry	**Haematology**	**Urinalysis**
Aspartate aminotransferase (AST)	RBC	Protein
Alanine aminotransferase (ALT/GPT)	Haemoglobin	pH
Lactate dehydrogenase (LDH)	Haematocrit	Glucose
Blood urea nitrogen (BUN)	WBC with differential count	Specific gravity
Alkaline phosphatase (AP)	Platelet count	Blood
Glucose		
Albumin		
Creatinine		
Total bilirubin		

9.5.1.2 Assessment of Pharmacokinetic Profiles

At the end of each treatment cycle (last inhalation) blood samples (3 – 4 ml) for the assessment of Tobramycin concentrations were collected into lithium-heparin tubes, pre-dose (30 - 15 minutes prior to inhalation), and at 30 min, 1, 1:30, 2, 4, 6, 8, 12 h after the end of drug inhalation. Blood could be taken from an indwelling cannula, placed in a forearm vein of the patient and kept patent or by venepuncture.

At the end of each treatment cycle (last inhalation) sputum samples for the assessment of Tobramycin concentrations were collected into sterile culture disks, pre-dose (30 - 15 minutes prior to inhalation), and at 10 min, 30 min, 1:30, 2 and 8 h after the end of drug inhalation. Culture disks were then collected in polypropylene containers and deep-frozen at -18 °C or below until transportation to the analytical laboratory.

Blood samples were gently inverted three times to assure adequate mixing with the anticoagulant (lithium-heparin) and then placed in an ice bath prior to centrifugation. Samples were centrifuged for 10 minutes at 1500 g in a refrigerated centrifuge (2-8 ºC) within approximately 10 min of collection. The plasma was then separated and rapidly divided over two labelled polypropylene storage tubes (T

[VANTOBRA] and R [TOBI]) and stored at -18 °C or below until transportation to the analytical laboratory.

Each storage tube was clearly and indelibly labelled using pre-printed labels. The labels had the following information: study number, study day, patient number, sample number (a three digit number), tube identifier (T [VANTOBRA] or R [TOBI]) and blood sampling time or urine collection period and number of the aliquot. The date and actual blood sampling time was recorded on CRF sheets.

All samples were shipped deep-frozen with sufficient quantity of dry ice and suitably packed to ACC GmbH, Leidersbach, Germany, by courier SAMPLES TRANSPORT, a company which is specialised in transports under dry ice. A sample specification list was enclosed in the shipment and a copy also sent to the CRO's clinical research associate (CRA). The two aliquots could be shipped on different days. At the analytical laboratory the samples were stored at or below -18 °C until assayed.

Before starting the analysis of the study samples the assay method was validated for both matrices, plasma and sputum (see **Section 9.5.1.3**).

To determine Tobramycin in plasma and sputum mass spectrometry and chromatography procedures were used (see below, **Section 9.5.1.3**). The analytical method used for all determinations was LC-MS/MS.

9.5.1.3 Plasma and Sputum Tobramycin Assays

Plasma and sputum concentrations of Tobramycin were determined using validated methods involving the use of LC-MS/MS procedure (the validation reports for plasma and sputum assays are documented in **Appendix 16.1.9.3.1** and **16.1.9.3.2** of this report). Before starting the analysis of the study samples the assay method was validated with respect to selectivity, including linearity, lower limit of quantification (LLOQ), dilution of samples, precision, accuracy, revovery rate and stability. By studying the relationship between concentrations vs. peak area ratios, linearity was established over the range of 100 to 50000 pg/ml. The lower limit of quantitation (LLQ) was 30 ng/ml (for the Validation Reports of Tobramycin Determination Method in Plasma, Final Report ACC B541-11 Val, and in Sputum, Final Report ACC B542-11 Val, see **Appendix 16.1.9.3**). Additional information on the sample processing and analytical procedures is provided in the Bioanalytical Report (**Appendix 16.1.9.3.3**).

9.5.2 Safety Evaluations

Laboratory Tests

Reference values for laboratory test results were provided by the investigators prior to study initiation. Each investigator was to use the same clinical laboratory of his hospital throughout the course of the study and notified the study monitor as soon as possible if normal laboratory test ranges were revised at any time during the study.

Results of all clinically significant abnormal laboratory tests, as identified by the principal investigators, were recorded on the appropriate CRF pages. The investigators had to comment if the values were clinically significant or not. In case they were clinically significant, an AE sheet had to be completed.

Adverse Events (AE)

Definition

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The official definition also extends to AEs occurring under placebo or in a reference group receiving drug or non-drug therapy.

Baseline recording of any symptoms of illness was performed at Visit 1. Only symptoms that increased in severity during the course of the clinical trial after study drug administration or new symptoms of illness, injuries etc. were to be recorded as AE in the CRF.

The severity/intensity of all AEs was evaluated as mild, moderate or severe using the following definitions:

- Mild: The event is easily tolerated
- Moderate: The event interferes with normal activity
- Severe: The event is incapacitating (causes inability to perform usual activity or work)

Each patient was closely observed and questioned for AEs during the study procedures and throughout the study period with non-leading questioning (e.g. how do you feel?). Patients were instructed to report immediately to the study staff any symptoms and/or signs which occurred between the scheduled observation times.

In addition to the investigator's own description of the AE, each AE was coded according to the MedDRA 15.0 code list. The verbatim term was recorded in the CRF.

Adverse Reaction (AR)

Definition

An AE will be considered as AR, if a causal relationship to the administration of IMP cannot be excluded, e.g. if the relationship is possible, probable or very likely according to the following definitions:

- Not related: An AE that is not related to the use of the investigational product
- Doubtful: An AE for which an alternative explanation is more likely - e.g. concomitant drug(s), concomitant disease(s), and/or the relationship in time suggests that a causal relationship is unlikely
- Possible: An AE that might be due to the use of the investigational product. An alternative explanation e.g. concomitant drug(s), concomitant disease(s), - is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded
- Probable: An AE that might be due to the use of the investigational product. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely - e.g. concomitant drug(s), concomitant disease(s)
- Very likely: An AE that is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation - e.g. concomitant drug(s), concomitant disease(s). The relationship in time is very suggestive (e.g. it is confirmed by de-challenge and re-challenge).

Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (immediate risk of death at the time of the event)
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect
- Other: Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

Documentation and Reporting of AEs to the Sponsor

All AEs reported by the patient or observed by the investigator or hospital personnel were reported in the CRF. The following information regarding each AE was obtained: date and time of onset and resolution (duration), serious or non-serious (as defined below), severity, treatment required, outcome, relationship to study drug, and if the AE caused withdrawal from the study.

Any Serious Adverse Event occurring

- between the first clinical trial procedure (Visit 1) and within 4 weeks after the completion of the EoS visit, whether or not considered related to the study drugs;

  or

- at any time after completion of the last follow-up and coming to the attention of the investigator, if it is judged as related to the patient's participation in the study

had to be reported to the sponsor's SAE Safety Officer within 24 h, as follows:

- Report all SAEs within 24 h of discovery of the event to the Safety Officer (indicated below) by telephone or fax
- Complete the SAE Form and send it to the sponsor's Safety Officer within 24 h after the discovery of the event
- Follow-up the SAE until the outcome is determined, providing periodic updates to the Safety Officer as requested
- Record the SAE in the patient's CRF on the AE page
- Provide any additional information if requested

The Safety Officer must be notified by telephone when a document has been sent by fax. If limited information on the event is initially available, follow-up reports will be required.

SAE Safety Officer	**Fax:**	**+32 (0)15 29 93 94**
Sylvie Devos, PhD		
SGS Life Science Services	**Phone:**	**+32 (0)15 29 93 38**
Mechelen Noord zone L		
Intercity Businesspark	**E-mail:**	**be.life.SAEprocessing@sgs.com**
Generaal De Wittelaan 19A bus 5		
2800 Mechelen		
Belgium		

Other Events to be treated as Serious Adverse Event (SAE)

Exposure to drug during pregnancy/lactation: Reportable with the pregnancy forms A and B. In principle, pregnancy and the lactation period are exclusion criteria. In the event of a pregnancy occurring during the course of a study, the patient had to be withdrawn from all IMP treatment immediately. The Sponsor had to be notified without delay and the patient followed during the entire course of the pregnancy and postpartum period. Parental and neonatal outcomes had to be recorded even if they were completely normal and without AEs. The SAE reporting procedure had to be followed, even though pregnancy was not considered an SAE. No "serious criterion" was to be checked. The SAE report form was solely used to ensure expedited reporting.

Investigational medicinal product (IMP) overdosing: An overdose was defined as a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol. For the purposes of this study, any dose of aerosolised IMP administered to a patient that exceeded the dose foreseen in the protocol by more than 50% over 4 weeks had to be reported as an overdose. It had to be reported as an SAE, irrespective of outcome and even if toxic effects were not observed.

Events Not Regarded as Adverse Events/Serious Adverse Events

The following events were not regarded as AEs/SAEs:

- Pre-scheduled (before any trial-related activity) hospitalisations/surgeries/interventions
- Trial endpoint-related worsening; these had to be assessed as treatment success or failure during trial endpoint analysis

The Sponsor's responsibilities in regards to reporting Suspected Unexpected Serious Adverse Drug Reactions (SUSARs) were in accordance with European Directive 2001/20/EC.

Monitoring of AEs

Any patient experiencing AEs, whether ascribed to the IMP or not, had to be followed closely until the outcome was determined in addition to the EoS visit to assess AEs. All AEs had to be documented in the patient's medical record. The occurrence of AEs and SAEs was monitored until 2 and 4 weeks after the EoS visit, respectively. The follow-up was recorded in the CRF (AE follow up pages) and entered into the clinical trial database. Any patient with ongoing SAEs was followed-up until recovery or stabilisation of the SAE.

Treatment of AEs

AE(s) and intercurrent illness(es) which occurred possibly during the study could be treated by appropriate therapeutic measures and followed up by further diagnostics. If such treatment resulted in a relevant deviation from the study protocol, the patient had to be withdrawn from the study.

Follow-up of AEs

An AE and/or SAE not resolved at the end of the clinical trial (serious and if possible non-serious AE as well) was to be followed up by the investigator 2 and 4 weeks after the EoS visit, respectively. Any patient with ongoing SAEs will be followed-up until recovery or stabilisation of the SAE. If necessary, a further visit will be scheduled by the investigator.

Reporting of AEs occurring after Termination of Study

If an AE occurs after termination of the clinical trial of the individual patient and if the investigator judged the AE to be related possibly to the clinical trial (i.e. AR), the investigator had to inform the Sponsor.

Timelines for SUSAR Reporting to Competent Supervisory Authorities, Ethics Committees and Investigators

All SUSARs were to be reported to the competent authority (CA) and to the Ethics Committee (EC) concerned as soon as possible, but within a maximum of 15 days (fatal or life-threatening SUSARs within a maximum of 7 days) of first knowledge by the Sponsor.

The sponsor, i.e. the Safety Officer, was obliged also to inform all investigators.

Relevant follow-up information of fatal or life-threatening SUSARs was to be communicated subsequently within an additional eight days.

Any circumstances which required a review of the risk-benefit assessment of the investigational medicinal product were to be reported to the Competent Authorities concerned and to the EC concerned as soon as possible but within a maximum of 15 days.

9.5.3 Study Endpoints

9.5.3.1 Primary Endpoint

Plasma $AUC_{0\text{-}12h}$ Area under the plasma concentration-time curve under the assumption of 90% confidence interval (CI) of Tobramycin from the first time point [t=0] to the time point of the last measured concentration [$t_{(last)}$].

9.5.3.2 Secondary Endpoints

Efficacy:

- C_{max} and trough levels of Tobramycin in plasma and sputum
- Tobramycin plasma trough level (C_0) and Tobramycin peak time (t_{max}) of VANTOBRA and TOBI at Visits 3 and 5
- Change of Colony Forming Units (CFU) of *P. aeruginosa*
- Changes in lung function (FEV_1, FVC, $FEF_{25\text{-}75}$, PEF[12])

Safety:

- Proportion of treated lung exacerbations until end of treatment
- Audiology: voice alterations and signs of tinnitus
- Change in vital signs; number of bronchospasms
- Proportion of patients reporting ARs, by severity and by action taken
- Proportion of patients reporting SARs/SUSARs
- Proportion of patients with clinically significant laboratory value abnormalities related to the study drug
- Discontinuations due to ARs
- Bronchospasms after the end of inhalation
- Proportion of resistant *P. aeruginosa* strains with a minimal inhibitory concentration of > 4 µg/ml

Others:

- Treatment complicance
- Mean inhalation time
- CFQ-R

[12] PEF was actually not mentioned in the protocol. However, spirometry measurements reveal this parameter automatically; PEF was therefore additionally evaluated.

9.6 Data Quality Assurance

9.6.1 Monitoring

Monitoring was performed according to the SOPs of AMCSS, Poland.

The clinical monitor visited the investigator at regular intervals during the course of the study to review the progress and conduct of the study and check the CRF for completeness and accuracy according to GCP and relevant national law. Monitors conducted study initiation visits at study site during which the protocol and study procedures were reviewed with the Principal Investigator and his staff. The study monitors were also on-site during the pre-screening, screening and treatment periods. At monitoring visits, the monitors checked that the protocol was being followed and reviewed the CRFs for completeness and accuracy, incl. source data verification (SDV) checks. The monitors also observed all the PK sampling handling procedures.

Inconsistencies subsequently identified during validation of the database was referred back to the investigator using data clarification forms (data query forms [DQF]).

In accordance with GCP, the respective clinical monitor was verifying the data recorded in the CRF against the investigator's source documentation on a 100% basis (Source Data Verification [SDV] Check).

9.6.2 Case Report Forms

CRFs as NCR sets for individual patients were provided by AMCSS. One copy remained in the binder with the investigator as a permanent record; the original was sent to the statistician, another copy remained with AMCSS.

The investigator was responsible for accuracy, compliance to protocol, completeness and legibility of data. CRF forms had to be kept current to reflect patient status at each phase during the course of trial.

The CRFs provided by the sponsor were completed in black ink. All CRF corrections made during the monitoring visits were initialled and dated by authorized study personnel. The study monitors forwarded those completed forms to the Data Management Department of ACC GmbH, Germany, by courier.

CRF data were double entered into a validated database (DB) structure, electronically compared and any discrepancies resolved. Questionable or missing entries were queried and any needed corrections were approved by the Principal Investigator or authorized personnel. Corrections were carefully tracked and documented both electronically (via audit trail) and on Correction Sheets or Data Query Forms (DQF), respectively.

Quality Control (QC) checks of the data entry as well as of the DB validation and the completed DB against patient data listings were performed (for details see Statistical Report, **Appendix 16.1.9.2**, and Audit Certificate, **Appendix 16.1.8**).

After all DB issues were resolved, the DB was locked by moving it to a protected area where no further changes were possible.

Patient Identification Form

Patients could not be identified on the CRF by name. Appropriatly coded identification (i.e. Patient Number) was used.

The investigator had to complete a separate confidential record of these details (Patient Identification Form). The Patient Identification Form contained a listing of the identities of all patients enrolled in the study.

Corrections

If corrections were necessary, they were entered by an authorised member of the investigator's staff in the following manner: The wrong entry was crossed out; however, it was still legible, and the correct entry was placed next to it. Corrections were initialled, dated and – if necessary – explained.

9.6.3 Archiving

Investigator Site File

The investigator had to retain the medical files of his/her trial patients in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

As the identification of the patients and the respective patient's records in each study centre has to be guaranteed, essential documents relating to this clinical trial have to be retained according to regulatory requirements.

Trial Master File

The original CRFs and other essential documents are the basis for a quality audit by the sponsor's independent auditor and for inspection by the Competent Authority. Essential documents have to be archived in a way that ensures that they are readily available, upon request, to the Competent Authorities.

Essential documents relating to this clinical trial have to be retained according to regulatory requirements.

9.6.4 Auditing

The following quality audits were conducted by independent auditors:

- Vendor Audit at ACC, Dr. Scheidel, Leidersbach, Germany.
- On-site Audit at the Coordinating Investigator, Prof. D. Sands, Warsaw, Poland.
- In-house Audit at the CRO AMCSS, Ruda Śląska, Poland.

The auditors had access to all medical records, the investigator's trial related files and correspondence, and the informed consent documentation that was relevant to this clinical trial.

Audit Certificates are attached (**Appendix 16.1.8**).

9.7 Statistical Evaluation

9.7.1 Statistical and Analytical Plans

Calculations of the pharmacokinetic parameters and the assessment of bioequivalence [Chow and Liu 2009; Hauschke et al. 1992; Hauschke et al. 2007] were carried out for tobramycin. The PK-data evaluation was performed using WinNonlin (WinNonlin® Software Release 5.2.1, Pharsight Products, USA).

Results were listed in tables considering the respective treatment groups of all individual data, the mean values (arithmetic or geometric means for linearly and logarithmically distributed endpoints, respectively), the minimum and maximum values as well as the standard deviation or CV. Descriptive statistics will be calculated for all patient and separately for group 1 (age 4-13 a) and group 2 (>13 a).

The plasma concentration-time curves were documented in graphics as individual curves (VANTOBRA and TOBI) and as arithmetic and geometric mean and median values.

The PK data were estimated using following parameters:

Primary plasma endpoints (parameters)

- $AUC_{0\text{-}12h}$ Area under the plasma concentration-time curve from the first time point [t=0] to the time point of the last measured concentration [$t_{(last)}$] (calculated using the trapezoidale rule)

Secondary plasma endpoints (parameters)

- C_{max} Maximum plasma concentration (directly obtained from measured values)

Other plasma endpoints (parameters)

- t_{max} Time of maximum plasma concentration (directly obtained from measured values)
- C_0 Plasma concentration at time point t=0

Calculations of the pharmacokinetic parameters were based upon the nominal blood sampling times if the difference of the scheduled sampling time and the actual time of blood sampling was < 1 minute. If this difference was ≥ 1 minute, the actual sampling time was used for calculation of the pharmacokinetic parameters.

Data of a patient were withdrawn from PK evaluation after bioanalysis for the following reasons:

- if there was lack of any measurable concentrations or only very low plasma concentrations for the reference product (patients' plasma $AUC_{0\text{-}12h}$ was less than 5 % of reference medicinal product geometric mean plasma $AUC_{0\text{-}12h}$)
- if a patient performed only one treatment period
- if technical difficulties strongly suggested unreliable sampling of plasma or sputum
- if two or more subsequent samples were missing or < LLOQ and thus a reliable calclulation of the $AUC_{0\text{-}12h}$ was impossible.

Analysis plan

The Statistical Analysis Plan is described in the following paragraphs. The original plan is presented in **Appendix 16.1.9.1**.

Primary (Confirmatory) Analyses

The statistical analysis [Chow and Liu, 2009; Hauschke et al., 1992; Hauschke et al., 2007] was performed by using SAS (SAS Software Release 9.2, Copyright© by SAS Institute Inc., Cary, NC, USA).

Non-zero log-transformed data were used for Analysis of Variance (ANOVA) for plasma $AUC_{0\text{-}12h}$ and plasma C_{max}.

The primary and secondary pharmacokinetic plasma parameters after logarithmic transformation was subjected to an Analysis of Variance (ANOVA) using the SAS GLM procedure.

To test the SEQUENCE effect the initial model contained the factors SEQUENCE, PATIENT nested within SEQUENCE, PERIOD and FORM (drug formulation). The significance of the SEQUENCE effect was tested using the PATIENT nested within SEQUENCE as the error term applying a 5% level of significance. The significance of the PERIOD and FORM effect was tested with a 5% level of significance.

For the estimation of the least squares means (LSM) for the factor FORM a simplified ANOVA was used comprising of PATIENT, PERIOD and FORM.

The test for normality of the residual distribution was performed on ln-transformed data using the Wilk-Shapiro procedure using a 5% level of significance.

Consistent with the two one-sided tests for bioequivalence, 90%-confidence intervals for the difference between drug formulation least-squares means (LSM) were calculated for the log-transformed parameters plasma AUC_{0-12h} and plasma C_{max}.

The acceptance range for the 90% confidence band for the ratio of the back-transformed LSMEANS of tobramycin was determined as 80% to 125% for the parameters plasma AUC_{0-12h} and 70% to 133% for plasma C_{max}.

The parameter plasma t_{max} was evaluated only descriptively.

Tobramycin sputum kinetic parameters will be assessed immediately before start of nebulisation (0 min) and 10, 30, 90, 120 min and 8 hours after completion of nebulisation (Visit 3 and Visit 5). Calculations of the pharmacokinetic parameters was carried out identically as for plasma values.

The sputum concentration-time curves are documented in graphics as individual curves (test and reference product) and for treatment groups as arithmetic mean, geometric mean and median values.

Following parameters were calculated:

Secondary sputum endpoints (parameters)

AUC_{0-8h}	Area under the sputum concentration-time curve from the first time point [t=0] to the time point of the last measured concentration [$t_{(last)}$] (calculated using the trapezoidale rule)
C_{max}	Maximum sputum concentration (directly obtained from measured values) (Visit 3 and Visit 5)

Other sputum endpoints (parameters)

t_{max}	Time of maximum sputum concentration
C_0	Sputum concentration at time point t=0

Interim Analysis

No interim analysis was planned or performed.

Secondary (Descriptive) Analyses

Sputum AUC_{0-8h} and sputum C_{max} values were evaluated descriptively.

9.7.2 Determination of Sample Size

Under the assumption of a point estimator of 95% – 105% and an intra-patient variability of CV of about 34% for plasma AUC_{0-12h} 50 patients are sufficient to show bioequivalence with sufficient power (80 - 90%).

A sample size of 25 patients per treatment arm available for analysis (total 50 evaluable patients) was calculated. Assuming a drop-out rate of 10% or more, a total of 60 patients had to be randomized.

Randomization to the treatment arms was performed centrally in a 1:1-ratio. Furthermore, a stratification according to age (4-13 year or > 13 years) was performed in a 1:1-ratio.

Eligible for study participation were male and female CF patients, at least 4 years old, with chronic *P. aeruginosa* infection. The participants had to be in stable condition (no exacerbation requiring i.v. antibiotics or hospitalisation within one month period prior to Screening Visit), documented PA presence in a sputum specimen and a FEV_1 between 25 and less or equal 75% of normal predicted values for age, sex and height. No restrictions concerning ethnic origin were foreseen.

9.7.3 Plasma and Sputum Concentration Data

The plasma and sputum Tobramycin concentration assays were conducted by the laboratory ACC GmbH, Leidersbach, Germany using a validated assay procedure (**Section 9.5.1.3**). The Validation Reports on Tobramycin determination methods in plasma (ACC 541B11-Val) are attached in **Appendix 16.1.9.3.1** and for sputum in **16.1.9.3.2** (ACC 542B11-Val).

Data and analytical reports (**Appendices 16.1.9.3.3 and 16.1.9.3.4**) were audited by the QA unit of ACC GmbH for compliance with applicable regulations and their SOPs. The results were then provided to the responsible statistician, the author of the final Clinical Study Report and the Sponsor additionally in EXCEL spread sheet files. The individual plasma and sputum concentration data of Tobramycin are provided in the Appendices of the PK-Data Evaluation and Statistical Report (see **Appendix 16.1.9.2**). The individual plasma concentration/time curves are also presented in the Statistical Report, **Appendix 16.1.9.2**.

9.8 Changes in Conduct of the Study or Planned Analyses

9.8.1 Changes in the Conduct of Study

There were no changes in the conduct of the study.

9.8.2 Changes in Data Management and/or the Planned Analyses

There were no changes made in data management.

The Statistical Analysis Plan (SAP) includes details of all planned analyses for this study. This plan is provided in **Appendix 16.1.9.1**. No changes were made to the planned analyses.

10 STUDY PATIENTS

10.1 Disposition of Patients

Accountability for the patients randomized to the study treatments is presented in **Figure 2**. 54 enrolled patients received both study treatments, 3 patients stopped the treatment after Visit 3 during the wash-out phase and one patient was withdrawn from study participation 3 days after start of TOBI treatment. The reason for withdrawal was impairment or worsening of the disease (CF) in one case and in three cases because of (S)AEs (see **Table 6**).

The allocation of patients to the treatment sequence is shown in **Section 14**, **Table 28**.

Patients who provided insufficient bio-analytical assessments to calculate reliable PK parameters were excluded from analysis (see **Table 6**).

Four patients (two in each sequence group) were excluded from the "Clinical Efficacy Population" (because not starting the cross-over Treatment Phase 2; see **Figure 2**); the same patients were consequently also excluded from the PK analyses. Five further patients (patients 1107, 1114, 4103, 4104, and 4106) were excluded from the PK analyses because of different reasons, which are listed in the following **Table 6**.

Figure 2 Patient Accountability/Disposition

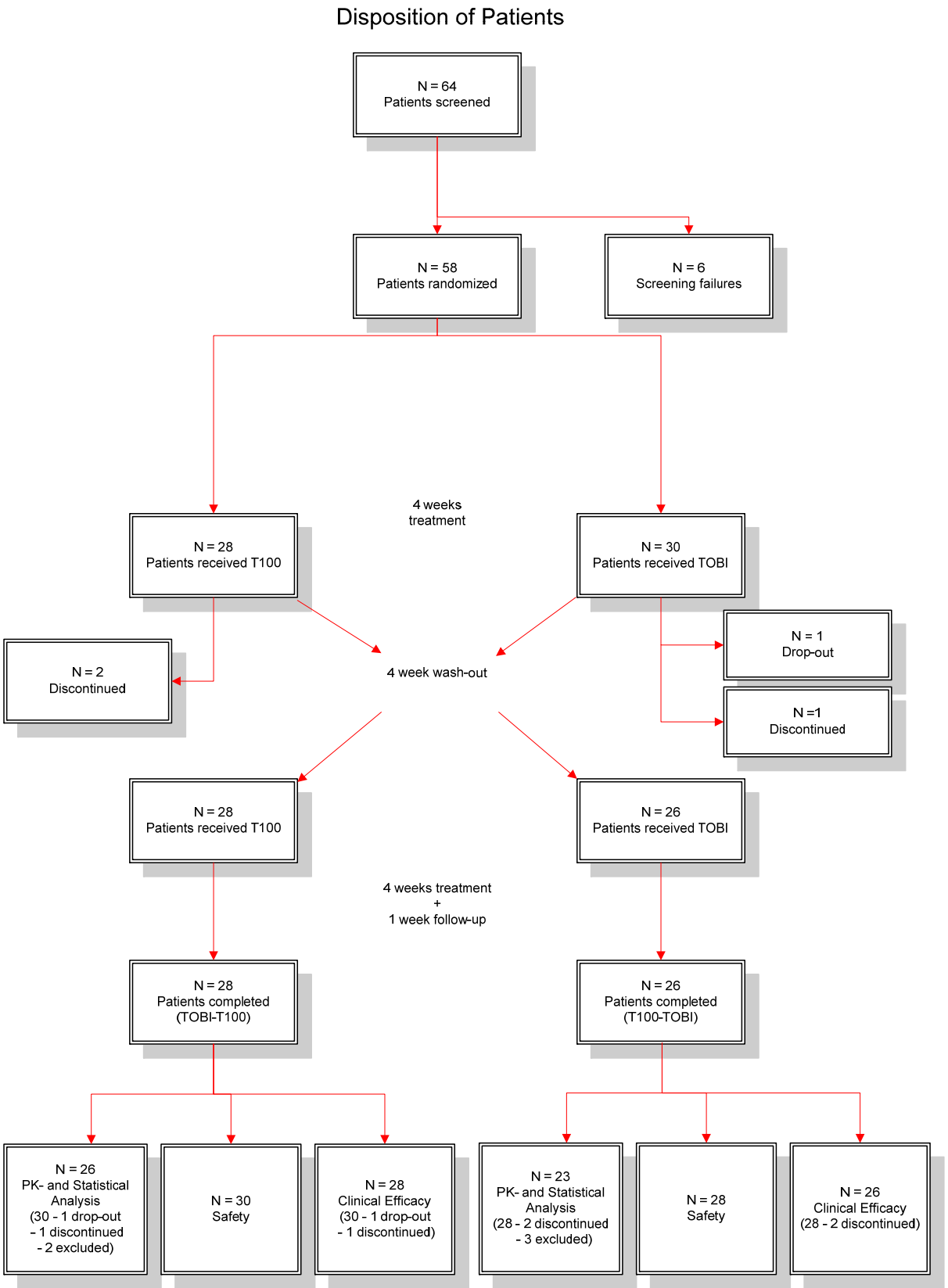


Table 6 Individual Reasons for Excluding Patients from the PK Analyses

Patient 1109	▪ Only TOBI treatment phase completed, received no VANTOBRA treatment ▪ Withdrawn due to SAE (CF-exacerbation) during wash-out period
Patient 2104	▪ Incomplete TOBI treatment phase, received no VANTOBRA treatment ▪ Withdrawn due to multiple AEs (increase of infection parameters) during TOBI treatment
Patient 1205	▪ Only VANTOBRA treatment phase completed, received no TOBI treatment ▪ Withdrawn due to SAE (pulmonary hemorrhage) during wash-out period
Patient 2108	▪ Only VANTOBRA treatment phase completed, received no TOBI treatment ▪ Withdrawn due to SAE (otitis media) during wash-out period
Patient 1107	▪ VANTOBRA plasma PK calculation not possible because of incomplete concentration-time profile ▪ All available samples revealed < LLOQ values in succession
Patient 1114	▪ Problems during blood sampling ▪ Incomplete blood and sputum sampling ▪ All available VANTOBRA plasma samples revealed < LLOQ values in succession
Patient 4103	▪ VANTOBRA plasma PK calculation not possible because of incomplete concentration-time profile ▪ All available samples revealed < LLOQ values in succession ▪ VANTOBRA sputum sampling incomplete ▪ Inappropriate device handling (extremely long inhalation times)
Patient 4104	▪ VANTOBRA and TOBI plasma PK calculation not possible due to missing slopes of concentration-time profiles ▪ All TOBI sputum samples revealed < LLOQ values in succession
Patient 4106	▪ VANTOBRA plasma PK calculation not possible because of incomplete concentration-time profile ▪ VANTOBRA sputum sampling incomplete ▪ Inappropriate device handling (extremely long inhalation times)

10.2 Protocol Deviations

There was only one major protocol deviation in the centre of Dr. Grzegorz Gąszczyk:

Sputum samples of most of his patients were correctly collected as per protocol but not transferred to the Bioanalytical Laboratory (ACC) for PK analysis. They were falsely sent to the Microbiology Laboratory of the hospital. This refers to the following samples:

- **from Visit 2 (trough level)** of patients: 06/4103, 05/4106, 04/4105, 02/4102, 03/4101, 07/4104, 08/4204, 09/4206, 10/4205
- **from Visit 3 (PK pre inhalation)** of patients: 06/4103, 05/4106, 04/4105, 02/4102, 03/4101, 07/4104
- **from Visit 4 (trough level)** of patients: 06/4103, 05/4106, 04/4105, 02/4102, 03/4101, 07/4104

These major protocol deviations as well as minor protocol deviations are presented completely in **Appendix 16.2.2**.

11 PHARMACOKINETICS AND CLINICAL EFFICACY EVALUATION

11.1 Data Sets Analysed

64 patients were screened for enrolment into the study; 6 patients failed the screening examinations (list of screening failures see **Section 14**, **Table 29**), thus, a total of 58 patients (25 male and 33 female) were randomized. All 58 patients were of Caucasian ethnic origin.

The safety population (SP) included 58 patients who received at least one administration of one of the two treatments. According to **Figure 2** the population for evaluation of clinical efficacy included 54 patients, whereas the population for analyzing the PK values included 49 patients (Per-Protocol [PP] Population).

11.2 Demographic and Other Baseline Characteristics

Table 7 summarizes the baseline demographic data of the 58 patients who received at least one dose of medication. Two patients (1109 and 2104) received only TOBI, two patients (2108 and 1205) received only VANTOBRA. These 4 patients stopped the treatment during or after the 1st treatment phase.

Table 7 Baseline demographic data

	All	4 – 13 a	> 13 a
N	58	28	30
Sex			
Male [n (%)]	25 (43)	15 (54)	10 (33)
Female [n (%)]	33 (57)	13 (46)	20 (67)
Age (a)			
Mean ± SD	15.4 ± 6.81	10.0 ± 1.84	20.6 ± 5.52
Range	7 – 36	7 – 13	13 – 36
Weight (kg)			
Mean ± SD	43.3 ± 13.9	32.1 ± 9.5	53.7 ± 7.8
Range	15.0 – 72.0	15.0 – 52.0	38.7 – 72.0
Height (cm)			
Mean ± SD	152.6 ± 16.4	139.6 ± 13.5	164.6 ± 7.0
Range	113 - 182	113 - 164	151 - 182

For details refer to **Section 14.1**, **Table 27** and **Appendix 16.2.4**.

Mean age of the patients was 15.4 ± 6.81 years (minimum 7, maximum 36 years; N=58). Mean height was 153 ± 16 cm (minimum 113, maximum 182 cm). Mean body weight at screening was 43.3 ± 13.9 kg (minimum 15, maximum 72 kg). Individual data per patient are provided in **Section 14.1** and in the **Appendix 16.2.4**.

11.3 Measurements of Treatment Compliance

An objective determination of treatment compliance was only possible for VANTOBRA treatment in combination with the eFlow as the device featured a monitoring system to record time and duration of inhalations. This control system is not available for the PARI LC PLUS device.

According to this electronic system the treatment compliance for VANTOBRA was > 99 %. (The individual "Inhalation Data Reports" of 54 patients are presented in **Appendix 16.2.5**.)

In the TOBI group patient compliance could only be determined based on patients' diaries. However, these data were incomplete and cannot be regarded as objective as an electronic control. According to the patients' diaries the treatment compliance for TOBI was 99%. The individual data and the evaluation for 31 patients are presented in **Appendix 16.2.5**.

11.4 Pharmacokinetic Results

11.4.1 Analysis of Plasma Tobramycin Pharmacokinetic Data

Plasma concentration versus time profiles (AUC_{0-12h}), maximum concentration (C_{max}), time to maximum concentration (t_{max}) and trough levels (C_0) of the test treatment VANTOBRA in comparison to TOBI were determined at the end of each treatment phase. Data of 49 patients were evaluable.

Table 8 presents the individual, mean arithmetic, mean geometric and median plasma AUC_{0-12h} values of Tobramycin for the two treatments VANTOBRA and TOBI.

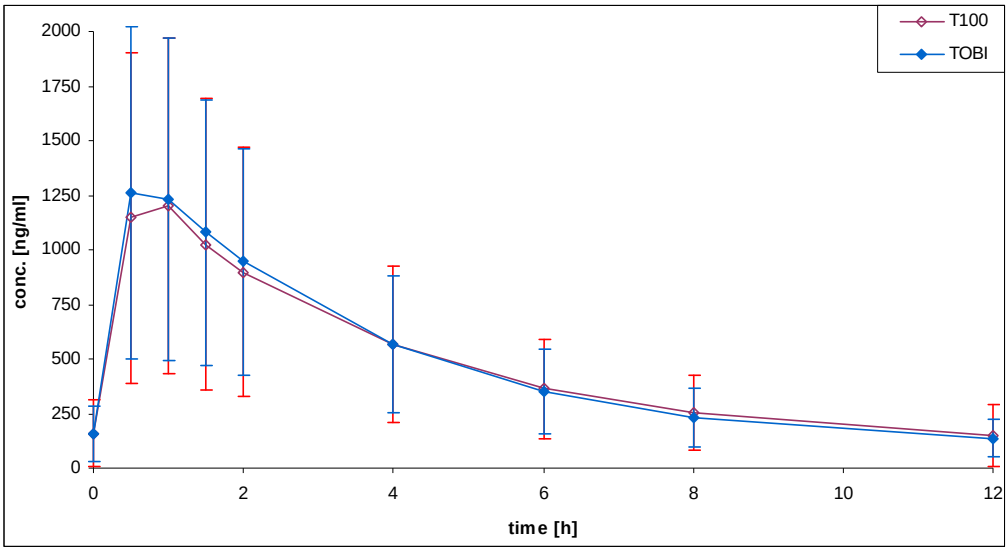
Table 8 Individual, arithmetic, geometric mean and median plasma AUC_{0-12h} values of VANTOBRA and TOBI (All)

Patient No.	AUC_{0-12h} (ng/ml·h) All		
	T100	TOBI	T100/TOBI
1101	7006.3	3312.2	2.12
1102	5801.3	3523.8	1.65
1103	4410.2	3177.1	1.39
1104	5279.3	6566.3	0.80
1105	3908.7	6760.9	0.58
1106	15825.5	15556.2	1.02
1108	693.4	10744.1	0.06
1110	7201.8	4524.4	1.59
1111	6964.2	6135.9	1.13
1112	9484.5	5538.1	1.71
1113	7380.4	6382.9	1.16
1201	2399.8	1862.0	1.29
1202	5269.9	1555.2	3.39
1203	6428.2	9803.5	0.66
1204	2990.0	2230.4	1.34
1206	8434.0	9932.6	0.85
1207	232.1	2560.8	0.09
1208	874.0	2637.9	0.33
2101	6011.6	3162.9	1.90
2102	4032.2	1603.7	2.51
2103	4441.0	6345.8	0.70
2105	9595.0	9454.4	1.01
2106	3893.4	9470.9	0.41
2107	6363.5	8291.9	0.77
2201	2472.5	4953.8	0.50
2202	11275.0	10369.3	1.09
2203	367.8	2957.3	0.12
2204	7733.9	7913.0	0.98
2205	286.1	3649.3	0.08
2206	10478.1	8833.8	1.19
3101	3017.8	8103.9	0.37
3102	263.8	535.3	0.49
3103	5731.9	3927.4	1.46
3201	2051.5	9225.9	0.22
3202	4509.9	5387.5	0.84
3203	7910.8	5107.4	1.55
3204	4715.8	1629.8	2.89
3205	11999.9	5155.2	2.33
3206	6705.5	4053.0	1.65
3207	6762.1	6858.7	0.99
3208	4215.9	7071.4	0.60
3209	13453.8	9881.6	1.36
3210	2476.1	5954.8	0.42
4101	1608.6	3598.6	0.45
4102	10446.7	8099.0	1.29
4105	7827.9	4878.5	1.60
4204	8174.9	4245.5	1.93
4205	5722.4	7889.9	0.73
4206	8034.9	3260.4	2.46
N	**49**	**49**	
Arithmetic mean	**5778.8**	**5809.7**	
SD (±)	**3569.15**	**3097.98**	
CV (%)	**61.8**	**53.3**	
Minimum	**232.1**	**535.3**	
Maximum	**15825.5**	**15556.2**	
Median	**5731.9**	**5387.5**	
Geometric mean	**4159.2**	**4904.9**	

Plasma concentration versus time profiles of the test treatment VANTOBRA in comparison to TOBI showed a comparable shape for all patients (**Figure 3**). Similar results were obtained when distinguishing data among children (4 – 13 a) and adolescents/adults (> 13 a). Numerical mean values of the two age groups (4-13 a and > 13 a) as well as individual curves of all 49 patients are provided in the Statistical Report in **Appendix 16.1.9.2**.

The plasma tobramycin concentrations revealed very high inter- and intraindividual variations. This variability was observed for both formulations and appears virtually related to the specific disorder in conjuction with the aminoglycoside antibiotic Tobramycin and the route of drug aministration.

Figure 3 Plasma Tobramycin concentration versus time profile (arithmetic mean ± SD; all groups)



The barr diagram below (**Figure 4**) shows the values for $AUC_{0\text{-}12h}$ (arithmetic mean ± SD) differentiated into "All" and the two age groups. The $AUC_{0\text{-}12h}$ was comparable between VANTOBRA and TOBI in all subgroups.

Figure 4 Barr diagram for plasma $AUC_{0\text{-}12h}$ (arithmetic mean ± SD; all groups)

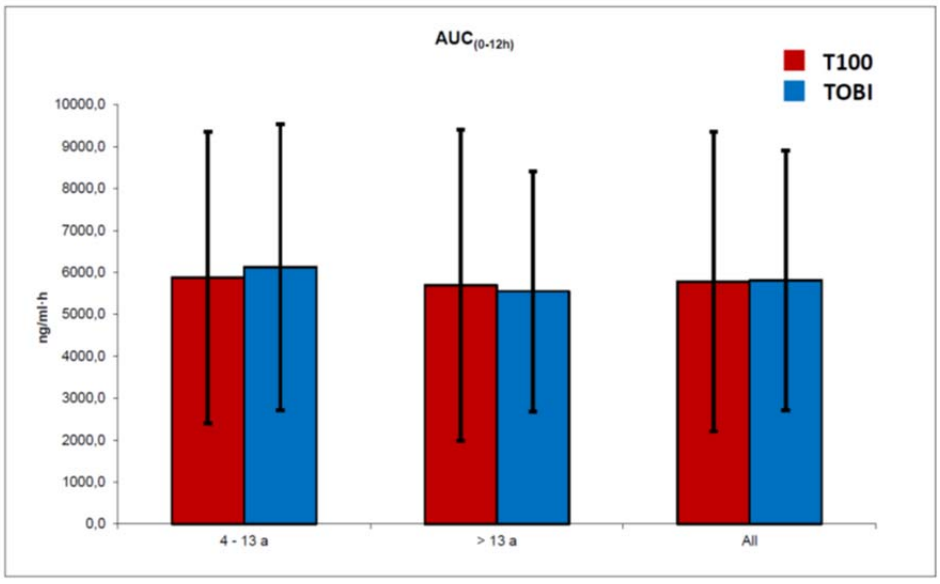


Figure 5 shows the corresponding point estimators for the geometric means of plasma AUC_{0-12h} for the overall study population as well as for the age subgroups. The test-to-reference ratios as well as the 90% CI for the parameter AUC_{0-12h} are given in **Table 9**. The decision procedure in favour of bioequivalence is based on the inclusion of the shortest 90% confidence interval for the ratio of expected geometric means (test-to-reference ratio) in the respective bioequivalence range. Accordingly, a bioequivalence range of 0.80 to 1.25 (80% to 125%) is usually demanded for AUC.

AUC_{0-12h} matched the acceptable upper limit (125%) regarding all patients or subgroups stratified by age. In contrast, the lower limit of acceptance 80% was failed for each group.

Figure 5 Point estimators and acceptance range for plasma AUC_{0-12h} (all groups)

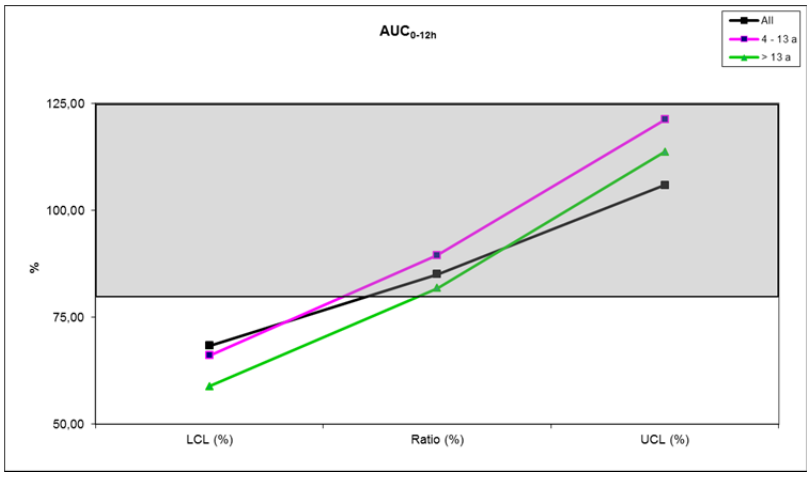


Table 9 Test-to-Reference Ratio and 90% CI of plasma AUC_{0-12h}

AUC_{0-12h}	LCL (%)	Ratio (%)	UCL (%)	CV_{res} (%)
All	68.32	85.03	105.83	71.87
4 - 13 a	66.09	89.51	121.22	63.64
> 13 a	58.84	81.78	113.68	80.66

LCL=Lower Confidence Limit; UCL=Upper Confidence Limit; CV_{res}=Residual Coefficient of Variation

Table 10 presents the individual, mean arithmetic, mean geometric and median plasma C_{max} values of Tobramycin for the two treatments VANTOBRA and TOBI.

Table 10 Individual, arithmetic, geometric mean and median plasma C_{max} values of VANTOBRA and TOBI (All)

Patient No.	C_{max} (ng/ml) All		
	T100	TOBI	T100/TOBI
1101	1513.1	861.1	1.76
1102	968.5	735.3	1.32
1103	1020.3	722.6	1.41
1104	1438.0	2032.8	0.71
1105	854.4	1553.0	0.55
1106	3244.2	3449.3	0.94
1108	203.2	3130.3	0.06
1110	1672.3	962.9	1.74
1111	1601.4	1412.9	1.13
1112	2587.0	1556.6	1.66
1113	1430.3	1394.1	1.03
1201	385.1	346.5	1.11
1202	1003.5	314.1	3.19
1203	1370.3	2147.3	0.64
1204	632.5	559.2	1.13
1206	2494.2	2907.0	0.86
1207	81.4	687.9	0.12
1208	98.3	529.2	0.19
2101	1128.2	635.5	1.78
2102	1001.2	334.0	3.00
2103	1064.5	1648.1	0.65
2105	2205.1	2037.0	1.08
2106	682.4	2335.5	0.29
2107	1046.9	1411.0	0.74
2201	506.2	1165.5	0.43
2202	2558.6	2415.5	1.06
2203	87.7	594.5	0.15
2204	1105.6	1226.2	0.90
2205	59.3	760.2	0.08
2206	2571.9	1752.2	1.47
3101	673.4	1954.9	0.34
3102	65.7	133.7	0.49
3103	1331.4	815.0	1.63
3201	365.6	1756.7	0.21
3202	873.1	1841.6	0.47
3203	1665.4	1055.3	1.58
3204	832.0	241.0	3.45
3205	2656.8	1080.1	2.46
3206	1354.0	933.3	1.45
3207	1512.3	1545.7	0.98
3208	821.7	2192.9	0.37
3209	1620.0	1776.1	0.91
3210	521.4	1299.1	0.40
4101	2008.4	656.0	3.06
4102	1877.7	1649.4	1.14
4105	1674.9	1187.7	1.41
4204	2171.9	1082.6	2.01
4205	997.5	1666.5	0.60
4206	2648.7	866.5	3.06
N	**49**	**49**	
Arithmetic mean	**1271.2**	**1333.7**	
SD (±)	**805.48**	**757.45**	
CV (%)	**63.4**	**56.8**	
Minimum	**59.3**	**133.7**	
Maximum	**3244.2**	**3449.3**	
Median	**1105.6**	**1226.2**	
Geometric mean	**911.0**	**1101.4**	

The barr diagram below (**Figure 6**) shows the values for plasma C_{max} (arithmetic mean ± SD) differentiated into "All" and the two age groups. The Tobramycin C_{max} was comparable between VANTOBRA and TOBI in all subgroups.

Figure 6 Barr diagram for plasma C_{max} (arithmetic mean ± SD; all groups)

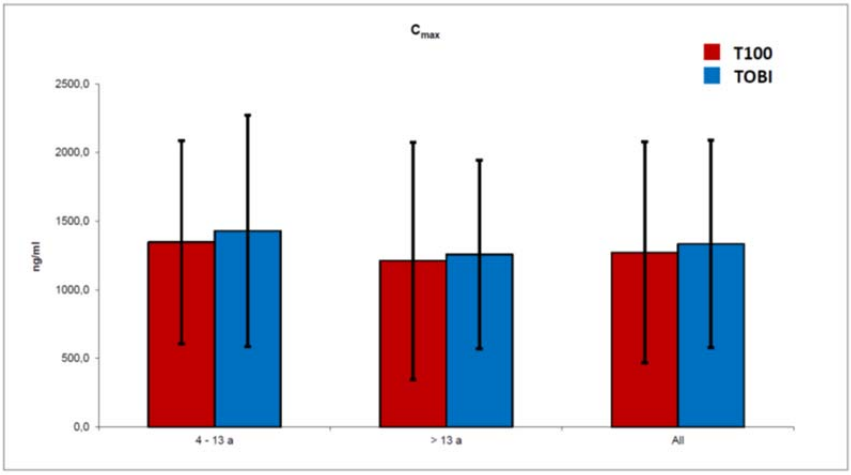


Figure 7 shows the corresponding point estimator for the geometric means of plasma C_{max} for the overall study population as well as for the age subgroups. The test-to-reference ratios as well as the 90% CI for the parameter C_{max} are given in **Table 11**. The decision procedure in favour of bioequivalence is based on the inclusion of the shortest 90% confidence interval for the ratio of expected geometric menas (test-to-reference ratio) in the respective bioequivalence range. Accordingly a bioequivalence range of 0.70 to 1.33 (70% to 133%) is usually demanded for C_{max}.

C_{max} fulfilled the widened acceptable upper limit of 133% for each patient group but also failed the widened lower acceptable limit (70%).

Figure 7 Point estimators and acceptance range for plasma C_{max} (all groups)

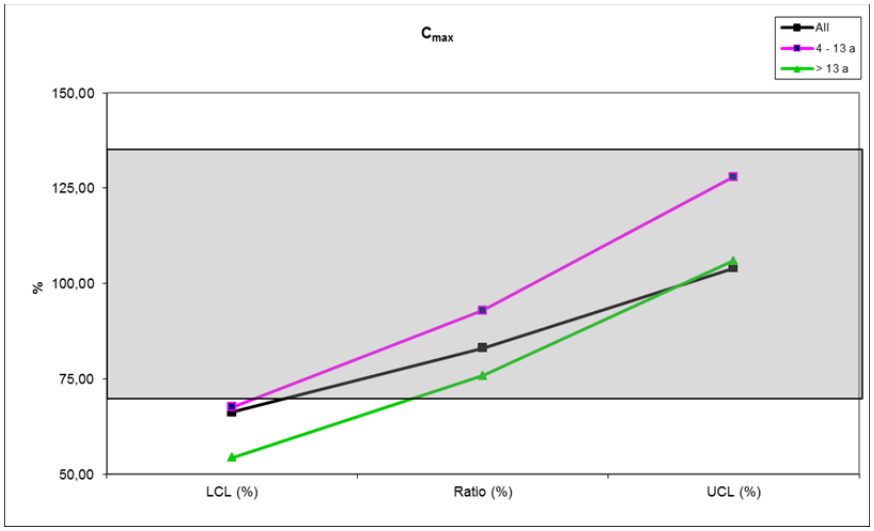


Table 11 Test-to-Reference Ratio and 90% CI of C_{max}

C_{max}	LCL (%)	Ratio (%)	UCL (%)	CV_{res} (%)
All	66.30	83.05	104.03	74.50
4 - 13 a	67.58	93.00	127.99	67.68
> 13 a	54.37	75.89	105.93	81.96

LCL=Lower Confidence Limit; UCL=Upper Confidence Limit; CV_{res}=Residual Coefficient of Variation

The barr diagram below (**Figure 8)** shows the values for plasma t_{max} (arithmetic mean ± SD) differentiated into "All" and the two age groups. Mean t_{max} was comparable between VANTOBRA and TOBI in all subgroups.

Figure 8 Barr Diagrams for plasma t_{max} (arithmetic mean and SD; all groups)

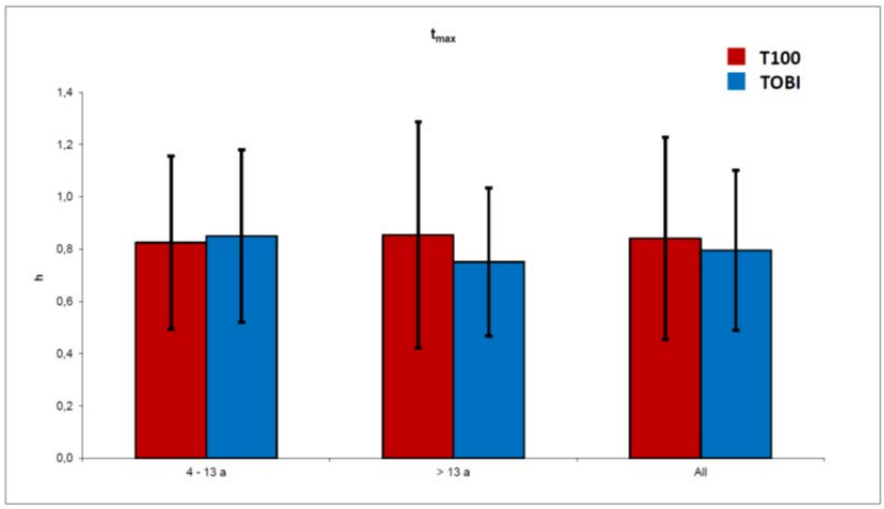


Table 12 shows the individual, arithmetic mean and median plasma C_0 values (Visit 2/4 and Visit 3/5) of VANTOBRA and TOBI for the group "All" (N=49).

Table 12 Individual, arithmetic mean and median plasma C_0 values (Visit 2/4 and Visit 3/5) of VANTOBRA and TOBI (All)

Patient No.	C_0 (ng/ml) All			
	T100		TOBI	
	Visit 2/4	Visit 3/5	Visit 2/4	Visit 3/5
1101	0.0	253.0	0.0	77.3
1102	0.0	192.8	0.0	148.4
1103	0.0	78.6	0.0	68.3
1104	0.0	277.8	0.0	139.3
1105	0.0	62.5	0.0	67.1
1106	0.0	294.1	0.0	311.0
1108	0.0	0.0	0.0	78.3
1110	0.0	173.5	0.0	202.3
1111	0.0	113.3	0.0	192.6
1112	0.0	83.9	0.0	52.1
1113	0.0	147.6	0.0	142.1
1201	0.0	34.9	0.0	62.5
1202	0.0	187.0	0.0	0.0
1203	0.0	136.4	0.0	292.5
1204	0.0	72.2	0.0	46.1
1206	0.0	105.1	0.0	242.9
1207	0.0	0.0	39.8	40.9
1208	39.3	63.3	0.0	76.1
2101	34.6	205.5	0.0	102.5
2102	0.0	96.5	0.0	106.3
2103	0.0	117.4	0.0	151.5
2105	0.0	115.4	0.0	122.6
2106	0.0	145.4	0.0	433.7
2107	0.0	230.1	0.0	140.6
2201	0.0	61.1	0.0	48.5
2202	0.0	317.0	0.0	50.7
2203	0.0	0.0	0.0	0.0
2204	0.0	256.8	0.0	299.7
2205	0.0	0.0	0.0	0.0
2206	0.0	322.4	0.0	285.8
3101	0.0	133.9	0.0	254.8
3102	0.0	0.0	0.0	0.0
3103	0.0	227.7	0.0	191.0
3201	0.0	39.0	0.0	412.4
3202	0.0	120.5	0.0	122.7
3203	0.0	264.7	0.0	328.6
3204	0.0	130.1	0.0	108.1
3205	0.0	189.7	0.0	49.5
3206	0.0	251.0	0.0	121.4
3207	0.0	126.6	0.0	0.0
3208	0.0	202.0	0.0	257.5
3209	374.7	1003.1	0.0	548.2
3210	0.0	53.6	0.0	34.6
4101	0.0	0.0	0.0	70.1
4102	0.0	145.1	0.0	286.5
4105	0.0	209.0	0.0	123.5
4204	0.0	232.9	0.0	202.3
4205	0.0	228.0	0.0	349.1
4206	0.0	155.8	0.0	101.0
N	**49**	**49**	**49**	**49**
Arithmetic mean	**8.3**	**151.7**	**0.7**	**148.0**
SD (±)	**51.29**	**153.64**	**5.42**	**123.26**
CV (%)	**617.4**	**101.3**	**734.8**	**83.3**
Minimum	**0.0**	**0.0**	**0.0**	**0.0**
Maximum	**374.7**	**1003.1**	**39.8**	**548.2**
Median	**0.0**	**132.0**	**0.0**	**122.0**

Lower limit of quantitation is 30.0 ng/ml.
Due to statistical reasons any concentration below this limit of quantitation is reported in this table as 0.0.

Trough-level (C_0) is defined as the lowest drug level immediately before a new dosage. Thus, trough-levels give information for adapting drug doses in a multiple dose design, i.e. this level should not decline below a certain value between two inhalation intervals to guarantee efficacy.

The values at Visit 2 or 4, respectively, should be low in all patients and near zero because the patients are just included into the study and did not inhale Tobramycin (Visit 2) or they were at the end of the wash-out phase (Visit 4). The value at Visits 3 could be a little increased in case of an accumulation of Tobramycin during the previous 4 weeks. However, it should be significantly lower as those values measured in the subsequent PK analysis.

Table 12 shows that for VANTOBRA the C_0 values of Visit 2/4 and Visit 3/5 were only 0.65% and 11.9% of C_{max}, respectively (**Table 10**). For TOBI the C_0 values of Visit 2/4 and Visit 3/5 were only 0.05% and 11.1% of C_{max}, respectively. The low C_0 values of Visit 2/4 indicate that patients of both treatment groups were naïve to Tobramycin when entering the clinical study. The modest increase of the C_0 values of Visit 3/5 of approx. 10% of the respective C_{max} values revealed that the duration of the wash-out period was long enough to re-start the cross-over therapy from almost baseline.

11.4.2 Analysis of Sputum Tobramycin Pharmacokinetic Data

Sputum concentration versus time profiles (AUC_{0-8h}), maximum concentration (C_{max}), time to maximum concentration (t_{max}) and trough levels (C_0) of the test treatment VANTOBRA in comparison to TOBI were determined at the end of each treatment phase. Data of 49 patients were evaluable.

Table 13 presents the individual, mean arithmetic, mean geometric and median sputum AUC_{0-8h} values for Tobramycin for the two treatments VANTOBRA and TOBI (All).

Table 13 Individual, arithmetic and geometric mean and median sputum AUC_{0-8h} values of VANTOBRA and TOBI (All).

Patient No.	AUC_{0-8h} (ng/g·h) All		
	T100	**TOBI**	**T100/TOBI**
1101	217441.9	58925.5	3.69
1102	162681.2	165081.0	0.99
1103	726443.9	188152.0	3.86
1104	233344.3	105980.8	2.20
1105	321431.8	558600.0	0.58
1106	4029225.3	3024850.0	1.33
1108	610245.6	627919.0	0.97
1110	1571062.4	1322681.1	1.19
1111	19535.1	47500.3	0.41
1112	824478.8	713905.6	1.15
1113	1057027.0	814965.5	1.30
1201	609158.3	346194.7	1.76
1202	3402527.6	654602.7	5.20
1203	2341214.0	2598531.0	0.90
1204	629253.4	275386.5	2.28
1206	589594.4	415038.0	1.42
1207	9842.9	192121.7	0.05
1208	36295.1	190278.5	0.19
2101	1978267.0	530148.6	3.73
2102	683551.5	394912.7	1.73
2103	1270501.1	1650301.5	0.77
2105	5019805.0	29477402	1.70
2106	313724.5	458733.5	0.68
2107	3180266.8	1827956.5	1.74
2201	449925.3	47043.9	9.56
2202	953750.3	1215078.3	0.78
2203	127459.9	643065.4	0.20
2204	3005451.5	953980.9	3.15
2205	57008.9	370147.3	0.15
2206	1049151.3	808568.3	1.30
3101	1661220.1	145216.4	11.44
3102	76056.5	301325.5	0.25
3103	1526807.3	555603.0	2.75
3201	2256532.5	1282090.7	1.76
3202	450676.0	1609541.8	0.28
3203	888190.0	1092074.8	0.81
3204	424647.8	412328.8	1.03
3205	937686.4	269778.4	3.48
3206	1193135.8	1980685.4	0.60
3207	2318264.3	669370.8	3.46
3208	218997.0	1293705.5	0.17
3209	564884.5	649813.5	0.87
3210	893828.9	433468.4	2.06
4101	111003.7	2140206.5	0.05
4102	1995075.6	2948335.0	0.68
4105	2296898.1	420487.3	5.46
4204	314057.8	325486.5	0.96
4205	1300825.3	1302782.3	1.00
4206	2896443.3	604087.5	4.79
N	**49**	**49**	
Arithmetic mean	**1179691.8**	**869077.1**	
SD (±)	**1154141.60**	**801424.12**	
CV (%)	**97.8**	**92.2**	
Minimum	**9842.9**	**47043.9**	
Maximum	**5019805.0**	**3024850.0**	
Median	**824478.8**	**604087.5**	
Geometric mean	**623440.2**	**556326.7**	

Sputum AUC_{0-8h} values of the test treatment VANTOBRA in comparison to TOBI were comparable for all patients. Similar results were obtained when distinguishing data among children (4 – 13 a) and adolescents/adults (> 13 a). Numerical mean values of the two age groups (4-13 a and > 13 a) as well as individual curves of all 49 patients are provided in the Statistical Report in **Appendix 16.1.9.2**.

The sputum tobramycin concentrations revealed even higher inter- and intraindividual variations than the plasma concentrations. This variability was observed for both formulations and appears virtually related to the specific disorder in conjuction with the aminoglycoside antibiotic Tobramycin and the route of drug aministration.

The barr diagram below (**Figure 9**) shows the values for AUC_{0-8h} (arithmetic mean ± SD) differentiated into "All" and the two age groups. The AUC_{0-8h} was comparable between VANTOBRA and TOBI in all subgroups.

Figure 9 Barr diagram for sputum AUC_{0-8h} (arithmetic mean ± SD; all age groups)

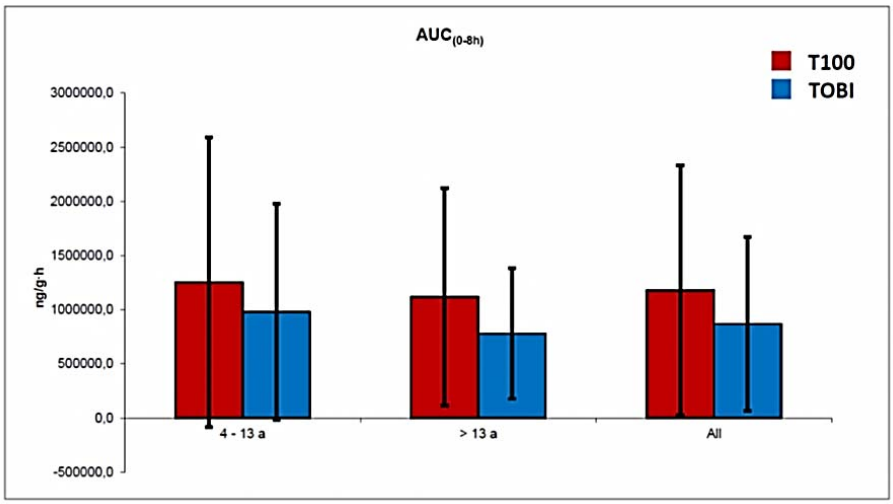


Table 14 presents the individual, mean arithmetic, mean geometric and median sputum C_{max} values of Tobramycin for the two treatments VANTOBRA and TOBI.

Table 14 Individual arithmetic and geometric mean and median of sputum C_{max} of VANTOBRA and TOBI (All)

Patient No.	C_{max} (ng/g) All		
	T100	TOBI	T100/TOBI
1101	304400.0	86650.0	3.51
1102	111400.0	322750.0	0.35
1103	289650.0	150000.0	1.93
1104	717700.0	155100.0	4.63
1105	836250.0	628900.0	1.33
1106	3679000.0	3199500.0	1.15
1108	1676100.0	1309400.0	1.28
1110	4877500.0	379050.0	12.87
1111	59300.0	51150.0	1.16
1112	2162450.0	1655350.0	1.31
1113	864500.0	530300.0	1.63
1201	1296600.0	1017850.0	1.27
1202	8227500.0	1831000.0	4.49
1203	5292500.0	3169350.0	1.67
1204	1068150.0	473750.0	2.25
1206	968600.0	711000.0	1.36
1207	24500.0	136400.0	0.18
1208	40050.0	458150.0	0.09
2101	6881500.0	1740450.0	3.95
2102	602800.0	745450.0	0.81
2103	1357850.0	1387200.0	0.98
2105	5319500.0	3981300.0	1.34
2106	72400.0	1067250.0	0.07
2107	2408850.0	1363300.0	1.77
2201	1151650.0	37550.0	30.67
2202	325150.0	1270700.0	0.26
2203	173450.0	258750.0	0.67
2204	2913800.0	1242150.0	2.35
2205	73544.0	177450.0	0.41
2206	889950.0	1532250.0	0.58
3101	6451000.0	124000.0	52.02
3102	30350.0	42600.0	0.71
3103	908400.0	1008600.0	0.90
3201	7078500.0	2973100.0	2.38
3202	243300.0	5165000.0	0.05
3203	1447150.0	3741350.0	0.39
3204	969850.0	748400.0	1.30
3205	1213650.0	522600.0	2.32
3206	3183400.0	6042500.0	0.53
3207	3385850.0	1774150.0	1.91
3208	39166.0	2771050.0	0.01
3209	1625900.0	691600.0	2.35
3210	2841850.0	962500.0	2.95
4101	373650.0	6106000.0	0.06
4102	1209300.0	1067000.0	1.13
4105	1568450.0	844750.0	1.86
4204	539950.0	105750.0	5.11
4205	1579000.0	1524350.0	1.04
4206	6231000.0	2123800.0	2.93
N	**49**	**49**	
Arithmetic mean	**1950741.0**	**1416501.0**	
SD (±)	**2186546.79**	**1505653.04**	
CV (%)	**112.1**	**106.3**	
Minimum	**24500.0**	**37550.0**	
Maximum	**8227500.0**	**6106000.0**	
Median	**1151650.0**	**1008600.0**	
Geometric mean	**846201.6**	**748916.0**	

The barr diagram below (**Figure 10**) shows the values for sputum C_{max} (arithmetic mean ± SD) differentiated into "All" and the two age groups. The Tobramycin C_{max} was higher after VANTOBRA than after TOBI treatment in all subgroups.

Figure 10 Barr diagram for sputum C_{max} (arithmetic mean ± SD; all groups)

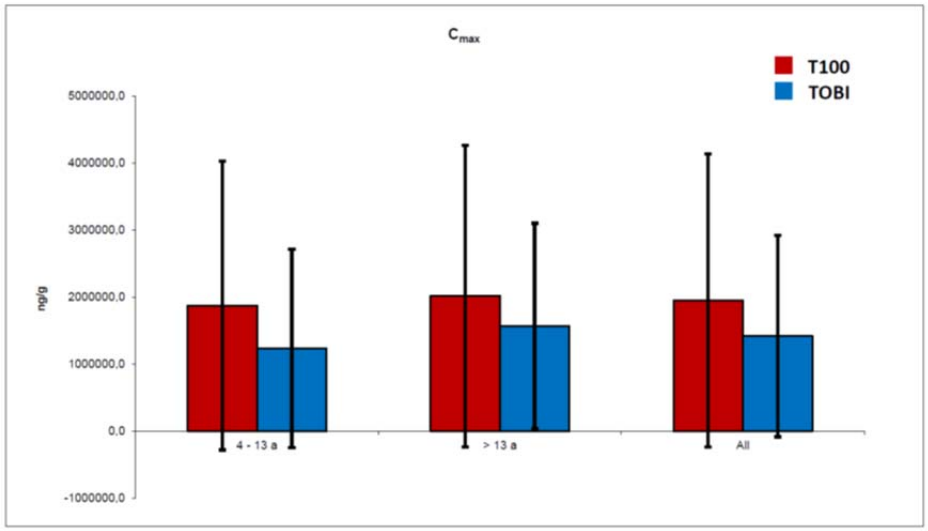


Table 15 presents the individual, mean arithmetic and median sputum t_{max} values of Tobramycin for the two treatment VANTOBRA and TOBI.

Table 15 Individual arithmetic mean and median of sputum t_{max} of VANTOBRA and TOBI (All)

Patient No.	t_{max} (h)	All
	T100	TOBI
1101	0.17	0.17
1102	0.17	0.17
1103	0.17	0.17
1104	0.17	0.17
1105	0.17	0.17
1106	0.50	0.17
1108	0.17	0.17
1110	0.17	2.00
1111	0.17	0.17
1112	0.17	0.17
1113	0.50	0.17
1201	0.17	0.17
1202	0.17	0.17
1203	0.17	0.17
1204	0.17	0.17
1206	0.17	0.17
1207	0.17	0.17
1208	0.17	0.17
2101	0.17	0.17
2102	0.17	0.17
2103	0.17	0.17
2105	0.17	0.17
2106	8.00	0.17
2107	0.17	0.17
2201	0.17	0.17
2202	0.17	0.17
2203	0.17	0.17
2204	0.17	0.17
2205	0.50	1.50
2206	0.53	0.17
3101	0.17	0.17
3102	0.17	8.00
3103	0.50	0.17
3201	0.17	0.17
3202	0.62	0.00
3203	0.17	0.17
3204	0.17	0.17
3205	0.17	0.17
3206	0.17	0.17
3207	0.17	0.17
3208	0.17	0.17
3209	0.17	0.17
3210	0.17	0.17
4101	0.17	0.17
4102	0.50	0.27
4105	0.17	0.17
4204	0.17	0.27
4205	0.17	0.17
4206	0.19	0.17
N	**49**	**49**
Arithmetic mean	**0.38**	**0.39**
SD (±)	**1.118**	**1.155**
CV (%)	**293.9**	**292.4**
Minimum	**0.17**	**0.00**
Maximum	**8.00**	**8.00**
Median	**0.17**	**0.17**

The barr diagram below (**Figure 11**) shows the values of sputum t_{max} (arithmetic mean ± SD) differentiated into "All" and the two age groups. The Tobramycin t_{max} was comparable between VANTOBRA and TOBI in all subgroups.

Figure 11 Barr diagram for sputum t_{max} (arithmetic mean ± SD); all groups)

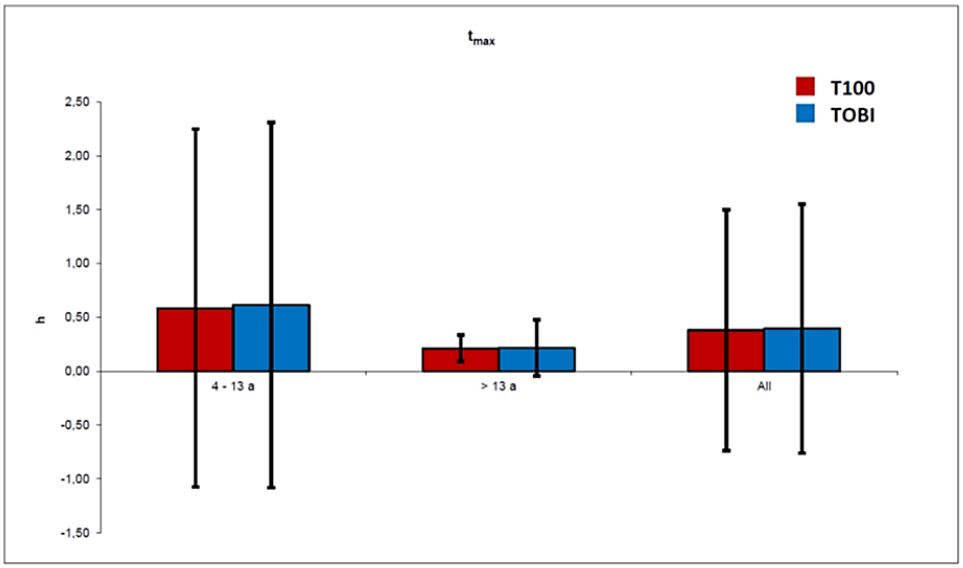


Table 16 shows the individual arithmetic mean and median sputum C_0 values (Visit 2/4 and Visit 3/5) of VANTOBRA and TOBI for the group "All" (N=49).

Table 16 Individual, arithmetic mean and median values of sputum C_0 (Visit 2/4 and Visit 3/5) of Tobramycin after administration of VANTOBRA and TOBI (All)

Patient No.	C_0 (ng/ml) All			
	T100		TOBI	
	visit 2/4	visit 3/5	visit 2/4	visit 3/5
1101	0.0	2714.0	0.0	4338.0
1102	0.0	3140.0	0.0	86300.0
1103	0.0	4866.0	0.0	4116.0
1104	0.0	38304.0	0.0	1700.0
1105	0.0	42700.0	0.0	8518.0
1106	0.0	55550.0	0.0	5918.0
1108	0.0	9128.0	0.0	48150.0
1110	0.0	10116.0	0.0	3786.0
1111	0.0	0.0	0.0	774.0
1112	0.0	0.0	0.0	1098.0
1113	0.0	395200.0	0.0	0.0
1201	0.0	29200.0	0.0	2594.0
1202	1166.0	4986.0	0.0	982.0
1203	0.0	75550.0	0.0	88650.0
1204	0.0	6360.0	0.0	48100.0
1206	0.0	2552.0	0.0	37650.0
1207	0.0	0.0	0.0	2190.0
1208	0.0	810.0	0.0	4424.0
2101	0.0	0.0	0.0	1442.0
2102	0.0	2524.0	614.0	0.0
2103	0.0	10192.0	0.0	71750.0
2105	0.0	42950.0	0.0	68500.0
2106	0.0	4352.0	0.0	7376.0
2107	648.0	78100.0	0.0	47800.0
2201	0.0	0.0	0.0	1454.0
2202	0.0	34450.0	0.0	*
2203	0.0	15750.0	0.0	1000.0
2204	0.0	15900.0	0.0	5708.0
2205	0.0	2078.0	0.0	0.0
2206	0.0	15650.0	0.0	58500.0
3101	0.0	1922.0	0.0	7614.0
3102	0.0	2576.0	0.0	29850.0
3103	0.0	15250.0	0.0	33400.0
3201	0.0	212650.0	0.0	3630.0
3202	0.0	62600.0	0.0	5165000.0
3203	0.0	67450.0	0.0	62000.0
3204	0.0	0.0	0.0	47600.0
3205	0.0	39300.0	0.0	622.0
3206	0.0	31250.0	0.0	17350.0
3207	0.0	16650.0	0.0	1518.0
3208	0.0	29350.0	0.0	104600.0
3209	0.0	16750.0	0.0	23450.0
3210	0.0	1110.0	0.0	1784.0
4101	*	*	*	15450.0
4102	*	17350.0	*	*
4105	*	*	*	2804.0
4204	0.0	127650.0	*	52850.0
4205	0.0	118986.0	*	251850.0
4206	*	23300.0	0.0	3636.0
N	**45**	**47**	**44**	**47**
Arithmetic mean	**40.3**	**35899.3**	**14.0**	**136975.0**
SD (±)	**196.93**	**67248.14**	**92.56**	**750638.29**
CV (%)	**488.5**	**187.3**	**663.3**	**548.0**
Minimum	**0.0**	**0.0**	**0.0**	**0.0**
Maximum	**1166.0**	**395200.0**	**614.0**	**5165000.0**
Median	**0.0**	**15650.0**	**0.0**	**5918.0**

Lower limit of quantitation is 600.0 ng/g. Due to statistical reasons any concentration below this limit of quantitation is reported in this table as 0.0.
*) missing value because of missing sputum sample

Table 16 shows that for VANTOBRA the C_0 values of Visit 2/4 and Visit 3/5 were only 0.002% and 1.8% of C_{max}, respectively (**Table 14**). For TOBI the C_0 values of Visit 2/4 and Visit 3/5 were only 0.1% and 9.7% of C_{max}, respectively. The low C_0 values of Visit 2/4 indicate that patients of both treatment groups were naïve to Tobramycin when entering the clinical study.

11.4.3 Statistical/Analytical Issues

All planned analyses and statistical details are provided in the Statistical Analysis Plan and Statistical Report (**Appendix 16.1.9.1** and **16.1.9.2**).

The logarithmically transformed pharmacokinetic (PK) parameters AUC_{0-12h} and C_{max} were subjected to ordinary least squares (OLS) analysis of variance (ANOVA) using the SAS – procedure GLM (SAS/STAT Version 9.2; Guideline on the Investigation of Bioequivalence 2010).

The model used includes the factors SEQUENCE, PATIENT/SEQUENCE, PERIOD and FORM. The term SEQUENCE was tested against the mean square of the random PATIENT (SEQUENCE) term. For the computation of the least squares means and confidence bands the model including PATIENT, PERIOD and FORM was applied [Guideline on the Investigation of Bioequivalence 2010; Chow and Liu JP 2009; Hauschke et al. 2007]).

The test for normality of the residual distribution was performed using the Wilk-Shapiro procedure [Shapiro and Wilk 1965].

The residuals from the ANOVA were plotted as normal probability plots showing the studentized residuals (= residuals normalised to the residual standard deviation) to check Gaussian distribution.

Pharmacokinetic parameter t_{max} was evaluated descriptively [(Guideline on the Investigation of Bioequivalence 2010].

For assessment of bioequivalence in plasma AUC_{0-12h} and plasma C_{max} the 90% confidence bands for the true formulation ratio of the geometric means μ_T/μ_R for plasma AUC_{0-12h} must reside within the interval 80.00% to 125.00% and for plasma C_{max} within the interval 70.00% to 133.00% [Guideline on the Investigation of Bioequivalence 2010]. In other words, the confidence limits LCL and UCL must obey

$$80.00\% \leq LCL(\mu_T/\mu_R) \wedge UCL(\mu_T/\mu_R) \leq 125.00\% \text{ for plasma } AUC_{0-12h}$$

and

$$70.00\% \leq LCL(\mu_T/\mu_R) \wedge UCL(\mu_T/\mu_R) \leq 133.00\% \text{ for plasma } C_{max}$$

Test on Normal Distribution

All:

The Wilk-Shapiro test does indicate significant deviation from the assumption of a normal distribution in the log-transformed AUC_{0-12h}.

4 – 13 a:

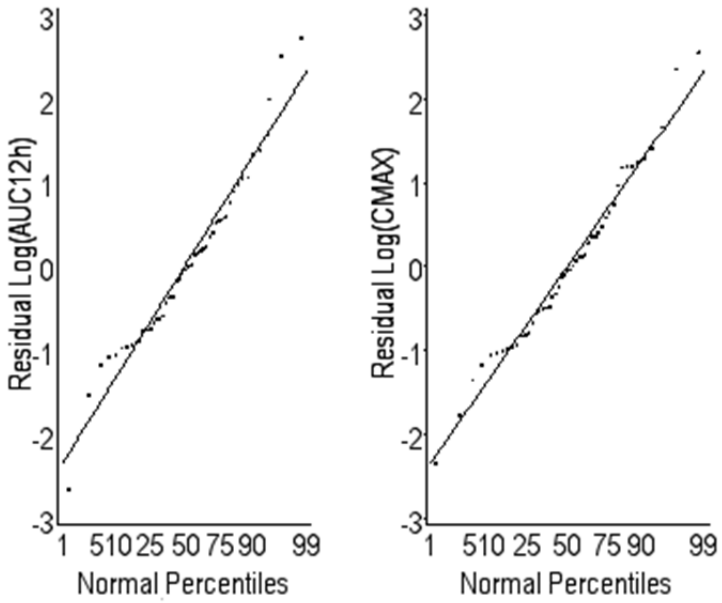
The Wilk-Shapiro test does indicate significant deviation from the assumption of a normal distribution in the log-transformed AUC_{0-12h}.

> 13 a:

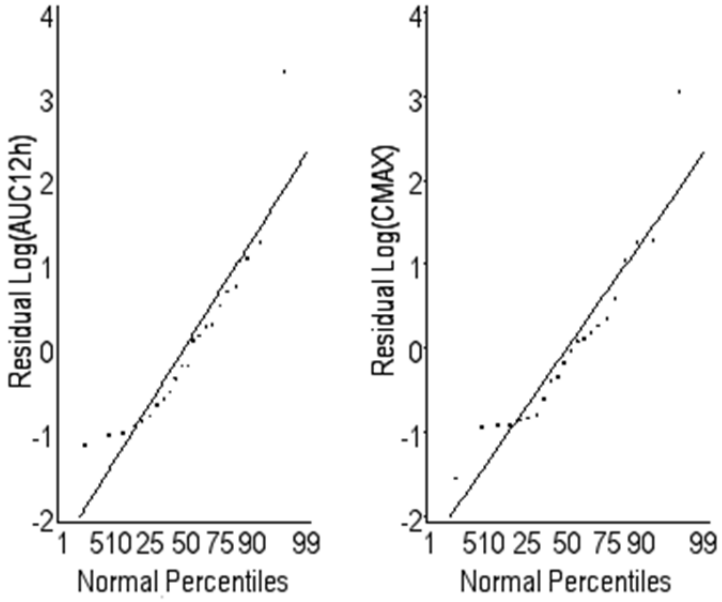
The Wilk-Shapiro test does not indicate significant deviation from the assumption of a normal distribution in the log-transformed AUC_{0-12h} and C_{max}.

Normal Probability Plots of the Residual Distribution of the ANOVA for Tobramycin

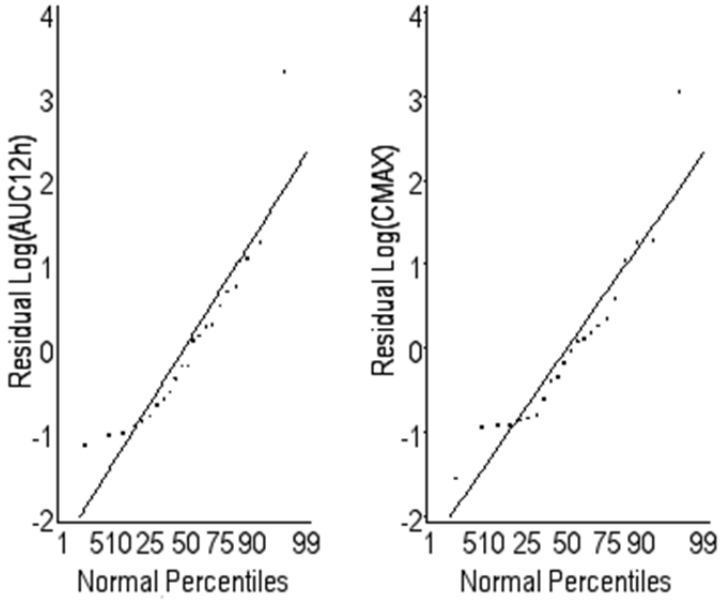
All:



4 – 13 a



> 13 a



Test on Product (FORM) and Period Effect

All:

No significant difference ($p < 0.05$) was observed in any of PK-endpoints for any factor.

4 – 13 a:

No significant difference ($p < 0.05$) was observed in any of PK-endpoints for any factor.

> 13 a:

No significant difference ($p < 0.05$) was observed in any of PK-endpoints for any factor.

Test on Sequence Effect

All:

No significant sequence effect was observed ($p < 0.05$) in any of PK-endpoints.

4 – 13 a:

No significant sequence effect was observed ($p < 0.05$) in any of PK-endpoints.

> 13 a:

No significant sequence effect was observed ($p < 0.05$) in any of PK-endpoints.

Residual Coefficient of Variation (CV_{res}):

All:

The residual coefficients of variation for tobramycin were determined for $AUC_{0\text{-}12h}$ as 71.87% and for C_{max} as 74.50%.

4 – 13 a:

The residual coefficients of variation for tobramycin were determined for $AUC_{0\text{-}12h}$ as 63.64% and for C_{max} as 67.68%.

> 13 a:

The residual coefficients of variation for tobramycin were determined for $AUC_{0\text{-}12h}$ as 80.66% and for C_{max} as 81.96%.

11.4.3.1 Adjustments for Covariates

No covariate adjustments have been performed.

11.4.3.2 Handling of Dropouts or Missing Data

Two patients of each sequence of the treatment group stopped the study after Visit 3 during the wash-out phase or at beginning of Treatment Phase 2. Patients 2108 and 1205 received only the test preparation (VANTOBRA); patients 1109 and 2104 received only the reference preparation (TOBI).

Drop-out patients were not replaced according to the protocol; missing data were indicated as “MD” and captured under protocol deviation (see **Appendix 16.2.2**).

11.4.3.3 Interim Analysis and Data Monitoring

There was no interim analysis or involvement of a Data Monitoring Committee.

11.4.3.4 Multicenter Studies

This study was conducted in 4 centers in Poland, which are described in **Section 6**.

11.4.3.5 Multiple Comparisons/Multiplicity

No applicable multiple comparisons have been performed.

11.4.3.6 Use of an "Efficacy Subset" of Patients

No efficacy subset of patients was defined in this study.

11.4.3.7 Active-Control Studies Intended to Show Equivalence

This study was intended to compare VANTOBRA, a more efficient drug/device combination with the marketed TOBI.

11.4.3.8 Examination of Subgroups

The following subgroups were analyzed: patients from 4 up to 13 years and patients > 13 years.

11.4.4 Tabulation of Individual PK Data

Listings of individual plasma and sputum Tobramycin concentration data are provided in the PK-Data Evaluation and Statistical Report in **Appendix 16.1.9.2**.

11.5 Pharmacokinetic Conclusions

In summary, the following conclusions on the PK results can be drawn:

A total of 54 patients suffering from CF and chronic PA infection received Tobramycin, both as VANTOBRA (170 mg/1.7 ml) and TOBI (300 mg/5 ml) per inhalation in a cross-over design.

Three randomized patients completed one treatment period only; one patient discontinued after only 3 days of TOBI treatment. Five further patients were excluded from the PK analyses because of insufficient data (see **Table 6** and **Figure 2** Disposition of Patients). Thus, the remaining PP population for the PK analysis was N=49.

Plasma and sputum concentrations of Tobramycin were measured using a validated LC-MS/MS method. The relationship between concentrations *versus* peak area ratios was found to be linear from 100 pg/ml to 50.000 pg/ml for both compounds. The limit of quantification was 30 ng/ml for the analyte.

The plasma concentrations of Tobramycin, and even more the sputum concentrations, showed extremly high inter- and intra-individual variability.

Not only VANTOBRA was characterised by high coefficients of variation but also the reference product TOBI. Beyond that, even PK data of i.v. Tobramycin administration resulted in similar high coefficients of variation.

The problems of the investigation of Tobramycin pharmacokinetics originate mainly from three factors:

- The CF disease status exerts a significant impact on the properties of mucus (viscous, aqueous, central/peripheral, surface covering), lung morphology, inflammation/exercerbation, hydration status of the patient, severity of the disease).
- The efficiency of inhalation, and thus the drug deposition in the lung, depends on the breathing pattern of patients
- The different efficiency of the devices
- Tobramycin PK values resulted also in a high coefficient of variation even when administered intravenously, although eliminating one parameter (inhalation) which mainly contributes to an increased variability.

Regarding CF it has to be considered that the properties of mucus (viscous, aqueous, central/peripheral, surface covering), lung morphology, inflammation/exercerbation, hydration status of the patient, and severity of the disease are influencing the resorption of Tobramycin from the lung into the systemic circulation.

The determination of drug levels in sputum is even more subjected to variation due to inhomogenous drug distribution in the lung resulting in locally different drug concentrations as well as the patient-individual capability to produce sputum.

Another disturbing factor is the inhalation behavior of CF patients, especially children, who hardly can be trained for a standardized breathing pattern.

In summary it could be concluded that for the extent of absorption (plasma AUC) and the rate of absorption (plasma C_{max}) the confidence intervals exceed the lower acceptance limit for the analysis of all patients as well as for the group separated analysis.

Considering the impact of these disruptive factors for the PK-analysis of a substance with well-known challenging pharmacokinetic properties and the rigid formalities of statistical calculations it may be justified to postulate at least a comparability and similarity of VANTOBRA and TOBI pharmacokinetics.

This conclusion is underlined by the observation that the point estimator resides within the accepted corridor, as does the UCL.

Finally, this part of the study demonstrated again, that CF patients cannot be regarded as a suitable model for PK-assessment of inhaled antibiotics.

11.6 Clinical Efficacy with Respect to Reduction of CFU of *P. aeruginosa* and Functional Lung Parameters

As outlined in detail in **Section 11.5**, the model "CF patient" is not the optimal one to draw conclusions regarding comparability of efficacy of two systems which differ in the concentration of the drug as well as in the efficiency of the device on the exclusive basis of PK data.

Therefore, it is nothing more important than to consider also clinical parameters to complete the picture of overall clinical utility of a therapy and to allow a sound benefit/risk assessment.

In the following it is illustrated that treatment with VANTOBRA positively contributes to the clinical improvement of patients suffering from CF with chronic PA infection with special emphasis on CFU and lung function parameters. Data of 54 patients were evaluable.

11.6.1 Reduction of CFU of *P. aeruginosa*

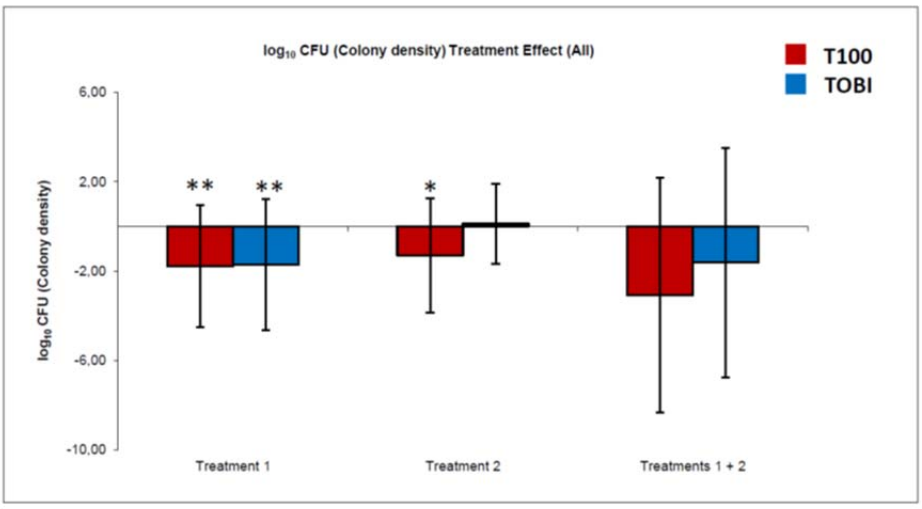
Treatment with Tobramycin resulted in an overall reduction in CFU density of *P. aeruginosa* (PA), irrespective of the specific drug/device combination. In general, the treatment effect was more pronounced in the first than in the second treatment period.

The overall reduction of CFU density of PA as a consequence of Tobramycin treatment is shown in **Figure 12** for the group of all patients. **Figures 13** and **14** show the changes in CFU for the PA subtypes "planctonic" and "mucoid". The values for the stratified age groups (4-13 a and >13 a) are shown in **Section 14.2.2** (**Tables 36-38**).

Discrimination into planctonic and mucoid subtypes of PA can be of clinical importance as the latter is an indicator of late stage CF disease where thick layers of lung mucus and alginate surrounding mucoid bacterial cells diminish the diffusion of oxygen. Hence, the present data suggest clinical efficacy also against the mucoid PA phenotype.

Figure 12 depicts the treatment effects in the total study population regarding total pathogen reduction. During the first treatment phase a similar $\log_{10}$ CFU reduction was achieved with VANTOBRA and TOBI (-1.77 ± 2.74 vs. -1.70 ± 2.93, $p < 0.01$), in the second treatment phase the reduction was -1. 30 ± 2.55 and 0.12 ± 1.78, respectively. The calculation over the complete treatment period revealed an overall reduction of PA CFU density of -3.07 ± 5.26 and -1.62 ± 5.14 for VANTOBRA and TOBI, respectively.

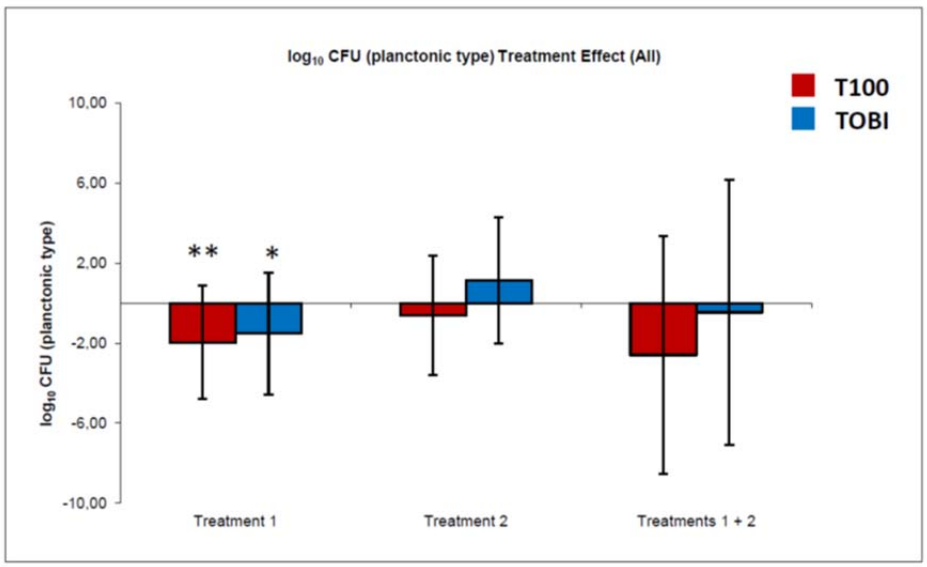
Figure 12 Colony Forming Units (CFU): Overall reduction of PA (All); normalized on Visit 2 as Baseline



*: p < 0.05; **: p < 0.01; ***: p < 0.001

Figure 13 depicts the treatment effects in the total study population regarding the planctonic type of PA. During the first treatment phase a similar log_{10} CFU reduction was achieved with VANTOBRA and TOBI (-1.96 ± 2.84 vs. -1.51 ± 3.05, $p < 0.01$), in the second treatment phase the reduction was -0.62 ± 2.99 and 1.14 ± 3.15, respectively. The calculation over the entire treatment period revealed an overall reduction of PA CFU density of -2.59 ± 5.94 and -0.46 ± 6.64 for VANTOBRA and TOBI, respectively.

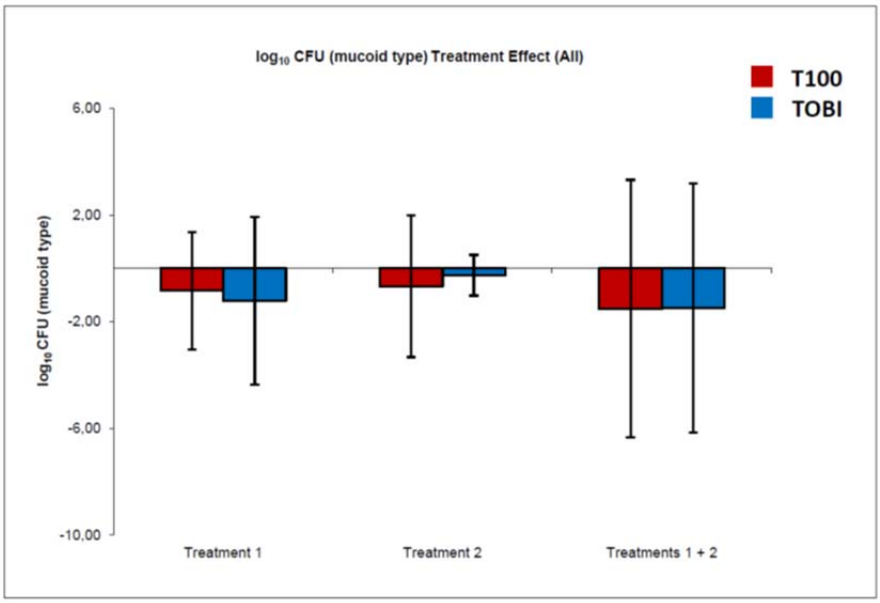
Figure 13 Colony Forming Units (CFU): Reduction of PA (planctonic type); normalized on Visit 2 as Baseline



*: p < 0.05; **: p < 0.01; ***: p < 0.001

Figure 14 depicts the treatment effects in the total study population regarding the mucoid type of PA. During the first treatment phase a similar log_{10} CFU reduction was achieved with VANTOBRA and TOBI (-0.83 ± 2.20 vs. -1.22 ± 3.15), in the second treatment phase the reduction was -0.67 ± 2.65 and -0.26 ± 0.76, respectively. The calculation over the complete treatment period revealed an overall reduction of PA CFU density of -1.51 ± 4.83 and -1.49 ± 4.68 for VANTOBRA and TOBI, respectively.

Figure 14 Colony Forming Units (CFU): Reduction of PA (mucoid type); normalized on Visit 2 as Baseline



Explorative statistical tests (Student's paired t-test) have revealed that the treatment effect of both Tobramycin products regarding reduction of PA CFU density for Treatment 1 in the group "All" was statistically highly significant (Table 17):

Table 17 Treatment effect of VANTOBRA and TOBI on PA CFU (p-values, Student's paired t-test; All)

	Treatment 1		**Treatment 2**	
	T100	**TOBI**	**T100**	**TOBI**
PA density	0.0020	0.0049	0.0120	0.7341
PA planktonic	0.0011	0.0142	0.2815	0.0766
PA mucoid	0.0549	0.0497	0.1886	0.0991

11.6.2 Improvement of Functional Lung Parameters

The changes in the different lung function parameters under investigation (FEV_1 % predicted, FEV_{25-75} % predicted, FVC and PEF) were consistently indicative for an improvement under both therapies with a tendency of better improvement under VANTOBRA therapy. In the following the data are given exemplarily for all patients except for FEV_1% predicted where in addition the data are shown for subpopulations stratified by age. Figures and Tables for all lung function parameters and age groups are shown in the Statistical Report, **Appendix 16.1.9.2**.

Figure 15 shows the time course of FEV_1 % predicted for the entire group of patients.

Figure 15 Time course of FEV_1 % predicted (All), normalized to Visit 2 as Baseline

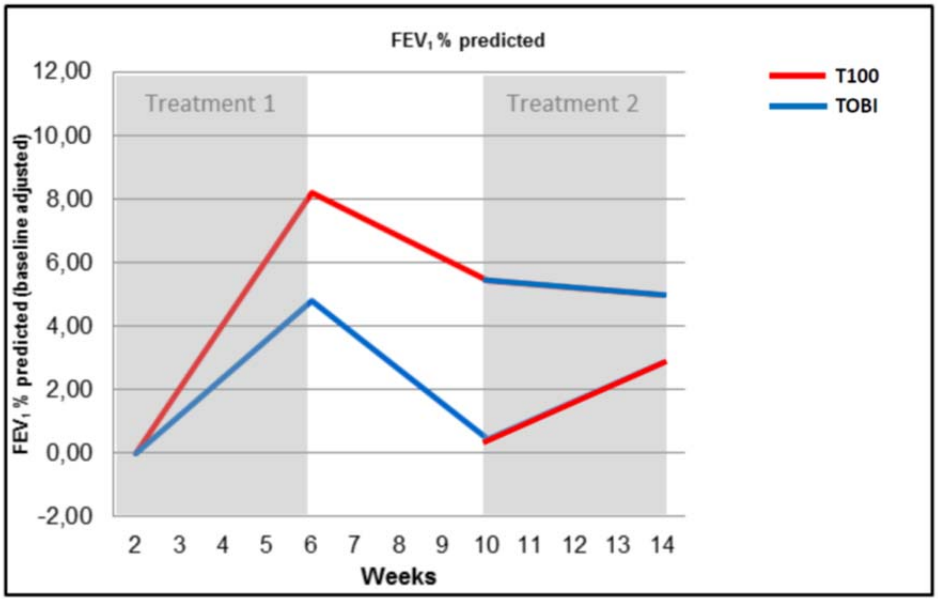
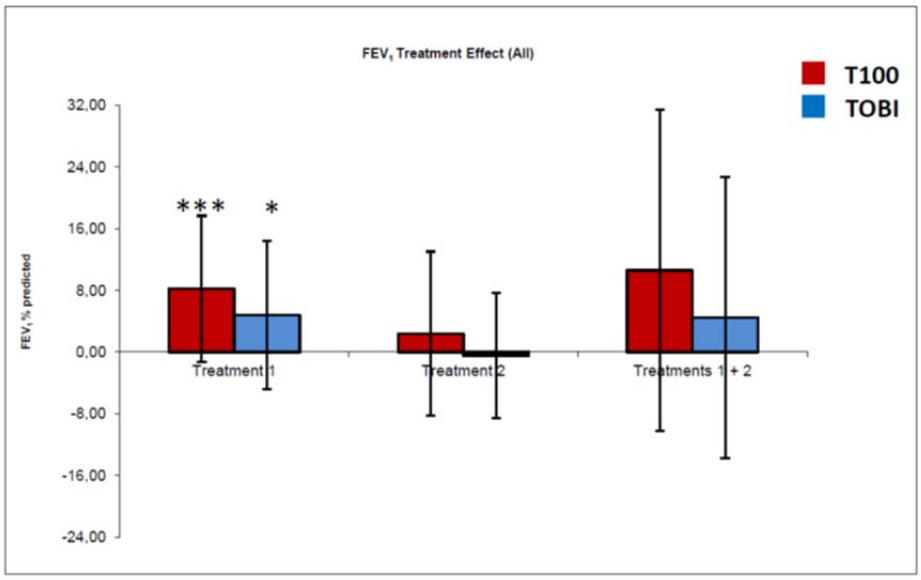


Figure 16 depicts the absolute changes of FEV_1 % predicted in the total study population. During the first treatment phase a significant percentual improvement of FEV_1 % predicted was achieved with VANTOBRA and TOBI (8.20 ± 9.49, $p < 0.001$ and 4.80 ± 9.58, $p < 0.05$, respectively), in the second treatment phase the percentual improvement was 2.40 ± 10.64 under VANTOBRA therapy, whereas under TOBI this parameter decreased by -0.44 ± 8.10%. The calculation over the complete treatment period revealed an overall percentual improvement of FEV_1 % predicted of 10.59 ± 20.81 and 4.48 ± 18.24 for VANTOBRA and TOBI, respectively.

Figure 16 Absolute changes in FEV_1 % predicted (All), normalized to Visit 2 as Baseline



*: p < 0.05; **: p < 0.01; ***: p < 0.001

Figure 17 shows the time course of FEV_1 % predicted for the subgroup of children (4 – 13 a).

Figure 17 Time course of FEV_1 % predicted (4 – 13 a), normalized to Visit 2 as Baseline

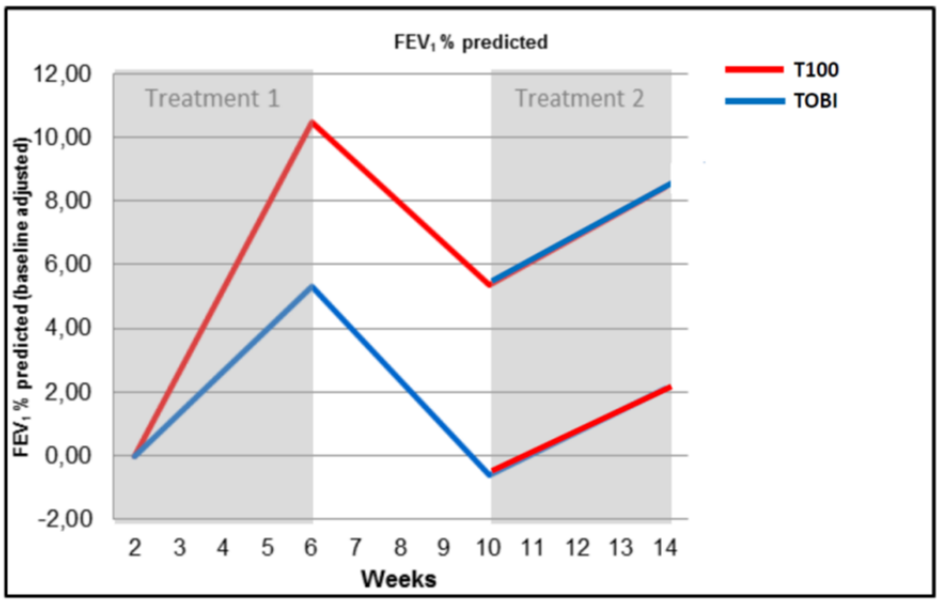
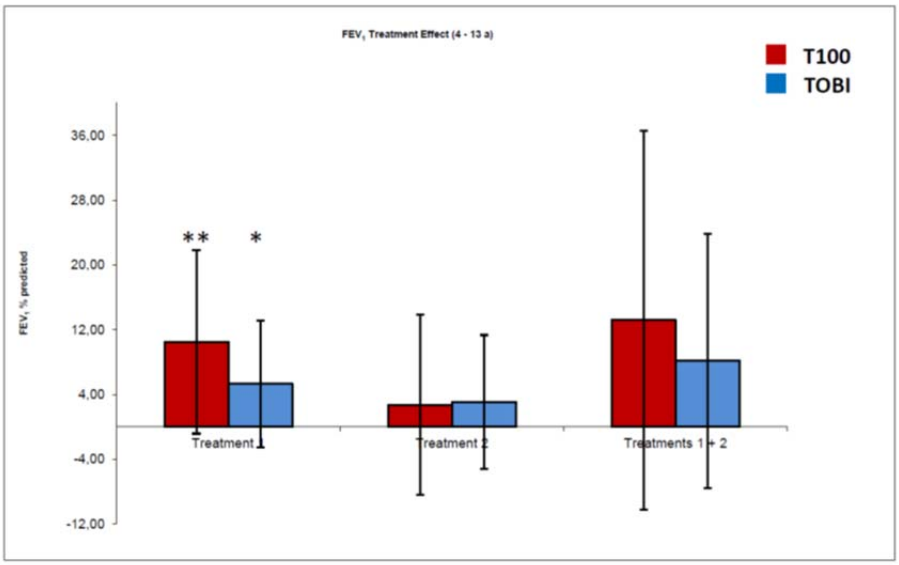


Figure 18 depicts the absolute changes of FEV_1 % predicted in the subgroup of children (4 – 13 a). During the first treatment phase a significant percentual improvement of FEV_1 % predicted was achieved with VANTOBRA and TOBI (10.48 ± 11.33, $p < 0.01$ and 5.31 ± 7.65, $p < 0.05$, respectively), in the second treatment phase the percentual improvement was 2.71 ± 11.13 under VANTOBRA therapy and 3.07 ± 8.27 under TOBI, respectively. The calculation over the complete treatment period revealed an overall percentual improvement of FEV_1 % predicted of 13.19 ± 23.39 and 8.15 ± 15.69 for VANTOBRA and TOBI, respectively.

Figure 18 Absolute changes in FEV_1 % predicted (4 – 13 a), normalized to Visit 2 as Baseline



*: p < 0.05; **: p < 0.01; ***: p < 0.001

Figure 19 shows the time course of FEV_1 % predicted for the subgroup of adolescents/adults (> 13 a).

Figure 19 Time course of FEV_1 % predicted (> 13 a), normalized to Visit 2 as Baseline

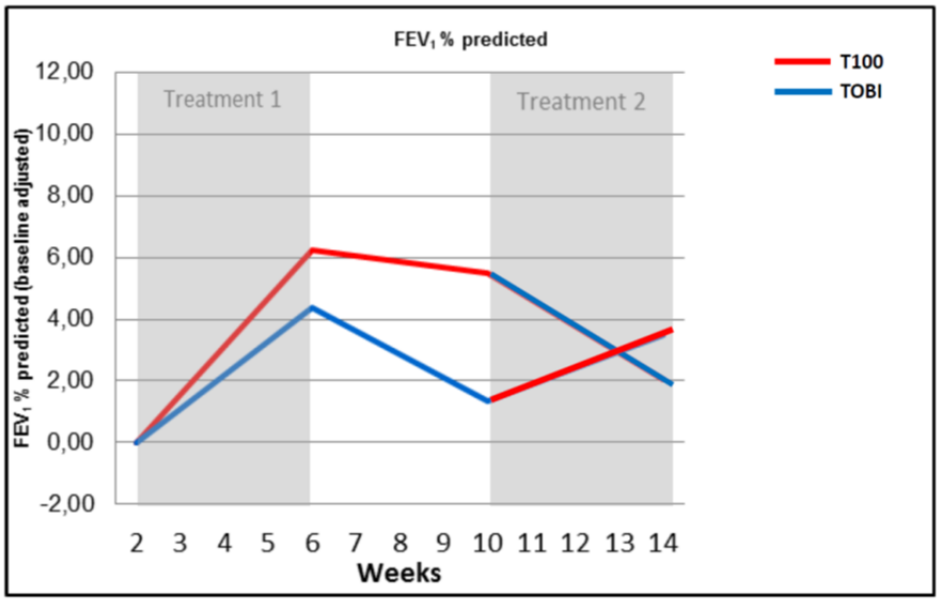
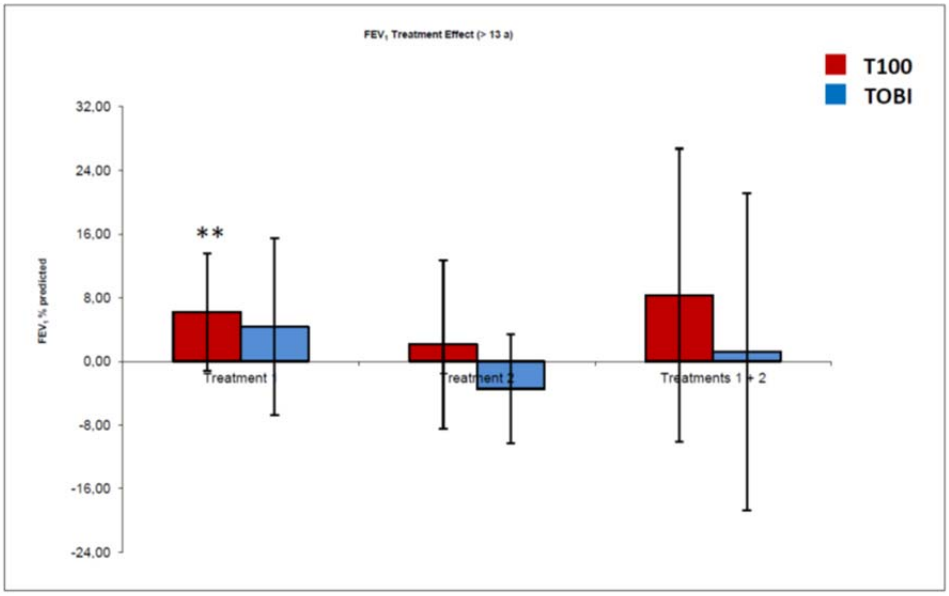


Figure 20 depicts the absolute changes of FEV_1 % predicted in the subgroup of adolescents/adults (>13 a). During the first treatment phase a significant percentual improvement of FEV_1 % predicted was achieved with VANTOBRA (6.22 ± 7.36, $p < 0.01$), whereas under TOBI the improvement did not reach statistical significance (4.36 ± 11.12). In the second treatment phase the percentual improvement was 2.13 ± 10.57 under VANTOBRA therapy, whereas under TOBI this parameter decreased by -3.44 ± 6.87%. The calculation over the complete treatment period revealed an overall percentual improvement of FEV_1 % predicted of 8.34 ± 18.39 and 1.18 ± 19.95 for VANTOBRA and TOBI, respectively.

Figure 20 Absolute changes in FEV_1 % predicted (>13 a), normalized to Visit 2 as Baseline



*: p < 0.05; **: p < 0.01; ***: p < 0.001

Explorative statistical tests (Student's paired t-test) have revealed that the treatment effect of both Tobramycin products on FEV_1 % predicted for Treatment 1 in the group "All" was statistically highly significant (see **Table 18**).

Table 18 Treatment effect of VANTOBRA and TOBI on FEV_1 % predicted (p-values, Student's paired t-test; All)

	Treatment 1		Treatment 2	
	T100	**TOBI**	**T100**	**TOBI**
All	<0.0001	0.0132	0.2436	0.78.62
4 – 13 a	0.0059	0.0311	0.39.78	0.2245
>13 a	0.0057	0.1516	0.4490	0.0835

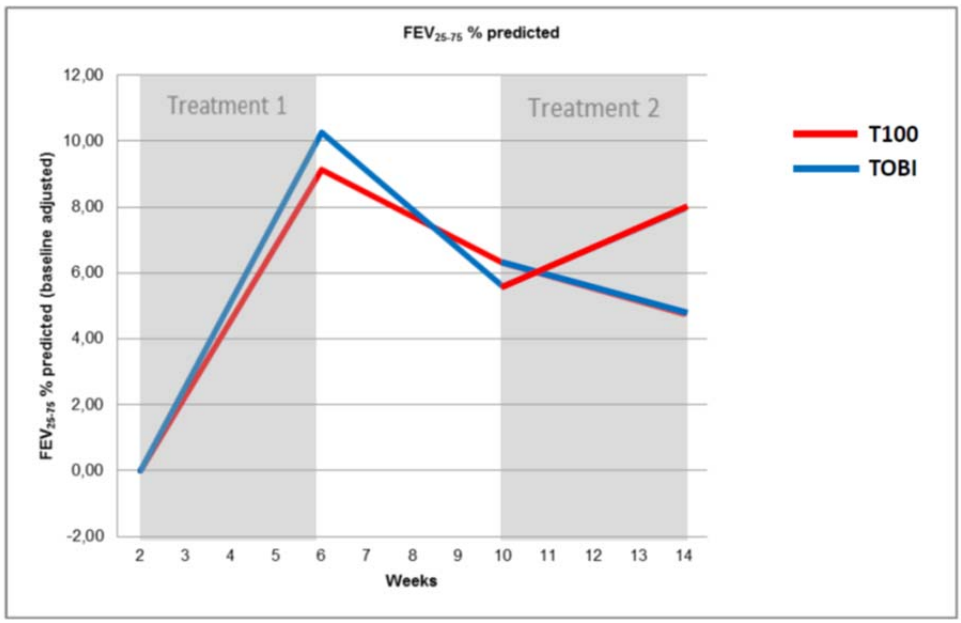
A reasonable explanation for the decrease of lung function in the adolescents/adults subgroup during the second treatment phase may be due to treatment compliance: if TOBI was inhaled in the second treatment cycle the compliance was reduced because of the prior experienced convenience of the more efficient VANTOBRA / eFlow combination during the first treatment period. This effect was not observed in the subgroup of the children (4 – 13 a) because in this age these patients are under close supervision of their parents.

In case the patients were randomized on TOBI / PARI LC PLUS during the first treatment cycle they were naïve regarding the Tobramycin treatment. After experiencing the beneficial effect of the therapy the patients may be more encouraged to continue with permanent inhalation if a more comfortable drug/device system like VANTOBRA / eFlow is applied in the second treatment phase.

The treatment effects of FEV_{25-75} % predicted were very similar for both groups, VANTOBRA and TOBI, in the first treatment period. However, a positive treatment effect was also observed for VANTOBRA in the second treatment phase. **Figure 21** shows the time course of FEV_{25-75} % predicted for the entire group of patients.

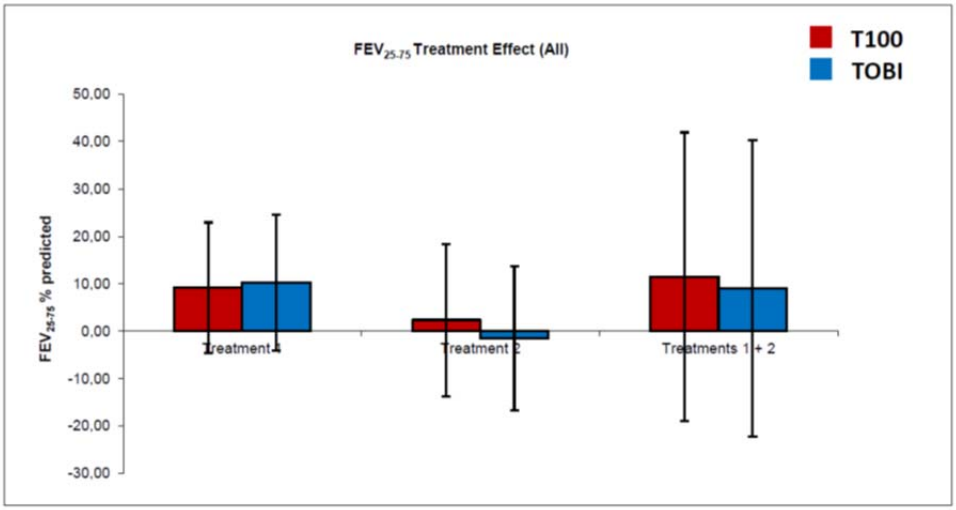
The corresponding Figures and Tables for the age groups are shown in the Statistical Report, **Appendix 16.1.9.2**.

Figure 21 Time course of FEV_{25-75} (All), normalized to Visit 2 as Baseline



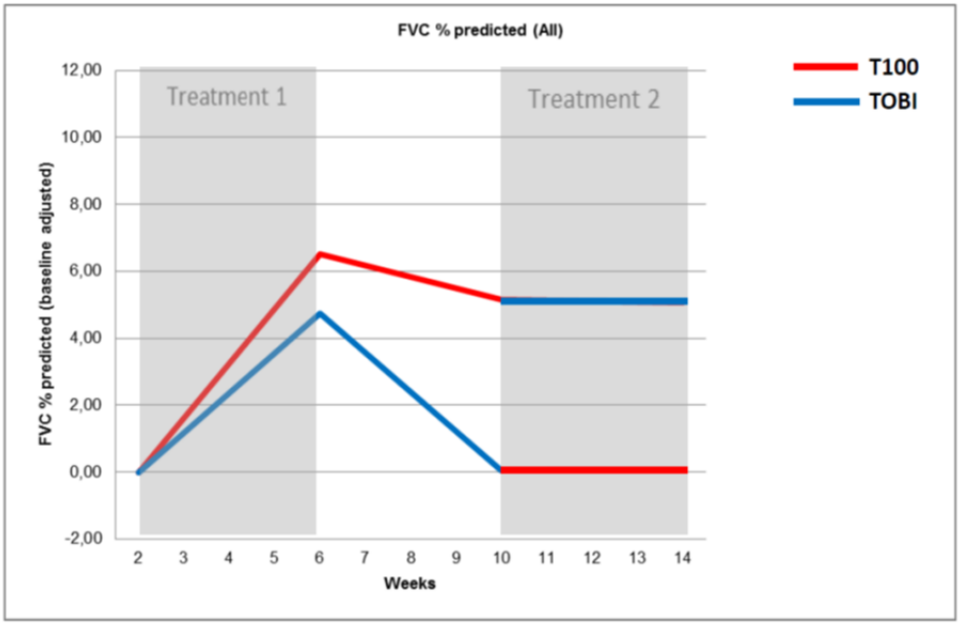
During the first treatment phase a similar percentual increase in FEV_{25-75} % predicted was achieved with VANTOBRA and TOBI (9.15 ± 13.76 vs. 10.28 ± 14.32, respectively), whereas in the second treatment phase a moderate increase of 2.35 ± 16.08 was observed for VANTOBRA, whereas under TOBI this parameter decreased by -1.54 ± 15.20%, respectively. The calculation over the complete treatment period revealed an overall increase in FEV_{25-75} % predicted of 11.50 ± 30.43 and 9.01 ± 31.29 for VANTOBRA and TOBI, respectively (**Figure 22**).

Figure 22 Absolute changes in FEV_{25-75} (All), normalized to Visit 2 as Baseline



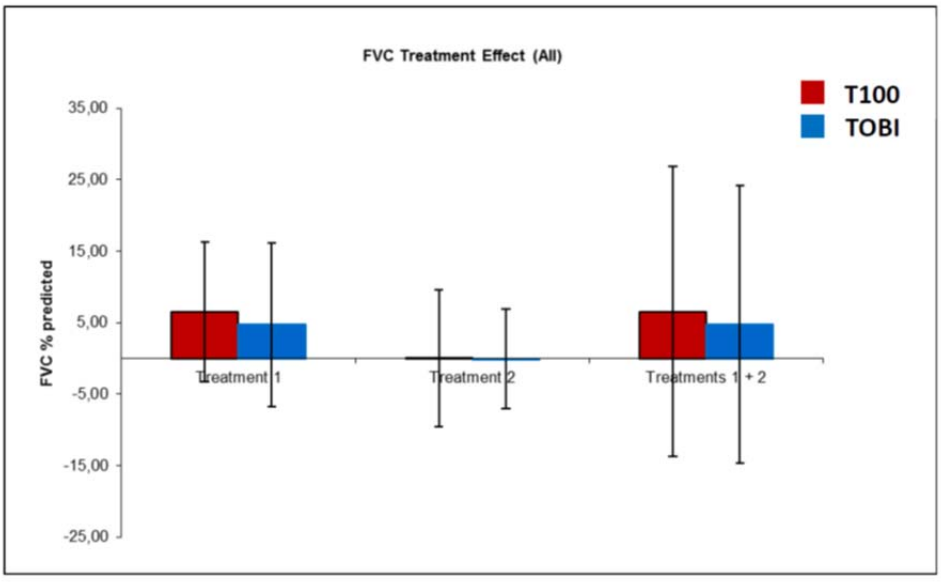
The treatment effects on FVC were comparable between VANTOBRA and TOBI. However, a positive treatment effect was also recognized in patients who received T100 in the second treatment phase, whereas in patients who received TOBI during the second treatment period the positive effect could not be preserved. **Figure 23** shows the time course of FVC % predicted for the entire group of patients. The corresponding Figures and Tables for the age groups are shown in the Statistical Report, **Appendix 16.1.9.2**.

Figure 23 Time course of FVC (All), normalized to Visit 2 as Baseline



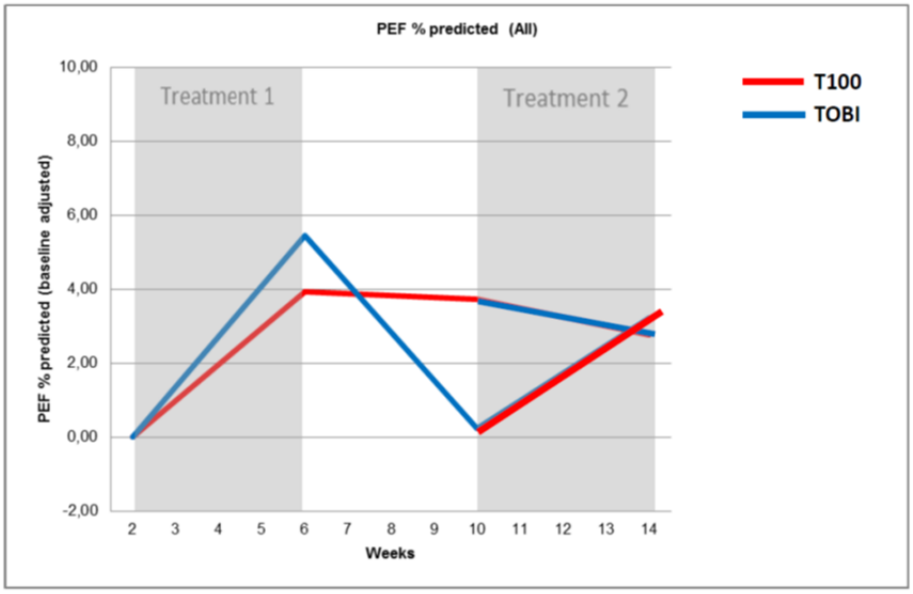
During the first treatment phase a similar percentual increase in FVC was achieved with VANTOBRA and TOBI (6.53 ± 9.78 vs. 4.74 ± 11.45, respectively), in the second treatment phase FVC remained unchanged under either treatment (0.03 ± 9.56 and -0.07 ± 6.99 for VANTOBRA and TOBI, respectively). The calculation over the complete treatment period revealed an overall increase in FVC of 6.56 ± 20.25 and 4.75 ± 19.40 for VANTOBRA and TOBI, respectively (**Figure 24**).

Figure 24 Absolute changes in FVC (All), normalized to Visit 2 as Baseline



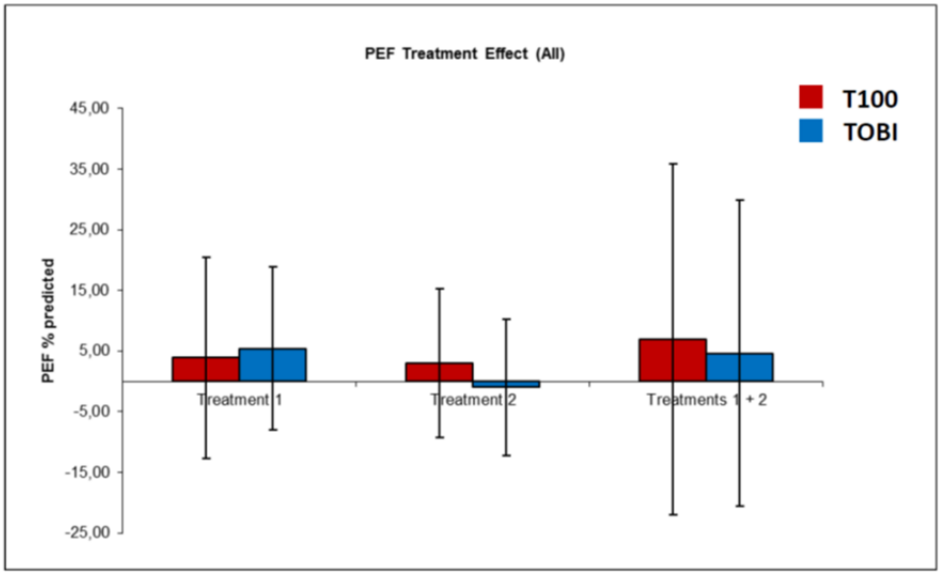
The treatment effects of PEF are not different between the both groups VANTOBRA and TOBI. However, a positive treatment effect was seen in patients who received VANTOBRA in the second treatment phase. **Figure 25** shows the time course of FVC % predicted for the entire group of patients. The corresponding Figures and Tables for the age groups are shown in the Statistical Report, **Appendix 16.1.9.2**.

Figure 25 Time course of PEF (All), normalized to Visit 2 as Baseline



During the first treatment phase a similar percentual increase in PEF was achieved with VANTOBRA and TOBI (3.92 ± 16.60 vs. 5.44 ± 13.41, respectively), in the second treatment phase the change was 3.00 ± 12.30 and -0.95 ± 11.23, respectively. The calculation over the complete treatment period revealed an overall increase in PEF of 6.92 ± 28.96 and 4.65 ± 25.19 for VANTOBRA and TOBI, respectively (**Figure 26**).

Figure 26 Absolute changes in PEF (All), normalized to Visit 2 as Baseline



11.6.3 Clinical Efficacy Conclusions

The analysis of the investigated clinical parameters (CFU and lung function) were consistent with respect to a concomitant improvement of lung function as an function of decreasing PA density:

During the first treatment cycle both drugs provided a similar reduction in density of PA colony forming units. This effect could be repeated when administering VANTOBRA as the second treatment whereas in patients receiving TOBI as second course such an effect was missing.

An improvement in lung function was observed for all lung function parameters investigated and more pronounced in the first than in the second treatment phase for both products. A continuous decline in clinical efficacy is well known also from the treatment with other antibiotics when administered in an on-treatment/off-treatment schedule. Anyhow, under VANTOBRA therapy in the second phase patients were able to reverse the decline in lung function during the wash-out phase, whereas this effect could not be observed under TOBI therapy.

Treatment with both products resulted in a comparable overall clinical efficacy, leading to a reduction of PA density and an improvement of lung function. Accordingly, the available clinical data clearly are indicative for Therapeutic Equivalence of both drug/device systems.

12 SAFETY EVALUATION

The safety evaluation was conducted on the basis of 58 patients, all of whom received at least one dose of the study drugs (safety population).

12.1 Extent of Exposure

The maximum exposure to study drugs was:

- 28 days for VANTOBRA 170 mg twice daily via the eFlow

  and

- 28 days for TOBI 300 mg twice daily via the PARI LC PLUS.

Both treatment phases were separated by a 28-day wash-out period.

A total of 54 patients received both treatments for 28 days each, leading to a cumulative exposure of 56 days to inhaled Tobramycin. Two patients received only VANTOBRA for 28 days and another patient received only TOBI for 28 days. One patient discontinued the TOBI treatment after 3 days.

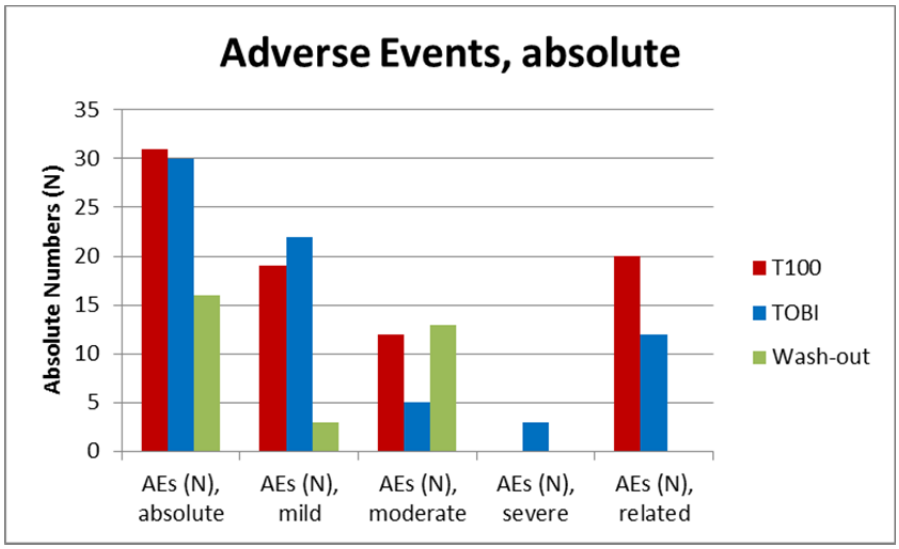
Three patients were hospitalized after Visit 3, i.e. during the wash-out phase, all are identical with those patients reporting (S)AEs (patients 1109, 1205 and 2108). One patient discontinued the TOBI treatment after 3 days because of severe symptoms originated from deterioration of CF (patient 2104).

12.2 Adverse Events (AEs)

Data are presented following accepted guidelines. System Organ Class (SOC) as well as term of the symptom is defined according to LLT following MedDRA Coding (complete MedDRA 15.0 numerical and alpha-coding of all AEs, ARs and SAEs are listed in **Appendix 16.2.7.2**).

Overall, 29 out of the 58 patients (50%) reported a total of 76 events, including AEs, ARs and SAEs (see **Figure 27**).

Figure 27 Adverse Events, absolute Number



Adverse Events (AEs)

Overall, most of the events were considered to be mild (53.9%) or moderate (22.3%) in severity.

In the VANTOBRA treatment phase 25% of the AEs were classified as mild and 15.8% as moderate, whereas the figures for the TOBI treatment phase were 28.9% and 6.6%, respectively. In addition, severe AEs (4.0%; 1 gastrointestinal and 2 respiratory) were only reported under TOBI treatment.

As expected the majority of AEs were seen in the SOC "Respiratory, thoracic and mediastinal disorders" with a frequency of > 10% for both products (**Table 19**, **Figure 28**).

In the TOBI group 1 patient suffering from 4 events with elevated clinical laboratory parameters contributed to the 8% in the SOC "Investigations".

Figure 28 Adverse Events according to SOC

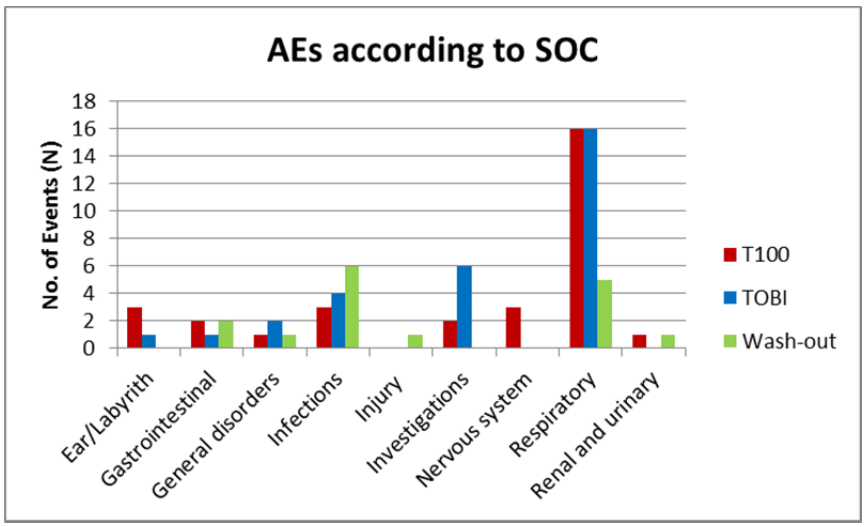


Table 19 Adverse Events by Severity and Treatment phase (All)

SOC	T100						TOBI						WASH-OUT						ALL					
	Mild		moderate		severe		mild		moderate		severe		mild		moderate		severe		mild		moderate		severe	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
General disorders and administration site conditions	**0**		**1**	*1.3*	**0**		**1**	*1.3*	**1**	*1.3*	**0**		**0**		**1**	*1.3*	**0**		**1**	*1.3*	**2**	*2.6*	**0**	
Infections and manifestations	**3**	*4.0*	**0**		**0**		**2**	*2.6*	**2**	*2.6*	**0**		**2**	*2.6*	**4**	*5.3*	**0**		**7**	*9.2*	**6**	*7.9*	**0**	
Respiratory, thoracic and mediastinal disorders	**10**	*13.1*	**6**	*7.9*	**0**		**12**	*15.8*	**2**	*2.6*	**2**	*2.6*	**0**		**5**	*6.6*	**0**		**22**	*28.9*	**13**	*17.1*	**2**	*2.6*
Ear and labyrinth disorders	**2**	*2.6*	**1**	*1.3*	**0**		**1**	*1.3*	**0**		**0**		**0**		**0**		**0**		**4**	*5.3*	**0**		**0**	
Gastrointestinal disorders	**0**	*0*	**2**	*2.6*	**0**		**0**		**0**		**1**	*1.3*	**1**	*1.3*	**1**	*1.3*	**0**		**1**	*1.3*	**3**	*4.0*	**1**	*1.3*
Renal and urinary disorders	**1**	*1.3*	**0**		**0**		**0**		**0**		**0**		**0**		**1**	*1.3*	**0**		**1**	*1.3*	**1**	*1.3*	**0**	
Nervous system disorders	**1**	*1.3*	**2**	*2.6*	**0**		**0**		**0**		**0**		**0**		**0**		**0**		**1**	*1.3*	**2**	*2.6*	**0**	
Injury, poisoning and procedural complications	**0**		**0**		**0**		**0**		**0**		**0**		**0**		**1**	*1.3*	**0**		**0**		**1**	*1.3*	**0**	
Investigations	**2**	*2.6*	**0**		**0**		**6**	*7.9*	**0**		**0**		**0**		**0**		**0**		**8**	*10.5*	**0**		**0**	
Total	**19**	***25***	**12**	***15.8***	**0**		**22**	***28.9***	**5**	***6.6***	**3**	***4.0***	**3**	***4.0***	**13**	***17.1***	**0**		**45**	***59.2***	**28**	***36.8***	**3**	***4.0***

In the age stratum 4-13 years AEs were reported twice as frequent as in the stratum group > 13 years (40 vs. 19 events). However, the distribution within the SOCs was similar (**Figure 28; Table 20**).

Table 20 Adverse Events by Age Groups

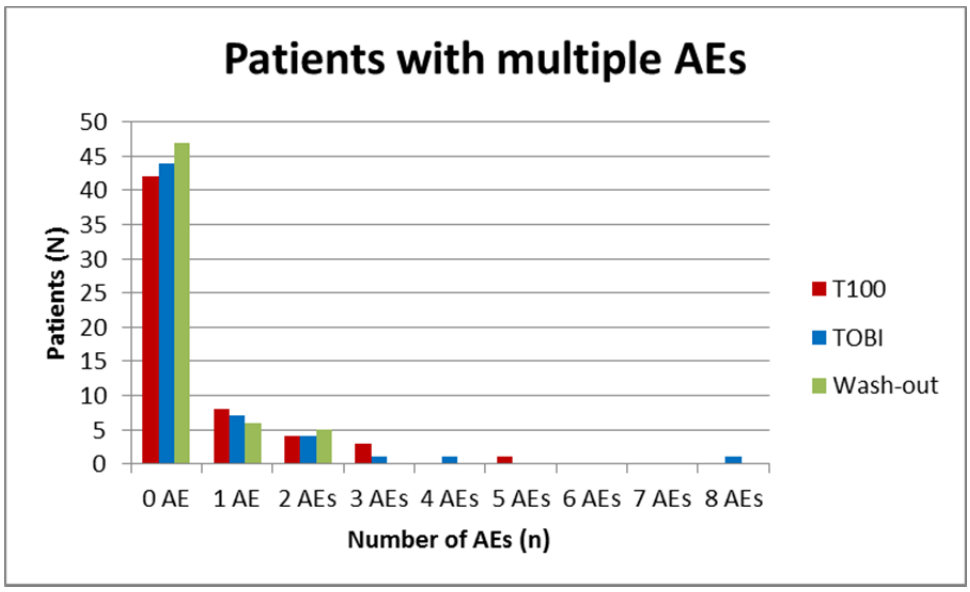
	Age Group 4-13 a									
Class LLT	Mild			Moderate			Severe			Total (N = 40)
	N (%)			N (%)			N (%)			N (%)
	T100 or TOBI	not related	related	T100 or TOBI	not related	related	T100 or TOBI	not related	related	
General disorders and administration site conditions	TOBI		1 (2.5)	TOBI T100	1 (2.5) 1 (2.5)					TOBI: 2 (5) T100: 1 (2.5)
Gastrointestinal disorders				T100	1 (2.5)					T100: 1 (2.5)
Infections and manifestations	T100 TOBI	2 (5) 2 (5)		TOBI	2 (5)					T100: 2 (5) TOBI: 4 (7.5)
Respiratory, thoracic and mediastinal disorders	T100 TOBI	1 (2.5) 4 (10)	6 (15) 6 (15)	T100	1 (2.5)	3 (7.5)	TOBI	2 (5)		T100: 8 (20) TOBI: 12 (27.5)
Ear and labyrinth disorders	T100 TOBI		2 (5) 1 (2.5)	T100		1 (2.5)				T100: 3 (7.5) TOBI: 1 (2.5)
Nervous system disorders				T100	1 (2.5)	1 (2.5)				T100: 2 (5)
Investigations	TOBI	4 (10)								TOBI: 4 (10)

	Age Group > 13 a									
Class LLT	Mild			Moderate			Severe			Total (N = 19)
	N (%)			N (%)			N (%)			N (%)
	T100 or TOBI	not related	related	T100 or TOBI	not related	related	T100 or TOBI	not related	related	
Gastrointestinal disorders				T100	1 (5)		TOBI	1 (5)		T100: 1 (5) TOBI: 1 (5)
Infections and manifestations	T100	1 (5)								T100: 1 (5)
Respiratory, thoracic and mediastinal disorders	T100 TOBI	 1 (5)	3 (15) 1 (5)	T100 TOBI		2 (10) 2 (10)				T100: 5 (25) TOBI: 4 (22)
Renal and urinary disorders	T100	1 (5)								T100: 1 (5)
Nervous system disorders	T100		1 (5)							T100: 1 (5) TOBI: 1 (5)
Investigations	T100 TOBI	1 (5) 2 (10)	1 (5)							T100: 2 (10) TOBI: 2 (10)

In general the study was characterized by a low overall AE / patient ratio of 0.52.

An analysis separated for treatment phases revealed that only 3 patients experienced multiple episodes of AEs (1 VANTOBRA patient with 5 AEs and 2 TOBI patients with 4 and 8 AEs each; see also **Figure 29**).

Figure 29 Patients with Multiple Adverse Events



The 5 SAEs due to hospitalisation reported for 4 patients (patients 1106, 1109, 1205 and 2108) are listed in **Table 21**; none of the 5 SAEs were considered to be in causal relationship to VANTOBRA or TOBI by the investigator. For an overview of those SAEs see **Table 22**; for narratives of the SAEs please refer to **Section 14.3.3** of this report.

A detailed patient-by-patient presentation of documented AEs and adverse reactions (AR) is provided in **Appendix 16.2.7.1**.

Adverse Reactions (AR)

Overall, 42.1% of AEs were considered to be in causal relationship to an investigational product.

A relationship was assessed in 26.3% of the AEs for VANTOBRA and in 15.8% for TOBI.

As expected the majority of ARs were seen in the SOC “Respiratory, thoracic and mediastinal disorders” with a frequency of >10% for both products.

The total number of AEs in this SOC was equal in both treatment groups, anyhow cough and hoarseness was attributed with higher frequency to VANTOBRA.

In both age strata the distribution of ARs was comparable. The assignment of ARs to VANTOBRA or TOBI is shown in **Table 21**.

Table 21 Adverse Events by Relationship and Treatment Phase (All)

SOC	T100				TOBI				WASH-OUT				ALL			
	related		not related		related		not related		related		not related		related		not related	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
General disorders and administration site conditions			**1**	*1.3*	**1**	*1.3*	**1**	*1.3*			**1**	*1.3*	**1**	*1.3*	**3**	*4*
Infections and manifestations			**3**	*4*			**4**	*5.3*			**5**	*6.6*			**12**	*15.8*
Respiratory, thoracic and mediastinal Disorders	**14**	*18.4*	**2**	*2.6*	**10**	*13.2*	**6**	*7.9*			**5**	*6.6*	**24**	*31.6*	**13**	*17.1*
Ear and labyrinth disorders	**3**	*4*			**1**	*1.3*							**4**	*5.3*		
Gastrointestinal disorders			**2**	*2.6*			**1**	*1.3*			**3**	*4*			**6**	*7.9*
Renal and urinary Disorders			**1**	*1.3*							**1**	*1.3*			**2**	*2.6*
Nervous system Disorders	**2**	*2.6*	**1**	*1.3*									**2**	*2.6*	**1**	*1.3*
Injury, poisoning and procedural Complications											**1**	*1.3*			**1**	*1.3*
Investigations	**1**	*1.3*	**1**	*1.3*			**6**	*7.9*					**1**	*1.3*	**7**	*9.2*
Total	**20**	*26.3*	**11**	*14.5*	**12**	*15.8*	**18**	*23.7*			**16**	*21.1*	**32**	*42.1*	**44**	*57.9*

A detailed patient-by-patient presentation of documented AEs and adverse reactions (AR) is provided in **Appendix 16.2.7.1**.

Serious Adverse Events (SAEs)

Overall, 5 SAEs in 4 patients (patients 1106, 1109, 1205 and 2108) were reported (see **Table 22**). Reason for categorizing these events as serious was hospitalisation.

None of the 5 SAEs were considered to be in causal relationship to VANTOBRA or TOBI by the investigator.

All events occurred during the wash-out phase between the both treatment periods.

Three patients were withdrawn from study participation due to medical requirement of prohibited antibiotic medication. The patient with the humerus fracture continued participation.

Table 22 Listing of Serious Adverse Events

PATIENT	SEX	BIRTH_DATE	EVENT_TERM	LLT_NAME	PT_NAME	AE_ONSET	AE_STOP	CAUSALITY	SOC_NAME
2108	M	22.07.2004	Bacterial otitis media	Otitis media bacterial	Otitis media bacterial	08.12.2011	21.12.2011	NOT RELATED	Infections and infestations
			Mastoiditis	Mastoiditis	Mastoiditis	09.12.2011	21.12.2011	NOT RELATED	Infections and infestations
1205	M	20.12.1992	Pulmonary haemorrhage	Pulmonary haemorrhage	Pulmonary haemorrhage	26.09.2011	03.10.2011	NOT RELATED	Respiratory, thoracic and mediastinal disorders
1106	M	31.12.2000	Supracondylar fracture of the left humerus	Humerus fracture	Humerus fracture	06.10.2011	24.11.2011	NOT RELATED	Injury, poisoning and procedural complications
1109	M	07.11.1998	Cystic fibrosis pulmonary exacerbation	Cystic fibrosis pulmonary exacerbation	Infective pulmonary exacerbation of cystic fibrosis	15.11.2011	30.11.2011	NOT RELATED	Infections and infestations

M: Male; LLT: Lowest Level Term; PT: Preferred Term; SOC: System Organ Class

Serious Adverse Reactions

No SARs occurred in the study 12012.101.

12.3 List of Deaths, Other Serious Events and Other Significant Adverse Events

No deaths occurred during the study; 5 SAEs were reported, all of them categorized as serious because of hospitalisation (**Table 22**). No other significant AEs were reported by the patients or their parents.

12.4 Narratives of Serious Adverse Events

The narratives of the patients with SAEs as reported by the investigators are presented in **Section 14.3.3**.

12.5 Clinical Laboratory Evaluations

12.5.1 List of Individual Laboratory Measurements by Patient and each Abnormal Laboratory Value

None of the randomized patients had any laboratory values significantly outside the reference range that precluded study entry.

Only one of the randomized patients (2104) showed clinically significant changes in laboratory values outside the reference range in the Treatment Phase 1 (TOBI). This patient discontinued the TOBI treatment after 3 days because of severe symptoms originated from deterioration of CF.

Individual clinical laboratory evaluations obtained at screening (Visit 1), at pre- and post-drug at each of the treatment periods, and at the End-of-Study visit (Visit 6) are provided in **Appendix 16.2.10**. Abnormal laboratory values are provided in **Tables 41-89**.

As nephrotoxicity is a well-known adverse class effect of systemic administration of Tobramcyin the mean serum levels of creatinine (**Figure 30**) and BUN (**Figure 31**) are presented here as representative for the other analysed laboratory parameters (see **Appendix 16.2.10**).

Figure 30 Mean Creatinine Values over Treatment Period

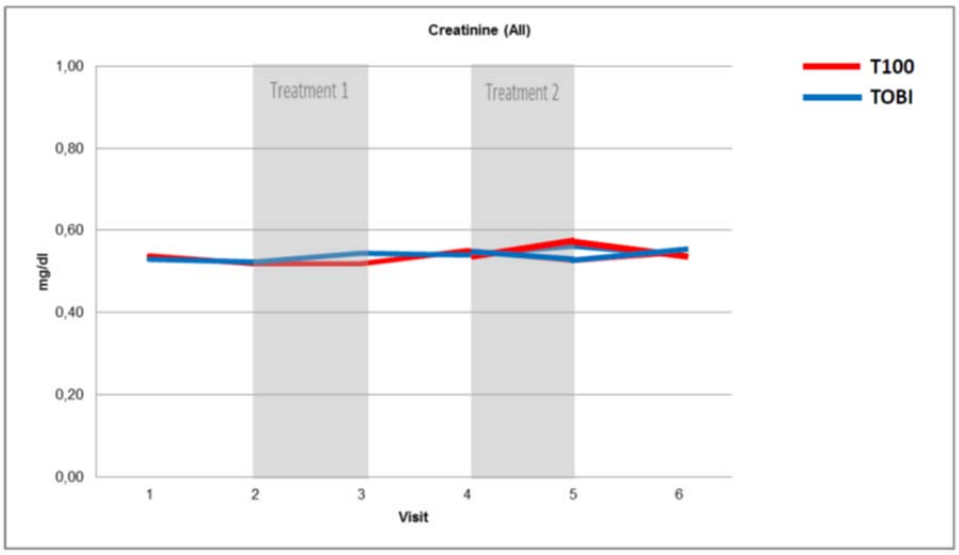
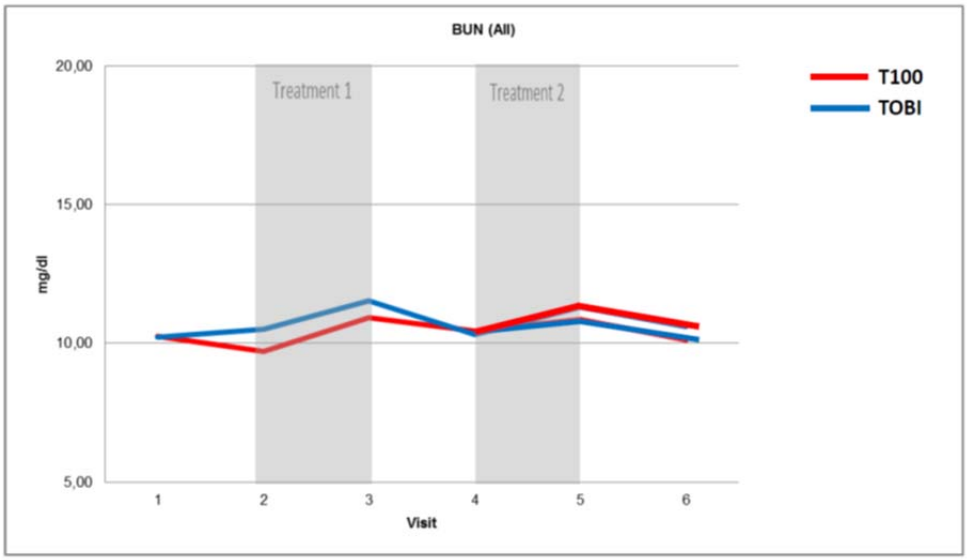


Figure 31 Mean BUN Values over Treatment Period



The same picture was found for all the other laboratory parameters: None of the parameters showed significant or clinically relevant changes from baseline (**Appendix 16.2.10**).

12.6 Vital Signs, Physical Examination Findings and other Observations related to Safety

There were no clinically significant changes in vital signs or physical signs. Average values pre- vs. post-study changes in vital signs are provided in **Section 14**, **Tables 90-95**. Individual values are provided in **Listing 16.2.7.3** in the Appendix.

By-patient pre- vs. post-study changes in physical examinations are provided in **Listing 16.2.7.1** in the Appendix. Data on chest X-ray are provided in **Listing 16.2.7.2.** There was no unusual finding.

12.7 Number of Bronchospasms

Bronchospasms within 30 min after the end of inhalation occurred only in two patients: patient 3210 at Visit 5 and patient 4103 at Visit 3. Both patients were under TOBI treatment at that visits; both events were considered to be possibly related to TOBI by the investigator. Thus, the percentage of patients with bronchospasms is approximately 3.4 % (data derived from **Appendix, 16.2.6.3)**.

12.8 Audiology

Audiology testing revealed two cases of tinnitus in patients under VANTOBRA treatment (3.4% of all patients; see **Table 23**). Both cases were mild in severity and transient as resolving shortly after inhalation. One patient in the VANTOBRA group showed pathological signs in pure tone audiometry measured by bone connectivity (highest value for left ear at 2 KHz was 35 dB).

Table 23 Audiology

	Visit 1		**Visit 2**		**Visit 3**		**Visit 4**		**Visit 5**		**Visit 6**	
	Tinnitus	Path. signs	Tinnitus	Path. signs	Tinnitus	Path. signs	Tinnitus	Path. signs	Tinnitus	Path. signs	Tinnitus	Path. signs
T100	0	0	0	0	1	1*	0	0	1	0	0	0
TOBI	0	0	0	0	0	0	0	0	0	0	0	0

* highest value for left ear at 2 KHz was 35 dB

12.9 Pulmonary Exacerbation

Pulmonary exacerbation was observed in one patient (1109) only during the wash-out phase after TOBI treatment. This patient required treatment with antibiotics which were prohibited as per study protocol and thus was withdrawn from further study participation.

12.10 Resistance of *P. aeruginosa*

Investigations on the occurrence of resistant PA revealed only inconclusive results as cultures of sputum samples showed no growth of the pathogen in approx. half of the assays (**Table 24**). Therefore, it was not possible to determine the development of resistance of this pathogen on a patient basis.

Table 24 Resistance of *P. aeruginosa*

		T100			**TOBI**	
	N*	**MIC < 4 µg/ml**	**MIC > 4 µg/ml**	**N***	**MIC < 4 µg/ml**	**MIC > 4 µg/ml**
Visit 2	28	13/23 (**57%**)	10/23 (**43%**)	30	21/25 (**84%**)	4/25 (**16%**)
Visit 3	28	9/18 (**50%**)	9/18 (**50%**)	30	12/17 (**71%**)	5/17 (**29%**)
Visit 4	30	14/22 (**64%**)	8/22 (**36%**)	28	9/17 (**53%**)	8/17 (**47%**)
Visit 5	30	14/18 (**78%**)	4/18 (**22%**)	28	7/18 (**39%**)	11/18 (**61%**)

*Data not available for all patients (see **Appendix 16.2.4.8**). MIC: Minimal Inhibitory Concentration.

12.11 Safety Conclusion

In summary, the following conclusion on the safety results can be drawn:

There are no significant or unexpected safety problems associated with the inhalation of Tobramycin; 32 AEs were related to Tobramycin (42.1 % ARs of a total of 76 AEs). All ARs were of mild to moderate intensity.

Regarding the SAEs, in all cases the reason for seriousness was hospitalisation; none of the 5 reported SAEs were related to the study drug.

There were no relevant safety findings as indicated by physical examinations, vital signs measurements, number of bronchospasms, and clinical laboratory evaluations. All laboratory values numerically outside the reference range were not clinically significant, except for one patient who stopped the treatment (2104).

The study provided no evidence that patients were posed on risk for Tobramycin in neither of the two treatment arms. Thus, treatment with VANTOBRA and TOBI can be regarded as comparable with respect to the products' safety profile.

12.12 CFQ-R

The analysis of the CFQ-R revealed only inconclusive results. Neither relevant differences nor even trends were found between treatment groups or age strata. For patient individual data see **Appendix 16.2.13**.

12.13 Inhalation Time

The time per inhalation was impressively reduced in the drug/device combination of VANTOBRA / eFlow (mean: 4.4 min) as compared to the combination TOBI / PARI LC PLUS (mean: 24.3 min; see **Tables 25 and 26**).

This result confirms the good performance and high efficiency of the newly developed drug/device combination of VANTOBRA / eFlow.

Table 25 Mean Nebulisation Times (± SD) for VANTOBRA / eFlow

Patients	Number of Patients (N)	Mean Nebulisation Times (min)	SD (min)	Range min – max (min)
All	54	**4.4**	± 1.2	3.1 – 13.2
> 13 years	28	**4.5**	± 1.3	3.1 – 13.3
4 - 13 years	26	**4.3**	± 1.2	3.2 – 7.1

For patient-individual data see **Appendix 16.2.12**.

Table 26 Nebulisation Times for TOBI / PARI LC PLUS (mean and range)

Patient Group	Number of Patients (N)	Mean [min]	Range min – max [min]
All	31	**24.3**	15 – 34.6
> 13 years	12	**26.3**	15 – 34.6
4 - 13 years	19	**23**	16 – 28

For patient-individual data see **Appendix 16.2.12**.

12.14 Treatment Compliance

Compliance to therapy of the patients was generally high in both groups with 99% for VANTOBRA patients (based on an electronic Monitoring System of the device) and 99% for TOBI patients (based on records in patient diaries). Generally, the reliability in completion of the diaries was higher in the age stratum 4 – 13 years than in the age group > 13 years. For patient-individual data see **Appendix 16.2.5**.

13 DISCUSSION AND OVERALL CONCLUSIONS

In summary, the following conclusions on the PK results can be drawn:

A total of 54 patients suffering from CF and chronic PA infection received Tobramycin, both as VANTOBRA (170 mg/1.7 ml) and TOBI (300 mg/5 ml) per inhalation in a cross-over design.

Three randomised patients completed one treatment period only; one patient discontinued after only 3 days of TOBI treatment. Five further patients were excluded from the PK analyses because of insufficient data (see **Table 6** and **Figure 2** Disposition of Patients). Thus, the remaining PP population for the PK analysis was N=49.

Plasma and sputum concentrations of Tobramycin were measured using a validated LC-MS/MS method. The relationship between concentrations *versus* peak area ratios was found to be linear from 100 pg/ml to 50.000 pg/ml for both compounds. The limit of quantification was 30 ng/ml for the analyte.

The plasma concentrations of Tobramycin, and even more the sputum concentrations, showed extremly high inter- and intra-individual variability.

Not only VANTOBRA was characterized by high coefficients of variation but also the reference product TOBI. Beyond that, even PK data of i.v. Tobramycin administration resulted in similar high coefficients of variation.

The problems of the investigation of Tobramycin pharmacokinetics originate mainly from three factors:

- The CF disease status exerts a significant impact on the properties of mucus (viscous, aqueous, central/peripheral, surface covering), lung morphology, inflammation/exercerbation, hydration status of the patient, severity of the disease).
- The efficiency of inhalation, and thus the drug deposition in the lung, depends on the breathing pattern of patients
- The different efficiency of the devices
- Tobramycin PK values resulted also in a high coefficient of variation even when administered intravenously, although eliminating one parameter (inhalation) which mainly contributes to an increased variability.

Regarding CF it has to be considered that the properties of mucus (viscous, aqueous, central/peripheral, surface covering), lung morphology, inflammation/exercerbation, hydration status of the patient, and severity of the disease are influencing the resorption of Tobramycin from the lung into the systemic circulation.

The determination of drug levels in sputum is even more subjected to variation due to inhomogenous drug distribution in the lung resulting in locally different drug concentrations as well as the patient-individual capability to produce sputum.

Another disturbing factor is the inhalation behavior of CF patients, especially children, who hardly can be trained for a standardized breathing pattern.

In summary it could be concluded that for the extent of absorption (plasma AUC) and the rate of absorption (plasma C_{max}) the confidence intervals exceed the lower acceptance limit for the analysis of all patients as well as for the group separated analysis.

Considering the impact of these disruptive factors for the PK-analysis of a substance with well-known challenging pharmacokinetic properties and the rigid formalities of statistical calculations it may be justified to postulate at least a comparability and similarity of VANTOBRA and TOBI pharmacokinetics.

This conclusion is underlined by the observation that the point estimator resides within the accepted corridor, as does the UCL.

Finally, this part of the study demonstrated again, that CF patients cannot be regarded as a suitable model for PK-assessment of inhaled antibiotics.

In summary, the following conclusions on the clinical efficacy results can be drawn:

The analysis of the investigated clinical parameters (CFU and lung function) were consistent with respect to a concomitant improvement of lung function as an function of decreasing PA density:

During the first treatment cycle both drugs provided a similar reduction in density of PA colony forming units. This effect could be repeated when administering VANTOBRA as the second treatment whereas in patients receiving TOBI as second course such an effect was missing.

An improvement in lung function was observed for all lung function parameters investigated and more pronounced in the first than in the second treatment phase for both products. A continuous decline in clinical efficacy is well known also from the treatment with other antibiotics when administered in an on-treatment/off-treatment schedule. Anyhow, under VANTOBRA therapy in the second phase patients were able to reverse the decline in lung function during the wash-out phase, whereas this effect could not be observed under TOBI therapy.

Treatment with both products resulted in a comparable overall clinical efficacy, leading to a reduction of PA density and an improvement of lung function. The treatment effects are indicative for Therapeutic Equivalence.

In summary, the following conclusion on safety results can be drawn:

There are no significant or unexpected safety problems associated with the inhalation of Tobramycin; 32 AEs were related to Tobramycin (42.1 % ARs of a total of 76 AEs). All of the ARs were of mild to moderate intensity.

In all cases the reason for seriousness of 5 SAEs was hospitalisation; none of the 5 reported SAEs were related to the study drug.

There were no relevant safety findings as indicated by physical examinations, vital signs measurements, number of bronchospasms, audiometry, bronchospasms and clinical laboratory evaluations. All laboratory values numerically outside the reference range were not clinically significant, except one patient who stopped the treatment (2104).

The study provided no evidence that patients were posed on risk for Tobramycin in neither of the two treatment arms. Thus, treatment with VANTOBRA and TOBI can be regarded as comparable with respect to the products' safety profile.

Despite the fact that the primary endpoint (plasma AUC) was failed for formal reasons, the study provided evidence that the pharmacokinetic properties of VANTOBRA administered via the eFlow and TOBI administered via the PARI LC PLUS are comparable. Although the LCL for plasma AUC and plasma C_{max} of VANTOBRA were outside the accepted ranges, both, the point estimator and the UCL, resided well inside these corridors. The fall below limit of the LCL is explained with the high inter-individual patient variations, which was also recognised for the reference product TOBI. Thus, the study disclosed impressively the difficulties of PK-investigations with inhaled antibiotics in cystic fibrosis patients.

In this situation, clinical efficacy and safety must not be neglected:

Both products demonstrated efficacy for the anticipated target parameter "Reduction of PA density", which can be translated into improvement of lung function. For all individual parameters analysed VANTOBRA showed similar, if not even better results as TOBI.

Taking all together, Therapeutic Equivalence can be postulated for both antibiotic products.

Beyond that, the study has shown again a remarkably shorter inhalation time with the new VANTOBRA administered via the eFlow (only approximately 4 min) in contrast to TOBI administered via the PARI LC PLUS (approximately 24 min). This reduction in inhalation time of twice 20 min daily doses enhance the patients' compliance and as a consequence the therapeutic efficacy and safety.

14 TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Demographic Data Summary and Baseline Conditions

Table 27 Demographic Data

Enrolment No.	Date of birth	Treatment order	Patient is of age	Age	Gender	Height	Weight	Ethnic Origin	
	dd.mmm.yyyy					cm	kg		if "other"
1101	13. Dec. 1999	R, T	4-13	11	male	141	28.5	caucasian	
1102	13. Feb. 1999	T, R	4-13	12	male	153	44.4	caucasian	
1103	01. Jan. 2000	T, R	4-13	11	female	159	44.5	caucasian	
1104	09. Sep. 1999	R, T	4-13	11	female	145	33.5	caucasian	
1105	14. Mar. 2002	T, R	4-13	9	male	129	25.6	caucasian	
1106	31. Dec. 2000	R, T	4-13	10	male	142	29.5	caucasian	
1107	29. Sep. 2003	T, R	4-13	7	male	131	26.0	caucasian	
1108	21. Sep. 2002	R, T	4-13	9	female	126	22.0	caucasian	
1109	07. Nov. 1998	R	4-13	12	male	151	36.6	caucasian	
1110	09. Aug. 2004	T, R	4-13	7	male	131	27.0	caucasian	
1111	05. May 2003	T, R	4-13	8	female	127	31.6	caucasian	
1112	18. May 2002	R, T	4-13	9	female	138	31.5	caucasian	
1113	20. Mar. 2000	T, R	4-13	11	female	156	47.3	caucasian	
1114	10. Nov. 2003	R, T	4-13	8	male	120	22.4	caucasian	
2101	27. Jun. 1997	R, T	4-13	13	male	164	47.0	caucasian	
2102	21. Apr. 2000	T, R	4-13	11	female	146	30.0	caucasian	
2103	23. Oct. 1999	T, R	4-13	12	female	154	39.0	caucasian	
2104	09. Sep. 1998	R	4-13	12	female	156	52.0	caucasian	
2105	27. Nov. 2000	R, T	4-13	10	male	146	30.0	caucasian	
2106	23. Dec. 2000	T, R	4-13	10	female	124	21.0	caucasian	
2107	26. Jan. 2000	R, T	4-13	11	male	152	34.6	caucasian	
2108	22. Jul. 2004	T	4-13	7	male	119	19.5	caucasian	
3101	09. Dec. 2003	R, T	4-13	7	male	125	20.0	caucasian	
3102	15. Oct. 2001	T, R	4-13	9	male	139	38.0	caucasian	
3103	20. Oct. 2000	R, T	4-13	10	female	143	40.0	caucasian	
4101	15. Dec. 1998	T, R	4-13	12	female	145	36.0	caucasian	
4102	23. Jan. 2004	R, T	4-13	7	female	113	15.0	caucasian	
4106	14. Dec. 2000	R, T	4-13	10	male	139	25.0	caucasian	
1201	04. May 1995	R, T	>13	16	male	167	59.4	caucasian	
1202	31. Mar. 1996	T, R	>13	15	female	163	55.5	caucasian	
1203	19. Apr. 1992	R, T	>13	19	female	155	38.7	caucasian	
1204	24. Jun. 1993	T, R	>13	17	female	162	49.5	caucasian	
1205	20. Dec. 1992	T	>13	18	male	182	62.5	caucasian	
1206	20. Dec. 1992	R, T	>13	18	male	157	48.5	caucasian	
1207	02. Feb. 1995	T, R	>13	16	male	168	62.4	caucasian	
1208	12. Sep. 1997	R, T	>13	13	female	157	42.7	caucasian	
2201	10. Feb. 1989	T, R	>13	22	female	156	53.0	caucasian	
2202	27. Jul. 1991	R, T	>13	19	female	169	55.0	caucasian	
2203	25. Sep. 1994	R, T	>13	16	female	158	50.0	caucasian	
2204	16. Feb. 1989	T, R	>13	22	female	169	52.0	caucasian	
2205	27. Dec. 1994	R, T	>13	16	female	151	40.0	caucasian	
2206	28. May 1989	T, R	>13	22	female	160	57.0	caucasian	
3201	26. Apr. 1975	R, T	>13	36	female	168	62.0	caucasian	
3202	06. Mar. 1990	T, R	>13	21	female	169	51.0	caucasian	
3203	04. Jun. 1996	T, R	>13	14	female	161	51.0	caucasian	
3204	22. May 1996	R, T	>13	15	female	168	50.0	caucasian	
3205	10. Mar. 1984	T, R	>13	27	male	173	65.0	caucasian	
3206	17. Apr. 1993	R, T	>13	18	male	174	66.0	caucasian	
3207	15. Oct. 1987	T, R	>13	23	female	163	50.0	caucasian	
3208	21. Apr. 1978	R, T	>13	33	male	169	72.0	caucasian	
3209	14. Sep. 1990	R, T	>13	20	male	169	61.0	caucasian	
3210	13. Nov. 1988	T, R	>13	22	male	171	48.0	caucasian	
4103	01. Sep. 1983	R, T	>13	27	female	173	59.0	caucasian	
4104	09. Dec. 1983	T, R	>13	27	female	166	53.0	caucasian	
4105	26. Nov. 1985	T, R	>13	25	male	165	50.0	caucasian	
4204	03. Jun. 1993	R, T	>13	18	female	163	53.0	caucasian	
4205	05. Jul. 1985	R, T	>13	26	female	155	48.0	caucasian	
4206	06. Dec. 1993	T, R	>13	17	female	158	46.0	caucasian	
Age Group 4-13		**N**				**28**	**28**		
		Arithmetic mean				**139.8**	**32.1**		
		SD (±)				**13.50**	**9.52**		
		Minimum				**113**	**15.0**		
		Maximum				**164**	**52.0**		
Age Group >13		**N**				**30**	**30**		
		Arithmetic mean				**164.6**	**53.7**		
		SD (±)				**6.97**	**7.75**		
		Minimum				**151**	**38.7**		
		Maximum				**182**	**72.0**		
All		**N**				**58**	**58**		
		Arithmetic mean				**152.6**	**43.3**		
		SD (±)				**16.37**	**13.88**		
		Minimum				**113**	**15.0**		
		Maximum				**182**	**72.0**		

Table 28 Patients included in the Study

Enrolment No.	Date of birth	Treatment order	Date of informed consent	Was patient randomised?		Randomisation number assigned
	dd.mmm.yyyy		dd.mmm.yyyy		if yes dd.mmm.yyyy	
1101	13. Dec. 1999	R, T	26. May 2011	yes	02. Jun. 2011	1101
1102	13. Feb. 1999	T, R	26. May 2011	yes	02. Jun. 2011	1102
1103	01. Jan. 2000	T, R	27. Jun. 2011	yes	05. Jul. 2011	1103
1104	09. Sep. 1999	R, T	28. Jun. 2011	yes	05. Jul. 2011	1104
1105	14. Mar. 2002	T, R	28. Jun. 2011	yes	05. Jul. 2011	1105
1106	31. Dec. 2000	R, T	26. Aug. 2011	yes	02. Sep. 2011	1106
1107	29. Sep. 2003	T, R	28. Sep. 2011	yes	05. Oct. 2011	1107
1108	21. Sep. 2002	R, T	28. Sep. 2011	yes	05. Oct. 2011	1108
1109	07. Nov. 1998	R	28. Sep. 2011	yes	05. Oct. 2011	1109
1110	09. Aug. 2004	T, R	02. Nov. 2011	yes	09. Nov. 2011	1110
1111	05. May 2003	T, R	16. Nov. 2011	yes	23. Nov. 2011	1111
1112	18. May 2002	R, T	02. Nov. 2011	yes	09. Nov. 2011	1112
1113	20. Mar. 2000	T, R	16. Nov. 2011	yes	23. Nov. 2011	1113
1114	10. Nov. 2003	R, T	30. Nov. 2011	yes	07. Dec. 2011	1114
2101	27. Jun. 1997	R, T	16. Jun. 2011	yes	22. Jun. 2011	2101
2102	21. Apr. 2000	T, R	16. Jun. 2011	yes	22. Jun. 2011	2102
2103	23. Oct. 1999	T, R	16. Jun. 2011	yes	22. Jun. 2011	2103
2104	09. Sep. 1998	R	25. May 2011	yes	01. Jun. 2011	2104
2105	27. Nov. 2000	R, T	22. Jul. 2011	yes	29. Jul. 2011	2105
2106	23. Dec. 2000	T, R	05. Aug. 2011	yes	12. Aug. 2011	2106
2107	26. Jan. 2000	R, T	13. Oct. 2011	yes	20. Oct. 2011	2107
2108	22. Jul. 2004	T	13. Oct. 2011	yes	20. Oct. 2011	2108
3101	09. Dec. 2003	R, T	18. Aug. 2011	yes	25. Aug. 2011	3101
3102	15. Oct. 2001	T, R	26. Aug. 2011	yes	04. Sep. 2011	3102
3103	20. Oct. 2000	R, T	29. Aug. 2011	yes	04. Sep. 2011	3103
4101	15. Dec. 1998	T, R	09. Jun. 2011	yes	16. Jun. 2011	4101
4102	23. Jan. 2004	R, T	09. Jun. 2011	yes	16. Jun. 2011	4102
4106	14. Dec. 2000	R, T	30. Jun. 2011	yes	07. Jul. 2011	4106
1201	04. May 1995	R, T	26. May 2011	yes	02. Jun. 2011	1201
1202	31. Mar. 1996	T, R	14. Jun. 2011	yes	21. Jun. 2011	1202
1203	19. Apr. 1992	R, T	14. Jun. 2011	yes	21. Jun. 2011	1203
1204	24. Jun. 1993	T, R	14. Jun. 2011	yes	21. Jun. 2011	1204
1205	20. Dec. 1992	T	04. Aug. 2011	yes	11. Aug. 2011	1205
1206	20. Dec. 1992	R, T	04. Aug. 2011	yes	11. Aug. 2011	1206
1207	02. Feb. 1995	T, R	04. Aug. 2011	yes	11. Aug. 2011	1207
1208	12. Sep. 1997	R, T	26. Aug. 2011	yes	02. Sep. 2011	1208
2201	10. Feb. 1989	T, R	25. May 2011	yes	01. Jun. 2011	2201
2202	27. Jul. 1991	R, T	25. May 2011	yes	01. Jun. 2011	2202
2203	25. Sep. 1994	R, T	25. May 2011	yes	01. Jun. 2011	2203
2204	16. Feb. 1989	T, R	22. Jul. 2011	yes	29. Jul. 2011	2204
2205	27. Dec. 1994	R, T	22. Jul. 2011	yes	29. Jul. 2011	2205
2206	28. May 1989	T, R	05. Aug. 2011	yes	12. Aug. 2011	2206
3201	26. Apr. 1975	R, T	29. May 2011	yes	06. Jun. 2011	3201
3202	06. Mar. 1990	T, R	29. May 2011	yes	06. Jun. 2011	3202
3203	04. Jun. 1996	T, R	31. May 2011	yes	07. Jun. 2011	3203
3204	22. May 1996	R, T	08. Jun. 2011	yes	15. Jun. 2011	3204
3205	10. Mar. 1984	T, R	14. Jun. 2011	yes	21. Jun. 2011	3205
3206	17. Apr. 1993	R, T	14. Jun. 2011	yes	21. Jun. 2011	3206
3207	15. Oct. 1987	T, R	21. Jun. 2011	yes	30. Jun. 2011	3207
3208	21. Apr. 1978	R, T	28. Jun. 2011	yes	05. Jul. 2011	3208
3209	14. Sep. 1990	R, T	01. Jul. 2011	yes	08. Jul. 2011	3209
3210	13. Nov. 1988	T, R	05. Jul. 2011	yes	12. Jul. 2011	3210
4103	01. Sep. 1983	R, T	30. Jun. 2011	yes	07. Jul. 2011	4103
4104	09. Dec. 1983	T, R	30. Jun. 2011	yes	07. Jul. 2011	4104
4105	26. Nov. 1985	T, R	30. Jun. 2011	yes	07. Jul. 2011	4105
4204	03. Jun. 1993	R, T	18. Aug. 2011	yes	25. Aug. 2011	4204
4205	05. Jul. 1985	R, T	18. Aug. 2011	yes	25. Aug. 2011	4205
4206	06. Dec. 1993	T, R	18. Aug. 2011	yes	25. Aug. 2011	4206

Subjects 1109, 1205, 2104 and 2108 are drop outs.

Enrolment No.	Date of birth dd.mmm.yyyy	Treatment order	Site no.	Subject screening no.	Smoking status	If patient ever smoked cigarettes, number of pack-years Total pack-years=Average no. of cigarettes smoked per day/20 x no. years of smoking
1101	13. Dec. 1999	R, T	01	01	never smoked	
1102	13. Feb. 1999	T, R	01	02	never smoked	
1103	01. Jan. 2000	T, R	01	07	never smoked	
1104	09. Sep. 1999	R, T	01	08	never smoked	
1105	14. Mar. 2002	T, R	01	09	never smoked	
1106	31. Dec. 2000	R, T	01	13	never smoked	
1107	29. Sep. 2003	T, R	01	15	never smoked	
1108	21. Sep. 2002	R, T	01	16	never smoked	
1109	07. Nov. 1998	R	01	17	never smoked	
1110	09. Aug. 2004	T, R	01	19	never smoked	
1111	05. May 2003	T, R	01	20	never smoked	
1112	18. May 2002	R, T	01	18	never smoked	
1113	20. Mar. 2000	T, R	01	21	never smoked	
1114	10. Nov. 2003	R, T	01	22	never smoked	
2101	27. Jun. 1997	R, T	02	05	never smoked	
2102	21. Apr. 2000	T, R	02	06	never smoked	
2103	23. Oct. 1999	T, R	02	07	never smoked	
2104	09. Sep. 1998	R	02	04	never smoked	
2105	27. Nov. 2000	R, T	02	10	never smoked	
2106	23. Dec. 2000	T, R	02	12	never smoked	
2107	26. Jan. 2000	R, T	02	13	never smoked	
2108	22. Jul. 2004	T	02	14	never smoked	
3101	09. Dec. 2003	R, T	03	13	never smoked	
3102	15. Oct. 2001	T, R	03	14	never smoked	
3103	20. Oct. 2000	R, T	03	15	never smoked	
4101	15. Dec. 1998	T, R	04	03	never smoked	
4102	23. Jan. 2004	R, T	04	02	never smoked	
4106	14. Dec. 2000	R, T	04	05	never smoked	
1201	04. May 1995	R, T	01	03	never smoked	
1202	31. Mar. 1996	T, R	01	04	never smoked	
1203	19. Apr. 1992	R, T	01	05	never smoked	
1204	24. Jun. 1993	T, R	01	06	never smoked	
1205	20. Dec. 1992	T	01	10	never smoked	
1206	20. Dec. 1992	R, T	01	12	never smoked	
1207	02. Feb. 1995	T, R	01	11	never smoked	
1208	12. Sep. 1997	R, T	01	14	never smoked	
2201	10. Feb. 1989	T, R	02	01	never smoked	
2202	27. Jul. 1991	R, T	02	02	never smoked	
2203	25. Sep. 1994	R, T	02	03	never smoked	
2204	16. Feb. 1989	T, R	02	08	never smoked	
2205	27. Dec. 1994	R, T	02	09	never smoked	
2206	28. May 1989	T, R	02	11	never smoked	
3201	26. Apr. 1975	R, T	03	01	never smoked	
3202	06. Mar. 1990	T, R	03	02	never smoked	
3203	04. Jun. 1996	T, R	03	03	never smoked	
3204	22. May 1996	R, T	03	05	never smoked	
3205	10. Mar. 1984	T, R	03	06	never smoked	
3206	17. Apr. 1993	R, T	03	07	never smoked	
3207	15. Oct. 1987	T, R	03	08	never smoked	
3208	21. Apr. 1978	R, T	03	09	never smoked	
3209	14. Sep. 1990	R, T	03	10	never smoked	
3210	13. Nov. 1988	T, R	03	11	never smoked	
4103	01. Sep. 1983	R, T	04	06	never smoked	
4104	09. Dec. 1983	T, R	04	07	never smoked	
4105	26. Nov. 1985	T, R	04	04	never smoked	
4204	03. Jun. 1993	R, T	04	08	never smoked	
4205	05. Jul. 1985	R, T	04	10	never smoked	
4206	06. Dec. 1993	T, R	04	09	never smoked	

Subjects 1109, 1205, 2104 and 2108 are drop outs.

Table 29 Screening Failures

Site/Patient	Date of screening	DOB	Reason
SITE 01			
Patient No. 23	30 November 2011	15 Sep 2003	Inclusion criterion No. 5 was not met.
Patient No. 24	30 November 2011	15 Apr 2004	Inclusion criterion No. 5 was not met.
SITE 02			
Patient No. 15	13 October 2011	27 Jul 2003	Inclusion criterion No. 7 was not met.
SITE 03			
Patient No. 04	31 May 2011	29 Jun 1990	*Pseudomonas aeruginosa* resistance on Tobramycin.
Patient No. 12	25 July 2011	5 Nov 2003	Inclusion criterion No. 4 was not met.
SITE 04			
Patient No. 01	9 June 2011	30 Nov 2002	Inclusion criterion No. 5 was not met.

DOB: Date of Birth

Table 30 Medical History

Enrolment No.	Treatment order	Does the patient have any baseline conditions?	Medical condition / Concomitant diagnosis
1101	TOBI, T100	no	
1102	T100, TOBI	no	
1103	T100, TOBI	yes	Glucose intolerance
1104	TOBI, T100	no	
1105	T100, TOBI	yes	Oesophagitis
1106	TOBI, T100	yes	Bedwetting
1107	T100, TOBI	no	
1108	TOBI, T100	no	
1109	TOBI	yes	Glucose intolerance
			Gastroesophageal reflux
1110	T100, TOBI	no	
1111	T100, TOBI	yes	Sinuses polyposis
1112	TOBI, T100	yes	Sinuses polyposis
1113	T100, TOBI	no	
1114	TOBI, T100	no	
2101	TOBI, T100	yes	Pancreatic insufficiency, UNK Jul 2007
			Hepatic lesion, UNK Jul 2007
			Polypectomy, UNK Feb 2007
2102	T100, TOBI	yes	Pancreatic insufficiency, Jan 2001
			Hepatic lesion, 14. Jul 2009
			Gastrostomy, 04. Feb 2010
			Broncho pulmonary exacerbation, 03. May 2011 - 16. May 2011
			Hypotrophy, UN Jan 2001 - UN Apr 2010
2103	T100, TOBI	yes	Pancreatic insufficiency, Oct 1999
			Hepatic lesion, Sep 2008

Enrolment No.	Treatment order	Does the patient have any baseline conditions?	Medical condition / Concomitant diagnosis
2104	TOBI	yes	Pancreatic insufficiency, 01. Dec 2003
			Hepatic lesion, UNK 2006
			Nasal polyps, 2005
			Cholelithiasis, 2009
			Broncho-pulmonary exacerbation, 06. Apr - 20. Apr 2011
2105	TOBI, T100	yes	Pancreatic insufficiency, Feb 2001
			Hepatic lesion, May 2006
2106	T100, TOBI	yes	Pancreatic insufficiency, 2000
			Hepatic lesion, 2003
2107	TOBI, T100	yes	Pancreatic insufficiency, Jan 2000
			Nasal polyps, 06. Jan 2004
			Nasal polypectomy, 08. Dec 2005 - 12. Dec 2005
			Nasal polypectomy, 2009
			Infectio tractus respiratory, 07. Sep - 29. Sep 2011
2108	T100	yes	Pancreatic insufficiency, Feb 2005
			Broncho pulmonary exacerbation, 06. Sep - 19. Sep 2011
3101	TOBI, T100	no	
3102	T100, TOBI	no	
3103	TOBI, T100	no	
4101	T100, TOBI	no	
4102	TOBI, T100	no	
4106	TOBI, T100	no	
1201	TOBI, T100	yes	Sinusitis chronica
			GERD - gastro esophageal reflux disease
1202	T100, TOBI	no	
1203	TOBI, T100	yes	Hepatitis C

Enrolment No.	Treatment order	Does the patient have any baseline conditions?	Medical condition / Concomitant diagnosis
			GERD - gastro esophageal reflux disease
1204	T100, TOBI	yes	Sinusitis chronica
1205	T100	no	
1206	TOBI, T100	yes	Glucose intolerance
1207	T100, TOBI	yes	Cirrhosis hepatitis
			Portal hypertension
			Sinusitis chronica
1208	TOBI, T100	no	
2201	T100, TOBI	yes	Pancreatic insufficiency, 1989
			Hepatic lesion, 1993
			Nasal polyps, 21. Feb 2001
			I. Nasal polypectomy, 02. Feb 2004
			II. Nasal polypectomy, 14. Mar 2011
			Vascuport implantation, 2008
			Hypersensitivity on Tazocin, Apr 2011
			Bronchopulmonary exacerbation, 08. Apr 2011 - 22. Apr 2011
2202	TOBI, T100	yes	Pancreatic insufficiency, Jul 2000
			Hepatic lesion, 2004
			Nasal polyps, Aug 2000
			Cholelithiasis, 31. Mar 2011
			Dios, 14. Jun 2006 - 28. Jun 2006
			Bronchopulmonary exacerbation, 20. Mar 2011 - 03. Apr 2011
2203	TOBI, T100	yes	Pancreatic insufficiency, Mar 1995
			Hepatic lesion, Aug 2000
			Nasal polyps, May 2005
			Nasal polypectomy, Mar 2006
			Cholelithiasis, 25. May 2010
2204	T100, TOBI	yes	Pancreatic insufficiency, Sep 2003
			Nasal polyps, 06. Apr 2004
			Urticaria recurrent, UNK 2009

Enrolment No.	Treatment order	Does the patient have any baseline conditions?	Medical condition / Concomitant diagnosis
			Rectal prolapse, Start 1992, End 1992
2205	TOBI, T100	yes	Pancreatic insufficiency, 1995
			Hypotrophy, 1999
			Hepatic lesion, 2005
			Cholelithiasis, 10. Dec 2008
			Nephrolithiasis, 30. May 2011
			Broncho-pulmonary exacerbation, 24. May 2011 - 07. Jun 2011
2206	T100, TOBI	yes	Pancreatic insufficiency, 1996
			Hepatic lesion, 1996
			Nasal polyps, 2000
			Glucose intolerance, 2007
3201	TOBI, T100	yes	Scoliosis
			Allergic conjunctivitis
			Chronic abdominal pain
3202	T100, TOBI	yes	Hepatitis C
3203	T100, TOBI	yes	Chronic gastritis
3204	TOBI, T100	yes	Cholecystolithiasis
			Acne vulgaris
3205	T100, TOBI	yes	Allergy
			Syndroma Gilberti
3206	TOBI, T100	yes	Allergy to piperacyllin
3207	T100, TOBI	yes	Nasal polyps
3208	TOBI, T100	yes	Mild hypertension
			Hepatopathy
3209	TOBI, T100	no	
3210	T100, TOBI	yes	Nasal polyps
			Allergy to pollen
			Allergic rhinitis
4103	TOBI, T100	no	
4104	T100, TOBI	no	

Enrolment No.	Treatment order	Does the patient have any baseline conditions?	Medical condition / Concomitant diagnosis
4105	T100, TOBI	no	
4204	TOBI, T100	no	
4205	TOBI, T100	no	
4206	T100, TOBI	no	

Table 31 Not Allowed Concomitant Drugs

AMINOGLYCOSIDES

Gentamicin

Tobramycin* *Investigational drug

Amikacin

Neomycin

Paromomycin

Spectinomycin

Streptomycin

Netylmycin

Topical aminoglycosides (Neomycin, Kanamycin, Paromomycin) were not permitted.

The following antibiotics were not allowed within 7 days before the first administration of the investigational drug (Wash-out Phase), neither during the whole trial:

PENICILLINS

Carboxypenicillins	Ticarcillin
	Carbenicillin
Acylaminopenicillins	Piperacillin
	Azlocillin
	Mezlocillin
Penicillin + β-Lactamase inhibitors	Amoxicillin + Clavulanic acid
	Ampicillin + Sulbactan
	Piperacillin + Tazobactam
	Sultamicillin + Tazobactam
	Sulbactam
1st Generation Cephalosporins	Cefalotin (not active against *Pseudomonas* but interacts with tobramycin)
3rd Generation Cephalosporins	Cefotaxim
	Ceftriaxon
	Ceftazidim
4th Generation Cephalosporins	Cefepim
Carbapenems	Imipenen/Cilastatin
	Meropenem
	Ertapene
Monobactam	Aztreonam

MACROLIDES (Macrolides were permitted provided that they were taken as a maintenance therapy for at least 6 weeks before entering the trial).

Erythromycin

Clarithromycin

Roxithromycin

Azithromycin

Josamycin

Spiramycin

Telithromycin

FLUORCHINOLONES

Norfloxacin

Ofloxacin

Ciprofloxacin

Levofloxacin

Gatifloxacin

Moxifloxacin

DIAMINOPYRIDINES/SULFONAMIDES (Nephrotoxic)

Sulfadiazine

Sulfamethoxazol + Trimethoprim

Sulfadoxine + Pyrimethamine

GLYCOPEPTIDES(not active against *Pseudomonas* but ototoxic**)**

Vancomycin* *Ototoxic

Teicoplanin*

POLYPEPTIDES

Bacitracin

Colistin

Polymyxin B

FOSFOMYCIN

Table 32 Concomitant Therapy, coded according to ATC (WHO, Norwegian Institue of Public Health, Oslo 2012)

Enrolment No.	Treatment order	Concomitant Therapy						
		Drug/Strength		Administration p.o., inh., s.c., rectal, topical etc.	Daily Dose (mg, µg)	Start date	End date	Indication for use or reason for change
		ATC Code			(dose/unit)	dd.mmm.yyyy	hh:mm	
1101	TOBI, T100	A09AA02	Pancreatin	p.o.	275000 IU	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	500 mg	cont	cont	Cystic Fibrosis
		J01FA10	Azithromycin	p.o.	750 mg/ week	cont	cont	Cystic Fibrosis
		R03AC12	Salmeterol	inh	100 µg	cont	cont	Cystic Fibrosis
		R03BA05	Fluticasone	inh	200 µg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	2 tab	cont	cont	Cystic Fibrosis
		B03AA07	Ferrous sulfate	p.o.	1 tab	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	0.4 mg	02. Jun 2011	29. Jun 2011	Cystic Fibrosis
		R03AC02	Salbutamol	inh	0.4 mg	28. Jul 2011	24. Aug 2011	Cystic Fibrosis
1102	T100, TOBI	A09AA02	Pancreatin	p.o.	288000 IU	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	2 tab	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	500 mg	cont	cont	Cystic Fibrosis
		R03BA05	Fluticasone propionate	inh. nasal	200 µg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh.	2.5 mg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh.	400 µg	02. Jun 2011	29. Jun 2011	Cystic Fibrosis before IMP
		R03AC02	Salbutamol	inh.	400 µg	28. Jul 2011	24. Aug 2011	Cystic Fibrosis before IMP

1103	T100, TOBI	A09AA02	Pancreatin	p.o.	175000 IU	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	2 tab	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	600 mg	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	400 mg	cont	cont	Cystic Fibrosis
		J01FA10	Azitromycin	p.o.	1500 mg/week	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R05CB01	Acetylcysteine	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A07EA06	Budesonid	inh	200 µg	cont	cont	Cystic Fibrosis
		R03AC13	Formoterol	inh	24 µg	cont	cont	Cystic Fibrosis
1104	TOBI, T100	A09AA02	Pancreatin	p.o.	246000 IU	cont	cont	Cystic Fibrosis
		A11JC	Aquadeks	p.o.	2 caps	cont	cont	Cystic Fibrosis
		R05CB06	Ambroxol	p.o.	15 ml	cont	cont	Cystic Fibrosis
		J01FA10	Azithromycin	p.o.	750 mg / week	cont	cont	Cystic Fibrosis
		A02BC01	Omeprazole	p.o.	20 mg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	400 µg	cont	cont	Cystic Fibrosis
		R03BA05	Fluticasone	inh	500 µg	cont	cont	Cystic Fibrosis
1105	T100, TOBI	A09AA02	Pancreatin	p.o.	200000 IU	cont	cont	Cystic Fibrosis
		A11JC	Aquadeks	p.o.	2 caps	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	500 mg	cont	cont	Cystic Fibrosis
		A02BC01	Omeprazole	p.o.	20 mg	cont	cont	Cystic Fibrosis
		J01FA10	Azithromycin	p.o.	750 mg / week	cont	cont	Cystic Fibrosis
		R05CB01	Acetylcysteinum	p.o.	400 mg	cont	cont	Cystic Fibrosis
		R03AC12	Salmeterol	inh	100 µg	cont	cont	Cystic Fibrosis
		R03BA05	Fluticasone propionate	inh	200 µg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
1106	TOBI, T100	A09AA02	Pancreatin	p.o.	135000 IU	cont	cont	Cystic Fibrosis

		A11B	Multivitaminum	p.o.	2 tab	cont	cont	Cystic Fibrosis
		R05CB01	Acetylcysteine	p.o.	800 mg	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	500 mg	cont	cont	Cystic Fibrosis
		R07AA	Phospholipids	p.o.	600 mg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	i.v.	2.5 mg	cont	cont	Cystic Fibrosis
		D07AC13	Mometasone furoate	inh.	100 µg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh.	400 µg	02. Sep 2011	cont	Cystic Fibrosis before IMP
		S01FA01	Atropine	i.v.	0.3 mg	06. Oct 2011	06. Oct 2011	General anesthesia
		N01AX10	Propofol	i.v.	60 mg	06. Oct 2011	06. Oct 2011	General anesthesia
		N01AH03	Sufentanyl	i.v.	12.5 µg	06. Oct 2011	06. Oct 2011	General anesthesia
		N01AB08	Sevoflurane	inh.	1.5 Vol %	06. Oct 2011	06. Oct 2011	General anesthesia
		N02BE01	Paracetamol	i.v.	2.4 g	06. Oct 2011	07. Oct 2011	injury
		M01AE03	Ketoprofen	i.v.	90 mg	06. Oct 2011	07. Oct 2011	injury
		J01DC02	Cefuroxyme axetyl	i.v.	3 g	06. Oct 2011	07. Oct 2011	injury
		J01DC02	Cefuroxyme axetyl	p.o.	500 mg	08. Oct 2011	12. Oct 2011	injury
1107	T100, TOBI	A09AA02	Pancreatin	p.o.	150000 IU	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	1 caps	cont	cont	Cystic Fibrosis
		R05CB01	Acetylocysteine	p.o.	200 mg	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	500 mg	cont	cont	Cystic Fibrosis
		J01FA10	Azitromycin	p.o.	750 mg / week	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh.	400 µg	cont	cont	Cystic Fibrosis
		R03BA05	Fluticasone	inh.	200 µg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh.	2.5 mg	cont	cont	Cystic Fibrosis
1108	TOBI, T100	A09AA02	Pancreatin	p.o.	140000 IU	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	30 ml	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	200 mg	cont	cont	Cystic Fibrosis
		A11CC05	Colecalciferol	p.o.	500 IU	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	500 mg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh.	0.0025 g	cont	04. Oct 2011	Cystic Fibrosis
		R05CB13	Dornase alfa	inh.	2.5 mg	cont	cont	Cystic Fibrosis

		R03AC02	Salbutamol	inh	400 µg	05. Oct 2011	cont	Cystic Fibrosis
		J01FA10	Azithromycin	p.o.	750 mg / week	cont	cont	Cystic Fibrosis
1109	TOBI	A09AA02	Pancreatin	p.o.	325000 IU	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	2 tab	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	250 mg	cont	cont	Cystic Fibrosis
		J01FA10	Azithromycin	p.o.	750 mg / a week	cont		Cystic Fibrosis
		R03AC13	Formoterol	Inh	0.024 mg	cont	cont	Cystic Fibrosis
		R03BA02	Budesonide	Inh	0.4 mg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	Inh	2.5 mg	cont	cont	Cystic Fibrosis
		A02BC01	Omeprazole	p.o.	40 mg	cont	cont	Gastroesophageal reflux
		D10AD02	Retinol	p.o.	2500 IU	cont	cont	Cystic Fibrosis
		J01MA02	Ciprofloxacin	p.o.	1000 mg	31. Oct 2011	14. Nov 2011	Nasopharyngeal infection
		A07AA10	Colistin	i.v.	6000000 IU	15. Nov 2011	30. Nov 2011	Pulmonary exacerbation
		J01DH51	Imipenem	i.v.	3 g	15. Nov 2011	16. Nov 2011	Pulmonary exacerbation
		J01DH02	Meropenem	i.v.	2250 mg	16. Nov 2011	30. Nov 2011	Pulmonary exacerbation
1110	T100, TOBI	A09AA02	Pancreatinum	p.o.	140000 IU	cont	cont	Cystic Fibrosis
		J01FA10	Azithromycin	p.o.	750 mg/week	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	2 tab	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	500 mg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	0.4 mg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
1111	T100, TOBI	A09AA02	Pancreatin	p.o.	128000 IU	cont	cont	Cystic Fibrosis
		A11JC	Adeks (Multivitaminum)	p.o.	1 tab	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis

		J01FA10	Azitromycin	p.o	750 mg/week	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	400 µg	23. Nov 2011	20. Dec 2011	Cystic Fibrosis
		R03AC02	Salbutamol	inh	400 µg	18. Jan 2012	13. Feb 2012	Cystic Fibrosis
1112	TOBI, T100	A09AA02	Pancreatin	p.o.	120000 IU	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	2 tab/day	cont	cont	Cystic Fibrosis
		A11CC05	Cholecalciferol	p.o.	1000 IU	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R05CB06	Ambroxol	p.o.	0.09 g	cont	cont	Cystic Fibrosis
		B02BA01	Phytomenadione	p.o.	0.01 g / week	cont	cont	Cystic Fibrosis
		J01FA10	Azithromycin	p.o.	750 mg/week	cont	cont	Cystic Fibrosis
		A07EX06	Budesonide	nasal spray	0.1 mg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	400 µg	cont	cont	Cystic Fibrosis
1113	T100, TOBI	A09AA02	Pancreatin	p.o.	75000 IU	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A11HA03	Colecalciferol	p.o.	500 IU	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	2 tab	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	400 µg	23. Nov 2011	20. Dec 2011	Cystic Fibrosis before IMP
		R03AC02	Salbutamol	inh	400 µg	18. Jan 2012	13. Feb 2012	Cystic Fibrosis
1114	TOBI, T100	A09AA02	Pancreatin	p.o.	176000 IU	cont	cont	Cystic Fibrosis
		R05CB01	Acetylcysteine	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	200 mg	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	2 tab / day	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	375 mg	cont	cont	Cystic Fibrosis
		J01FA10	Azithromycin	p.o.	750 mg / week	cont	cont	Cystic Fibrosis

		R03AC02	Salbutamol	inh	400 mg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		B02BA01	Phytomenadione	p.o.	10 mg/week	cont	cont	Cystic Fibrosis
2101	TOBI, T100	R01AX03	Atrovent	inh	0.5 mg	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R05CB06	Mucosolvan	inh	75 mg	cont	cont	Cystic Fibrosis
		J01FA10	Azimycin	p.o.	250 mg every second day	cont	cont	Cystic Fibrosis
		R05CB01	Tussicom	p.o.	1200 mg	cont	cont	Cystic Fibrosis
		R03DC03	Singulair	p.o.	5 mg	cont	cont	Cystic Fibrosis
		A05AA02	Ursofalk	p.o.	500 mg	cont	cont	Hepatic lesion
		A09AA02	Lipancrea 16000	p.o.	PRN	cont	cont	Pancreatic insufficiency
		A03AA05	Debridat	p.o.	200 mg	cont	cont	Pancreatic insufficiency
		A11HA03	Vitaminum E	p.o.	200 mg	cont	cont	Pancreatic insufficiency
		A11CA02	B-Karoten	p.o.	10 mg	cont	cont	Pancreatic insufficiency
		A11CC05	Vigantoletten	p.o.	750 IU	cont	cont	Pancreatic insufficiency
		B02BA01	Vitacon	p.o.	10 mg once a week	cont	cont	Pancreatic insufficiency
		A07AA10	Colistin	inh	4 mln IU	cont	15. Jun 2011	Cystic Fibrosis
2102	T100, TOBI	R01AX03	Atrovent	inh	0.375 mg	cont	cont	Cystic Fibrosis
		R05CB06	Mucosolvan	inh every second day	30 mg	cont	cont	Cystic Fibrosis
		R05CB01	ACC	inh every second day	300 mg	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		J01FA10	Azimycin	p.o.	250 mg every second day	cont	cont	Cystic Fibrosis
		A05AA02	Ursofalk	p.o..	250 mg	cont	cont	Hepatic lesion
		A09AA02	Lipancrea 16000	p.o.	PRN	cont	cont	Pancreatic insufficiency

		A11B	Multivitaminum	p.o.	1 tab	cont	cont	Pancreatic insufficiency
		B02BA01	Vitacon	p.o.	10 mg once a week	cont	cont	Pancreatic insufficiency
		J01CA20	Timentin	i.v.	9 g	03. May 2011	16. May 2011	Broncho pulmonary exacerbation
		J01GB06	Amixin	i.v.	800 mg	03. May 2011	16. May 2011	Broncho pulmonary exacerbation
		D01AA01	Nystatyna	p.o.	6 tab	03. May 2011	16. May 2011	Broncho pulmonary exacerbation
		G01AX14	Lacidofil	p.o.	2 cap	03. May 2011	16. May 2011	Broncho pulmonary exacerbation
		A07AA10	Colistin	inh	4 mln IU	cont	15. Jun 2011	Cystic Fibrosis
2103	T100, TOBI	R03AC02	Ventolin	inh	7.5 mg	cont	cont	Cystic Fibrosis
		R05CB01	ACC	inh	900 mg	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R01AD05	Pulmicort	inh	1000 µg	cont	cont	Cystic Fibrosis
		J01FA10	Azimycin	p.o.	250 mg every second day	cont	cont	Cystic Fibrosis
		R03DC03	Singulair	p.o.	10 mg	cont	cont	Cystic Fibrosis
		R05CB01	Tussicom	p.o.	1200 mg	cont	cont	Cystic Fibrosis
		R06AE07	Zyrtec	p.o.	10 mg	cont	cont	Cystic Fibrosis
		A03AA05	Debridat	p.o.	200 mg	cont	cont	Pancreatic insufficiency
		A09AA02	Kreon 10000	p.o.	PRN	cont	cont	Pancreatic insufficiency
		A11JC	Adeks	p.o.	2 tab	cont	cont	Pancreatic insufficiency
		A05AA02	Ursofalk	p.o.	500 mg	cont	cont	Hepatic lesion
		R07AA02	Essentiale forte	p.o.	2 caps	cont	cont	Hepatic lesion
		A07AA10	Colistin	inh	4 mln IU	cont	14. Jun 2011	Cystic Fibrosis
2104	TOBI	R01AX03	Atrovent	inh	0.375 mg	cont	cont	Cystic Fibrosis
		B05CB	7% NaCl	inh	30 ml	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R05CB01	Tussicom	p.o.	1200 mg	cont	cont	Cystic Fibrosis
		03DC03	Singulair	p.o.	10 mg	cont	cont	Cystic Fibrosis

		J01FA10	Azitrolek	p.o.	250 mg every second day	cont	cont	Cystic Fibrosis
		R01AD05	Buderhin	Nasal inh.	0.2 mg	cont	cont	Nasal polyps
		A05AA02	Ursofalk	p.o.	500 mg	cont	cont	Hepatic lesion
		A02BC01	Bioprazol	p.o.	20 mg	cont	cont	Pancreatic insufficiency
		A03AA05	Debridat	p.o.	50 mg	cont	cont	Pancreatic insufficiency
		A09AA02	Kreon 25000	p.o.	PRN	cont	cont	Pancreatic insufficiency
		A09AA02	Kreon 10000	p.o.	PRN	cont	cont	Pancreatic insufficiency
		A11JC	Adeks	p.o.	2 tab	cont	cont	Pancreatic insufficiency
		A07FA02	Enterol	p.o.	2 caps	cont	cont	Pancreatic insufficiency
		J01MA02	Cipronex	p.o.	2 g	09. Jun 2011	cont	Broncho pulmonary exacerbation
		M01AE01	Ibufen	p.o.	400 mg	04. Jun 2011	12. Jun 2011	Fever
		A12BA51	Gastrolit	p.o.	2 bags	05. Jun 2011	07. Jun 2011	Vomitus
		R03AC02	Salbutamol	inh	0.3 mg	07. Jun 2011	cont	Cough more intense
		J01DD02	Fortum	i.v.	12 g	06. Apr 2011	20. Apr 2011	Broncho pulmonary exacerbation
		J01GB07	Netromycyna	i.v.	800 mg	06. Apr 2011	20. Apr 2011	Broncho pulmonary exacerbation
		D01AA01	Nystatyna	p.o.	6 tab	06. Apr 2011	20. Apr 2011	Broncho pulmonary exacerbation
		A07AA10	Colistin	inh	4 mln IU	cont	24. May 2011	Cystic Fibrosis
		A07AA10	Colistin	inh	4 mln IU	10. Jun 2011	cont	Cystic Fibrosis
2105	TOBI, T100	R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R03AC02	Ventolin	inh	5 mg	cont	cont	Cystic Fibrosis
		R05CB06	Mucosolvan	inh	60 mg	cont	cont	Cystic Fibrosis
		A07AA10	Colistin	inh	4 mln IU	cont	21. Jul 2011	Cystic Fibrosis
		A09AA02	Lipancrea 16000	p.o.	8 caps	cont	cont	Pancreatic insufficiency
		A03AA05	Debridat	p.o.	100 mg	cont	21. Oct 2011	Pancreatic insufficiency
		A05AA02	Ursofalk	p.o.	250 mg	cont	cont	Hepatic lesion
		R05CB01	ACC	p.o.	200 mg	cont	cont	Cystic Fibrosis
		A11B	Multivitamine	p.o.	1 tab	cont	cont	Pancreatic insufficiency
		R05CB01	Mucofluid	nasal	3 puff	18. Sep 2011	22. Sep 2011	Rhinitis
		A03AA05	Debridat	p.o.	200 mg	22. Oct 2011	24. Oct 2011	Abdominal pain
		A03AD02	No-spa	p.o.	40 mg	24. Oct 2011	24. Oct 2011	Abdominal pain

2106	T100, TOBI	G02CA +R01AX03	Berodual	inh	40 drops	cont	cont	Cystic Fibrosis
		R05CB06	Mucosolvan	inh	45 mg	cont	cont	Cystic Fibrosis
		B05CB	3% NaCl	inh	10 ml	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A07AA10	Colistin	inh	4 mln IU	cont		Cystic Fibrosis
		R03AC13	Oxis	inh	9 µg	cont	cont	Cystic Fibrosis
		R01AD05	Pulmicort	inh	400 µg	cont	cont	Cystic Fibrosis
		J01FA10	Azimycin	p.o.	250 mg / every second day	cont	cont	Cystic Fibrosis
		R06AE07	Alertec	p.o.	10 mg	cont	cont	Cystic Fibrosis
		R05CB01	Tussicom	p.o.	1200 mg	cont	cont	Cystic Fibrosis
		A09AA02	Lipancrea 16000	p.o.	8 caps	cont	cont	Pancreatic insufficiency
		A11B	Multivitamin	p.o.	1 tab	cont	cont	Pancreatic insufficiency
		N02BE01	Paracetamol	p.o.	1.5 g	27. Sep 2011	29. Sep 2011	Fever
				.				
2107	TOBI, T100	R05CB01	Tussicom	p.o.	1200 mg	cont	cont	Cystic Fibrosis
		A09AA02	Kreon 10000	p.o.	PRN	cont	cont	Pancreatic insufficiency
		A09AA02	Kreon 25000	p.o.	2 caps	cont	cont	Pancreatic insufficiency
		A05AA02	Ursofalk	p.o.	500 mg	cont	cont	Prophylaxis liver disease
		A12BA01	Kalipol	p.o.	1 tab	cont	cont	Pancreatic insufficiency
		R03DC03	Singulair	p.o.	5 mg	cont	cont	Cystic Fibrosis
		A12BA51	Gastrolit	p.o.	6 bags	cont	cont	Pancreatic insufficiency
		A11B	Multivitamin	p.o.	2 tab	cont	cont	Pancreatic insufficiency
		R01AX03	Atrovent	inh	0.375 mg	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R05CB06	Mucosolvan	inh	60 mg	cont	cont	Cystic Fibrosis
		A07AA10	Colistin	inh	4000000 IU	cont	12. Oct 2011	Cystic Fibrosis
2108	T100		Atrovent	inh	0.375 mg	cont	cont	Cystic Fibrosis
		B05CB	5% NaCl	inh	10 ml	cont	cont	Cystic Fibrosis

		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A07AA10	Colistin	inh	4000000 IU	cont	12. Oct 2011	Cystic Fibrosis
		R05CB01	Tussicom	p.o.	300 mg	cont	cont	Cystic Fibrosis
		A05AA02	Ursofalk	p.o.	250 mg	cont	cont	Prophylaxis liver disease
		A09AA02	Kreon 10000	p.o.	6 caps	cont	cont	Pancreatic insufficiency
		A09AA02	Lipancrea 16000	p.o.	3 caps	cont	cont	Pancreatic insufficiency
		A11B	Multivitamin	p.o.	1 tab	cont	cont	Pancreatic insufficiency
		J01CR05	Tazolin	i.v.	6 g	06. Sep 2011	19. Sep 2011	Broncho pulmonary exacerbation
		J01GB06	Amikin	i.v.	600 mg	06. Sep 2011	19. Sep 2011	Broncho pulmonary exacerbation
		A07AA02	Nystatyna	p.o.	6 tab	06. Sep 2011	19. Sep 2011	Prophylaxis
		G01AX14	Lacidofil	p.o.	2 caps	06. Sep 2011	19. Sep 2011	Prophylaxis
		J01DD01	Biotaksym	i.v.	1000 mg	09. Dec 2011	14. Dec 2011	Otitis media mastoiditis
		J01DC02	Zinnat	p.o.	500 mg	15. Dec 2011	21. Dec 2011	Otitis media mastoiditis
				.				
3101	TOBI, T100	A11B	Multivitaminum	p.o.	1 tab	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	200 mg	cont	cont	Cystic Fibrosis
		A11CC06	Calcifediol	p.o.	10 µg	cont	cont	Cystic Fibrosis
		B02BA01	Phytomenadione	p.o.	2.86 mg	cont	cont	Cystic Fibrosis
		A09AA02	Pancreatic Enz (Kreon 10000)	p.o.	2 caps	cont	cont	Cystic Fibrosis
		A09AA02	Pancreatic Enz (Lipancrea 16000)	p.o.	3 caps	cont	cont	Cystic Fibrosis
		A05AA02	UDCA (Proursan)	p.o.	250 mg	cont	cont	Cystic Fibrosis
		A02BC01	Omeprazol	p.o.	10 mg	cont	cont	Cystic Fibrosis
		J01FA10	Azithromycin	p.o.	62.5 mg	cont	cont	Cystic Fibrosis
		B05CB	5% NaCl	inh	6 ml	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme (Dornase alpha)	inh	2.5 mg	cont	cont	Cystic Fibrosis
3102	T100, TOBI	R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		B05CB	5% NaCl	inh	8 ml	cont	cont	Cystic Fibrosis
		A11JC	AquADEKs	p.o.	1 tab	cont	cont	Cystic Fibrosis
		A09AA02	Kreon 25000	p.o.	7 caps	cont	cont	Cystic Fibrosis
		A09AA02	Kreon 10000	p.o.	2 caps	cont	cont	Cystic Fibrosis
		M01AE01	Ibuprofen	p.o.	100 mg	04. Sep 2011	05. Sep 2011	Headache

		S01XA10	Isoprinosine	p.o.	2000 mg	06. Sep 2011	11. Sep 2011	Pharyngitis
		S01XA10	Isoprinosine	p.o.	1000 mg	23. Nov 2011	01. Dec 2011	Pharyngitis
				.				
3103	TOBI, T100	A09AA02	Kreon 25000	p.o.	3 caps	cont	cont	Cystic Fibrosis
		A11JC	AquADEKs	p.o.	1 caps	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A05AA02	Ursopol (UDCA)	p.o.	300 mg	cont	cont	Liver disease in Cystic Fibrosis
		R07AA02	Essentiale forte	p.o.	2 caps	cont	cont	Liver disease in Cystic Fibrosis
		A05BA	Hepatil	p.o.	1 tab	cont	cont	Liver disease in Cystic Fibrosis
				.				
4101	T100, TOBI	A09AA02	Kreon	p.o.	125000 Fip Lipaz	cont	cont	Cystic Fibrosis
		A11CC04	Vit. D3	p.o.	800 IU	cont	cont	Cystic Fibrosis
		A11CA01	Vit. A	p.o.	480 IU	cont	cont	Cystic Fibrosis
		A11HA03	Vit. E	p.o.	110 mg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	200 mg	cont	cont	Cystic Fibrosis
		R05CB13	rhDNase	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R01AD05	Budesonid nasal	inh	400 µg	cont	cont	Cystic Fibrosis
4102	TOBI, T100	A09AA02	Kreon	p.o.	60000 FIP	cont	cont	Cystic Fibrosis
		A11CA01	Vit. A	p.o.	800 IU	cont	cont	Cystic Fibrosis
		A11HA03	Vit. E	p.o.	110 mg	cont	cont	Cystic Fibrosis
		A11CC04	Vit. D3	p.o.	600 IU	cont	cont	Cystic Fibrosis
		R05CB01	Acetylcysteine	p.o.	200 mg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	600 µg	cont	cont	Cystic Fibrosis
		B05CB	7% NaCl	inh	8 ml	cont	cont	Cystic Fibrosis
		R05CB13	rhDNase	inh	2.5 mg	cont	cont	Cystic Fibrosis
4106	TOBI, T100	A09AA02	Kreon	p.o.	125000 FIP	cont	cont	Cystic Fibrosis
		B02BA	Vit. K	p.o.	10 mg	cont	cont	Cystic Fibrosis
		R05CB01	Acetylcysteine	p.o.	600 mg	cont	cont	Cystic Fibrosis
		A05AA02	UDCA	p.o.	300 mg	cont	cont	Cystic Fibrosis

		M01AE01	Ibuprofen	p.o.	450 mg	cont	cont	Cystic Fibrosis
		A02BC01	Omeprazol	p.o.	20 mg	cont	cont	Cystic Fibrosis
		R05CB06	Ambroxol hydrochlor.	inh	30 mg	cont	cont	Cystic Fibrosis
		R05CB13	rhDNase	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A11CC04	Vit. D3	p.o.	800 IU	cont	cont	Cystic Fibrosis
		A11HA03	Vit. E	p.o.	55 mg	cont	cont	Cystic Fibrosis
				.				
1201	TOBI, T100	A09AA02	Pancreatin	p.o.	400000 IU	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	2 tab	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	750 mg	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	400 mg	cont	cont	Cystic Fibrosis
		J01FA10	Azithromycin	p.o.	1500 mg / week	cont	cont	Cystic Fibrosis
		R03AC12	Salmeterol	inh	100 µg	cont	cont	Cystic Fibrosis
		R05CB01	Fluticasone	inh	500 µg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A11HA03	Colecalciferol	p.o.	1000 IU	cont	cont	Cystic Fibrosis
		A02BC01	Omeprazole	p.o.	40 mg	cont	cont	GERD
		B02BA01	Phytomenadione	p.o.	20 mg / week	cont	cont	Cystic Fibrosis
		A07AA02	Nystatin	p.o.	1 mln IU	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	0.4 mg	cont	cont	Cystic Fibrosis
1202	T100, TOBI	A09AA02	Pancreatin	p.o.	256000 IU	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	2 tab	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	500 mg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	0.4 mg	cont	cont	Cystic Fibrosis
		R05CB01	Acetylcysteine	p.o.	600 mg	cont	cont	Cystic Fibrosis
1203	TOBI, T100	A09AA02	Pancreatin	p.o.	250000 IU	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	400 mg	cont	cont	Cystic Fibrosis

		A11B	Multivitaminum	p.o.	2 tab	cont	cont	Cystic Fibrosis
		B02BA01	Phytomenadione	p.o.	20 mg/week	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	500 mg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R03AC12	Salmeterol	inh	100 µg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	200 µg	cont	cont	Cystic Fibrosis
		R05CB01	Fluticasone propionate	inh	1000 µg	cont	cont	Cystic Fibrosis
		A02BC01	Omeprazole	p.o.	20 mg	cont	cont	GERD
		R03AC02	Salbutamol	inh	400 µg	21. Jun 2011	18. Jul 2011	Cystic Fibrosis before inhalation IMP
		J01MA02	Ciprofloksacin	p.o.	1500 mg	18. Jul 2011	05. Aug 2011	Auscultatory changes
		R03AC02	Salbutamol	inh	400 µg	16. Aug 2011	12. Sep 2011	Cystic Fibrosis before IMP
1204	T100, TOBI	A09AA02	Pancreatin	p.o.	160000 IU	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	2 tab	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	500 mg	cont	cont	Cystic Fibrosis
		J01FA10	Azithromycin	p.o.	1500 mg/week	cont	cont	Cystic Fibrosis
		A07EA06	Budesonid	nasal spray	0.1 mg	cont	cont	Cystic Fibrosis
		R03AC13	Formoterol	inh	0.024 mg	cont	cont	Cystic Fibrosis
		R03BA05	Flutikazon	inh	0.5 mg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	400 µg	21. Jun 2011	18. Jul 2011	Cystic Fibrosis
		R03AC02	Salbutamol	inh	400 µg	16. Aug 2011	12. Sep 2011	Cystic Fibrosis
1205	T100	A09AA02	Pancreatin	p.o.	450000 IU	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	2 tab	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	400 mg	cont	cont	Cystic Fibrosis
		B02BA01	Phytomenadione	p.o.	20 mg / week	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	500 mg	cont	cont	Cystic Fibrosis

		R03AC02	Salbutamol	inh	400 mg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A12AA06	Calcium lactate gluconate	p.o.	500 mg	cont	cont	Cystic Fibrosis
		B02BX01	Etamsylate	i.v.	1500 mg	26. Sep 2011	28. Sep 2011	Pulmonary hemorrhage
		B02AA02	Tranexamic acid	i.v.	3 g	26. Sep 2011	03. Oct 2011	Pulmonary hemorrhage
		J01DD02	Ceftazydyme	i.v.	6 g	27. Sep 2011	03. Oct 2011	Pulmonary exacerbation
		J01MA02	Ciprofloxacine	p.o.	1000 mg	26. Sep 2011	cont	Pulmonary exacerbation
		A02BA02	Ranitidine	i.v.	0.15 g	27. Sep 2011	28. Sep 2011	Hemorrhage
		N02AA08	Codeine	p.o.	0.045 g	27. Sep 2011	03. Oct 2011	Pulmonary exacerbation
		B02BX01	Etamsylate	p.o.	1500 mg	29. Sep 2011	cont	Hemorrhage
1206	TOBI, T100	A09AA02	Pancreatin	p.o.	160000 IU	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	500 mg	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A11B	Multivitaminum	p.o.	2 tab	cont	cont	Cystic Fibrosis
		B02BA01	Phytomenadione	p.o.	1 tab / week	cont	cont	Cystic Fibrosis
		A11CC05	Cholekalcyferol	p.o.	800 IU	cont	cont	Cystic Fibrosis
		R05CB06	Ambroxol	p.o.	60 mg	cont	cont	Cystic Fibrosis
		A07EA06	Budesonid	inh	200 µg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	400 µg	11. Aug 2011	07. Sep 2011	Cystic Fibrosis
		R03AC02	Salbutamol	inh	400 µg	07. Oct 2011	04. Nov 2011	Cystic Fibrosis
1207	T100, TOBI	A09AA02	Pancreatin	p.o.	125000 IU	cont	cont	Cystic Fibrosis
		A11JC	Adeks	p.o.	2 caps	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	500 mg	cont	cont	Cystic Fibrosis
		B02BA01	Phytomenadione	p.o.	20 mg/week	cont	cont	Cystic Fibrosis
		A12AA	Calcium	p.o.	500 mg	cont	cont	Cystic Fibrosis
		A11CC05	Cholekalcyferol	p.o.	250 IU	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R03AC12	Salmeterol	inh	100 µg	cont	cont	Cystic Fibrosis

		R05CB01	Fluticasone	inh	100 µg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	400 µg	11. Aug 2011	07. Sep 2011	Cystic Fibrosis
		R03AC02	Salbutamol	inh	400 µg	07. Oct 2011	03. Nov 2011	Cystic Fibrosis
1208	TOBI, T100	A09AA02	Pancreatin	p.o.	120000 IU	cont	cont	Cystic Fibrosis
		A05AA02	Ursodeoxycholic acid	p.o.	500 mg	cont	cont	Cystic Fibrosis
		R05CB01	Acetylcysteine	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A11HA03	Colecalciferol	p.o.	0.025 mg	cont	cont	Cystic Fibrosis
		B02BA01	Phytomenadione	p.o.	0.02 g/week	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	400 µg	cont	cont	Cystic Fibrosis
		R05CB01	Fluticasone propionate	inh	400 µg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A11JC	Multivitaminum (Adeks)	p.o.	2 caps	cont	cont	Cystic Fibrosis
2201	T100, TOBI	G02CA +R01AX03	Berodual	inh	40 drop	cont	cont	Cystic Fibrosis
		R05CB01	ACC	inh	300 mg	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		B05CB	3% NaCl	inh	5 ml	cont	cont	Cystic Fibrosis
		A05AA02	Ursofalk	p.o.	1000 mg	cont	cont	Hepatic lesion
		R07AA02	Essentiale forte	p.o.	4 caps	cont	cont	Hepatic lesion
		R05CB01	Tussicom	p.o.	1200 mg	cont	cont	Cystic Fibrosis
		A02BC01	Bioprazol	p.o.	20 mg	cont	cont	Pancreatic insufficiency
		A09AA02	Lipancrea 16000	p.o.	PRN	cont	cont	Pancreatic insufficiency
		A11B	Multivitamins	p.o.	2 tab	cont	cont	Pancreatic insufficiency
		A03AD02	No-spa	p.o.	160 mg	23. Jun 2011	25. Jun 2011	Abdominal pain
		A07AA10	Colistin	inh	4 mln IU	cont	24. May 2011	Cystic Fibrosis
2202	TOBI, T100	R01AX03	Atrovent	inh	0.375 mg	cont	cont	Cystic Fibrosis
		R05CB06	Mucosolvan	inh	45 mg	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R05CB01	Tussicom	p.o.	1000 mg	cont	cont	Cystic Fibrosis
		A05AA02	Ursofalk	p.o.	500 mg	cont	cont	Hepatic lesion

		A09AA02	Kreon 25000	p.o.	PRN	cont	cont	Pancreatic insufficiency
		A09AA02	Kreon 10000	p.o.	PRN	cont	cont	Pancreatic insufficiency
		A11JC	Adeks	p.o.	2 tab	cont	cont	Pancreatic insufficiency
		J01CR05	Tazolin	i.v.	13.5 g	20. Mar 2011	03. Apr 2011	Broncho-pulmonary exacerbation
		J01GB06	Amikin	i.v.	1.4 g	20. Mar 2011	03. Apr 2011	Broncho-pulmonary exacerbation
		A07AA02	Nystatyna	p.o.	6 tab	20. Mar 2011	03. Apr 2011	Broncho-pulmonary exacerbation
		G01AX14	Lacidofil	p.o.	2 caps	20. Mar 2011	03. Apr 2011	Broncho-pulmonary exacerbation
2203	TOBI, T100	R01AX03	Atrovent	inh	0.5 mg	cont	cont	Cystic Fibrosis
		R05CB06	Mucosolvan	inh	37.5 mg	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R05CB01	Tussicom	p.o.	1000 mg	cont	cont	Cystic Fibrosis
		A05AA02	Proursan	p.o.	500 mg	cont	cont	Hepatic lesion
		A09AA02	Lipancrea 16000	p.o.	PRN	cont	cont	Pancreatic insufficiency
		B02BA01	Vitacon	p.o.	10 mg once a week	cont	cont	Pancreatic insufficiency
		A11B	Multivitamins	p.o.	1 tab	cont	cont	Pancreatic insufficiency
		A07AA10	Colistin	In.h	4 mln IU	cont	24. May 2011	Cystic Fibrosis
		A03AD02	No-spa	p.o.	160 mg	17. Jul 2011	17. Jul 2011	Abdominal pain
2204	T100, TOBI	R01AX03	Atrovent	inh	0.625 mg	cont	cont	Cystic Fibrosis
		A07AA10	Colistin	inh	4 mln IU	cont		Cystic Fibrosis
		B05CB	5% NaCl	inh	20 ml	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		J01FA10	Azimycin	p.o.	250 mg every second day	cont	cont	Cystic Fibrosis
		R06AX13	Claritine	p.o.	10 mg	cont	cont	Cystic Fibrosis
		R03DC03	Singulair	p.o.	10 mg	cont	cont	Cystic Fibrosis
		R03AC12+R03BA05	Seretide	inh	1000 µg	cont	cont	Cystic Fibrosis
		A09AA02	Kreon 25000	p.o.	10 caps	cont	cont	Pancreatic insufficiency
		A11B	Multivitamins	p.o.	2 tab	cont	cont	Pancreatic insufficiency
		A12BA51	Gastrolit	p.o.	1 bag	cont	cont	Pancreatic insufficiency

		G03AA07	Rigevidon	p.o.	1 tab	cont	cont	Contraception
		R02AA12	Cholisept	p.o.	2 tab	12. Sep 2011	17. Sep 2011	Rhinopharingitis
2205	TOBI, T100	R01AX03	Atrovent	inh	0.25 mg	cont	cont	Cystic Fibrosis
		R05CB06	Mucosolvan	inh	70 mg every second day	cont	cont	Cystic Fibrosis
		R05CB01	ACC	inh	600 mg every second day	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A09AA02	Kreon 25000	p.o.	5 caps	cont	cont	Pancreatic insufficiency
		A05AA02	Ursofalk	p.o.	500 mg	cont	cont	Hepatic lesion
		V06DX	Urosept	p.o.	2 tab	14. Jun 2011	cont	Nephrolithiasis
		A03AD02	No-spa forte	p.o.	160 mg	14. Jun 2011	cont	Nephrolithiasis
		J01FA10	Azimycin	p.o.	250 mg every second day	cont	cont	Cystic Fibrosis
		R05CB01	Fluimucil	p.o.	600 mg	cont	cont	Cystic Fibrosis
		A11B	Multivitamins	p.o.	2 tab	cont	cont	Pancreatic insufficiency
		J01CR05	Tazolin	i.v.	12 g	24. May 2011	07. Jun 2011	Broncho pulmonary exacerbation
		A07AA02	Nystatyna	p.o.	6 tab	24. May 2011	07. Jun 2011	Broncho pulmonary exacerbation
		G01AX14	Validofil (Lacidofil)	p.o.	2 caps	24. May 2011	07. Jun 2011	Broncho pulmonary exacerbation
		M01AE03	Ketonal	i.m.	100 mg	15. Sep 2011	15. Sep 2011	Nephrocolic
2206	T100, TOBI	R01AX03	Atrovent	inh	0.375 mg	cont	cont	Cystic Fibrosis
		R05CB06	Mucosolvan	inh	75 mg	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R03AC12+R03BA05	Seretide	inh	500 µg	cont	cont	Cystic Fibrosis
		R05CB01	Tussicom	p.o.	1200 mg	cont	cont	Cystic Fibrosis
		J01FA10	Azitrolek	p.o.	250 mg every second day	cont	cont	Cystic Fibrosis

		R06AX13	Claritine	p.o.	10 mg	cont	cont	Cystic Fibrosis
		R03DC03	Singulair	p.o.	10 mg	cont	cont	Cystic Fibrosis
		A05AA02	Ursofalk	p.o.	1000 mg	cont	cont	Hepatic lesion
		A09AA02	Kreon 25000	p.o.	2 caps	cont	cont	Pancreatic insufficiency
		A09AA02	Kreon 10000	p.o.	10 caps	cont	cont	Pancreatic insufficiency
		A11B	Multivitamine	p.o.	2 tab	cont	cont	Pancreatic insufficiency
3201	TOBI, T100	A09AA02	Kreon 10000	p.o.	20 caps	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		B05CB	10% NaCl	inh	4 ml	cont	cont	Cystic Fibrosis
		D07AC17	Flixotide	inh	1000 µg	cont	cont	Cystic Fibrosis
		A02BC01	Omeprazol	p.o.	20 mg	cont	cont	Cystic Fibrosis
		N02X02	Tramal	p.o.	75 mg	cont	cont	Abdominal pain
		N02AB02	Dolargan	i.v.	NK	18. Jun 2011	18. Jun 2011	AE 1
		A02BA02	Ranigast	i.v.	NK	18. Jun 2011	18. Jun 2011	AE 1
		A03AD02	No-Spa	i.v.	NK	18. Jun 2011	18. Jun 2011	AE 1
		A02BC05	Nexium	p.o.	NK	18. Jun 2011	18. Jun 2011	AE 1
		N01AH01	Fentanyl	i.v.	NK	18. Jun 2011	18. Jun 2011	AE 1
		A03BB01	Buscolysin	i.v.	NK	18. Jun 2011	18. Jun 2011	AE 1
		G03AA12	Yasminelle	p.o.	1 tab, comp. drug	cont	cont	Contraception
3202	T100, TOBI	A09AA02	Lipancrea 16000	p.o.	10 caps	cont	cont	Cystic Fibrosis
		A11JC	AquADEKs	p.o.	2 caps	cont	cont	Cystic Fibrosis
		A05AA02	Ursocam	p.o.	500 mg	cont	cont	Liver disease in Cystic fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		B05CB	7% NaCl	inh	3 ml	cont	cont	Cystic Fibrosis
		R03AC02	Sterineb salamol	inh	2.5 mg	cont	cont	Cystic Fibrosis
3203	T100, TOBI	A11B	Multivitaminum	p.o.	1 tab	cont	cont	Cystic Fibrosis
		A09AA02	Kreon 25000 IU	p.o.	9 caps	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A11CC06	Calcifediol	p.o.	10 µg	cont	cont	Cystic Fibrosis

		A11CA02	Betakarotene	p.o.	20 mg	cont	cont	Cystic Fibrosis
		A05AA02	UDCA	p.o.	500 mg	cont	cont	Cystic Fibrosis
		B02BA01	Phytomenadione	p.o.	2.85 mg	cont	cont	Cystic Fibrosis
		A02BC01	Omeprazolum	p.o.	20 mg	cont	cont	Chronic gastritis
		J01FA10	Azithromycin	p.o.	125 mg	cont	cont	Cystic Fibrosis
		R05C	Carbocisteine	p.o.	750 mg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alpha	inh	2.5 mg	cont	cont	Cystic Fibrosis
		B05CB	6% NaCl	inh	6 ml	cont	cont	Cystic Fibrosis
3204	TOBI, T100	A11B	Multivitamin	p.o.	2 tab	UN Jul 2004	cont	Cystic Fibrosis
		A11HA03	Vitamin E	p.o.	400 mg	UN Jul 2004	cont	Cystic Fibrosis
		A11CC06	Devisol 25	p.o.	10 µg	UN Jul 2004	cont	Cystic Fibrosis
		A11CA02	B-Carotene	p.o.	10 mg	UN Jul 2004	cont	Cystic Fibrosis
		A09AA02	Lipancrea 16000	p.o.	11 caps	UN Jul 2008	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	UN Sep 2003	cont	Cystic Fibrosis
		B05CB	5% NaCl	inh	8 ml	UN Aug 2009	cont	Cystic Fibrosis
		R01AD08	Flixonase	topical	2 puff	UN Jul 2006	cont	Cystic Fibrosis
		A05AA02	Ursopol	p.o.	300 mg	UN Jul 2008	cont	Cystic Fibrosis
3205	T100, TOBI	R05CB06	Mucosolvan	inh	30 mg	cont	cont	Cystic Fibrosis
		G02CA +R01AX03	Berodual	inh	20 gutt	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A09AA02	Lipancrea 16000	p.o.	14 caps	cont	cont	Cystic Fibrosis
		R06AE07	Zyrtec	p.o.	10 mg	cont	cont	Allergy
		R03DC03	Singulair	p.o.	10 mg	cont	cont	Allergy
3206	TOBI, T100	A11B	Multivitaminum	p.o.	1 tab	cont	cont	Cystic Fibrosis
		A11HA03	Vitaminum E	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A11CC06	Devisol-25	p.o.	20 µg	cont	cont	Cystic Fibrosis
		A11CA02	Beta Karoten	p.o.	30 mg	cont	cont	Cystic Fibrosis
		B02BA01	Vitacon	p.o.	2.86 mg	cont	cont	Cystic Fibrosis
		A05AA02	Ursopol	p.o.	300 mg	cont	cont	Cystic Fibrosis
		C10AX06	Galomega	p.o.	6 caps	cont	cont	Cystic Fibrosis

		A09AA02	Lipancrea 16000 I.U.	p.o.	14 caps	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		B05CB	7% NaCl	inh	10 ml	cont	cont	Cystic Fibrosis
3207	T100, TOBI	A11B	Multivitaminum	p.o.	2 tab	cont	cont	Cystic Fibrosis
		A11HA03	(Tocopherol) Vitaminum E	p.o.	400 mg	cont	cont	Cystic Fibrosis
		B02BA01	Phytomenadione (Vitacon)	p.o.	2.86 mg	cont	cont	Cystic Fibrosis
		A11CA02	Betakaroten	p.o.	20 mg	cont	cont	Cystic Fibrosis
		A11CC06	Calcifediol (Devisol)	p.o.	15 µg	cont	cont	Cystic Fibrosis
		A09AA02	Pancreatic enzymes (Kreon 25000)	p.o.	4 caps	cont	cont	Cystic Fibrosis
		A09AA02	Pancreatic enzymes (Kreon 10000)	p.o.	5 caps	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alpha	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R05CB06	Ambroxol	inh	8 ml	cont	cont	Cystic Fibrosis
		G02CA +R01AX03	Berodual	inh	2 ml	cont	cont	Cystic Fibrosis
		A07EA06	Buderhin (Budesonidum)	inh	4 puffs	cont	cont	Nasal p.o.lyps
		A05AA02	UDCA (Ursopol)	p.o.	900 mg	cont	cont	Cystic Fibrosis
		A02BC01	Omeprazol (Polprazol)	p.o.	20 mg	cont	cont	Cystic Fibrosis
		R07AA02	Essentiale forte	p.o.	2 caps	cont	cont	Cystic Fibrosis
		A05BA	Hepatil	p.o.	2 tab	cont	cont	Cystic Fibrosis
3208	TOBI, T100	A11B	Multivitaminum	p.o.	1 tab	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol (Vit. E)	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A11CA02	Beta Karotene	p.o.	20 mg	cont	cont	Cystic Fibrosis
		A11CC05	Cholekalciferol (Devisol-25)	p.o.	10 µg	cont	cont	Cystic Fibrosis
		J01FA10	Azithromycin	p.o.	250 mg	cont	cont	Cystic Fibrosis
		M01AE01	Ibuprofen	p.o.	800 mg	cont	cont	Cystic Fibrosis
		R05CB01	Acetylcysteinum (ACC)	p.o.	600 mg	cont	cont	Cystic Fibrosis
		A05AA02	UDCA (Ursopol)	p.o	600 mg	cont	cont	Cystic Fibrosis
		A05BA06	Hepatil	p.o	3 tab	cont	cont	Cystic Fibrosis
		R07AA02	Essentiale forte	p.o	3 tab	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alpha (Pulmozyme)	inh	2.5 mg	cont	cont	Cystic Fibrosis
		C09CA03	Co-Diovan 160/25	p.o.	0.5 tab	cont	cont	Mild Hypertension

3209	TOBI, T100	R05CB06	Mucosolvan	inh	30 mg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alfa	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A09AA02	Kreon 25000	p.o.	7 caps	cont	cont	Cystic Fibrosis
		A09AA02	Lipancrea 16000	p.o.	7 caps	cont	cont	Cystic Fibrosis
		A02BC01	Prazol	p.o.	20 mg	cont	cont	Cystic Fibrosis
		A11B	Multivitamin	p.o.	2 tab	cont	cont	Cystic Fibrosis
		A11HA03	Vitamin E	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A11CC06	Devisol	p.o.	10 µg	cont	cont	Cystic Fibrosis
		J01FA10	Azimycin	p.o.	250 mg every second day	cont	cont	Cystic Fibrosis
		A05AA02	Ursopol	p.o.	600 mg	cont	cont	Cystic Fibrosis
		R07AA02	Essentiale forte	p.o.	2 tab	cont	cont	Cystic Fibrosis
		B02BA01	Vitacon	p.o.	2 tab per week	cont	cont	Cystic Fibrosis
		J01CR02	Augmentin	p.o.	2 g	19. Sep 2011	26. Sep 2011	AE no 2
3210	T100, TOBI	A11B	Multivitaminum	p.o.	1 tab	cont	cont	Cystic Fibrosis
		A11HA03	Tocopherol	p.o.	400 mg	cont	cont	Cystic Fibrosis
		A11CC06	Calcifediol	p.o.	10 µg	cont	cont	Cystic Fibrosis
		B02BA01	Phytomenadione	p.o.	2.86 mg	cont	cont	Cystic Fibrosis
		A09AA02	Pancreatic enzymes (Kreon 25000 IU)	p.o.	12 cap	cont	cont	Cystic Fibrosis
		A09AA02	Pancreatic enzymes (Lipancrea 16000 IU)	p.o.	3 cap	cont	cont	Cystic Fibrosis
		J01FA10	Azithromycin	p.o.	250 mg	cont	cont	Cystic Fibrosis
		R05CB13	Dornase alpha	inh	2.5 mg	cont	cont	Cystic Fibrosis
		B05CB	5% NaCl	inh	8 ml	cont	cont	Cystic Fibrosis
		A05AA02	UDCA (Ursofalk)	p.o.	500 mg	cont	cont	Cystic Fibrosis
4103	TOBI, T100	A09AA02	Kreon	p.o.	25000 Fip	cont	cont	Cystic Fibrosis
		B02BA	Vit. K	p.o.	10 mg	cont	cont	Cystic Fibrosis
		A11CC04	Vit. D3	p.o.	800 IU	cont	cont	Cystic Fibrosis
		A11CA01	Vit. A	p.o.	6400 IU	cont	cont	Cystic Fibrosis
		A11HA03	Vit. E	p.o.	1100 mg	cont	cont	Cystic Fibrosis

		R05CB01	Acetylcysteine	p.o.	600 mg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	600 µg	cont	cont	Cystic Fibrosis
		R05CB13	rhDNase	inh	2.5 mg	cont	cont	Cystic Fibrosis
4104	T100, TOBI	A09AA02	Kreon	p.o.	200000 Fip	cont	cont	Cystic Fibrosis
		R05CB01	Acetylcysteine	p.o.	600 mg	cont	cont	Cystic Fibrosis
		G02CA +R01AX03	Berodual	inh	3 ml	cont	cont	Cystic Fibrosis
		R05CB13	rhDNase	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A11B	Multivitamin	p.o.	3 tab	cont	cont	Cystic Fibrosis
4105	T100, TOBI	A09AA02	Kreon	p.o.	150000 Fip	cont	cont	Cystic Fibrosis
		B02BA	Vit. K	p.o.	10 mg	cont	cont	Cystic Fibrosis
		R05CB01	Acetylcysteine	p.o.	600 mg	cont	cont	Cystic Fibrosis
		A05AA02	UDCA	p.o.	750 mg	cont	cont	Cystic Fibrosis
		A02BC01	Omeprazol	p.o.	20 mg	cont	cont	Cystic Fibrosis
		A11CC04	Vit. D3	p.o.	800 IU	cont	cont	Cystic Fibrosis
		A11HA03	Vit. E	p.o.	55 mg	cont	cont	Cystic Fibrosis
		A11CA01	Vit. A	p.o.	3600 IU	cont	cont	Cystic Fibrosis
		R05CB13	rhDNase	inh	2.5 mg	cont	cont	Cystic Fibrosis
		R05CB06	Ambroxol hydrochl.	inh	22.5 mg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	600 mg	cont	cont	Cystic Fibrosis
4204	TOBI, T100	A09AA02	Kreon 25000	p.o.	150000 IU	cont	cont	Cystic Fibrosis
		A11CC04	Vit. D3	p.o.	400 IU	cont	cont	Cystic Fibrosis
		A11CA01	Vit. A	p.o.	8000 IU	cont	cont	Cystic Fibrosis
		A11HA03	Vit. E	p.o.	110 mg	cont	cont	Cystic Fibrosis
		B02BA	Vit. K	p.o.	10 mg	cont	cont	Cystic Fibrosis
		R03AC02	Ventolin	inh	200 mg	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
4205	TOBI, T100	A09AA02	Kreon 25000	p.o.	25000 IU	cont	cont	Cystic Fibrosis
		A11CA01	Vit. A	p.o.	8000 IU	cont	cont	Cystic Fibrosis
		A11HA03	Vit. E	p.o.	110 mg	cont	cont	Cystic Fibrosis

		A11CC04	Vit. D3	p.o.	400 IU	cont	cont	Cystic Fibrosis
		B02BA	Vit. K	p.o.	10 mg	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 mg	cont	cont	Cystic Fibrosis
		A07AA10	Colistine	inh	4 Million IU	13. Apr 2011	20. Jul 2011	Cystic Fibrosis
		R03AC02	Salbutamol	inh	400 µg	cont	cont	Cystic Fibrosis
4206	T100, TOBI	A09AA02	Kreon 25000	p.o.	175000 IU	cont	cont	Cystic Fibrosis
		R05CB01	Acetylcysteine	p.o.	600 mg	cont	cont	Cystic Fibrosis
		A11CC04	Vit. D3	p.o.	400 IU	cont	cont	Cystic Fibrosis
		A11CA01	Vit. A	p.o.	8000 IU	cont	cont	Cystic Fibrosis
		A11HA03	Vit. E	p.o.	110 mg	cont	cont	Cystic Fibrosis
		R01AD05	Budesonid	nasal	64 mg	cont	cont	Cystic Fibrosis
		R03AC02	Salbutamol	inh	400 µg	cont	cont	Cystic Fibrosis
		B05CB	7% NaCl	inh	8 ml	cont	cont	Cystic Fibrosis
		R05CB13	Pulmozyme	inh	2.5 µg	cont	cont	Cystic Fibrosis
		B02BA	Vit. K	p.o.	10 mg	cont	cont	Cystic Fibrosis

Table 33 Visit 6

Enrolment No.	Treatment order		Visit 6				
		Has the patient ended the participation in the study prematurely?	Date of visit dd.mmm.yyyy	Are there AEs since last visit?	Has patient changed the concomitant therapy since last visit?	Has the CFQ-R been filled by the patient/parents?	If not on previous visits: Has the remaining study drug together with the inhalation devices been collected?
1101	R, T	no	30. Aug. 2011	no	no	yes	N/A
1102	T, R	no	30. Aug. 2011	no	no	yes	N/A
1103	T, R	no	04. Oct. 2011	no	no	yes	N/A
1104	R, T	no	04. Oct. 2011	no	no	yes	N/A
1105	T, R	no	04. Oct. 2011	no	no	yes	N/A
1106	R, T	no	01. Dec. 2011	no	no	yes	N/A
1107	T, R	no	04. Jan. 2012	no	no	yes	N/A
1108	R, T	no	04. Jan. 2012	no	no	yes	N/A
1109	R	yes	30. Nov. 2011	yes	yes	yes	N/A
1110	T, R	no	07. Feb. 2012	no	no	yes	N/A
1111	T, R	no	20. Feb. 2012	no	no	yes	N/A
1112	R, T	no	07. Feb. 2012	no	no	yes	N/A
1113	T, R	no	20. Feb. 2012	no	no	yes	N/A
1114	R, T	no	06. Mar. 2012	no	no	yes	N/A
2101	R, T	no	19. Sep. 2011	no	no	yes	N/A
2102	T, R	no	19. Sep. 2011	no	no	yes	N/A
2103	T, R	no	19. Sep. 2011	no	no	yes	N/A
2104	R	yes	21. Jun. 2011	yes	yes	yes	yes
2105	R, T	no	25. Oct. 2011	yes	yes	yes	N/A
2106	T, R	no	09. Nov. 2011	no	no	yes	N/A
2107	R, T	no	17. Jan. 2012	no	no	yes	N/A

2108	T	yes	30. Dec. 2011	yes	yes	yes	N/A
3101	R, T	no	24. Nov. 2011	no	no	yes	N/A
3102	T, R	no	01. Dec. 2011	no	no	no	N/A
3103	R, T	no	01. Dec. 2011	no	no	no	N/A
4101	T, R	no	15. Sep. 2011	no	no	yes	N/A
4102	R, T	no	15. Sep. 2011	no	no	yes	N/A
4106	R, T	no	04. Oct. 2011	no	no	yes	N/A
1201	R, T	no	30. Aug. 2011	no	no	yes	N/A
1202	T, R	no	19. Sep. 2011	no	no	yes	N/A
1203	R, T	no	19. Sep. 2011	no	yes	yes	N/A
1204	T, R	no	19. Sep. 2011	no	no	yes	N/A
1205	T	yes	07. Oct. 2011	yes	yes	yes	N/A
1206	R, T	no	10. Nov. 2011	no	no	yes	N/A
1207	T, R	no	10. Nov. 2011	no	no	yes	N/A
1208	R, T	no	01. Dec. 2011	no	no	yes	N/A
2201	T, R	no	29. Aug. 2011	yes	no	yes	N/A
2202	R, T	no	29. Aug. 2011	no	no	yes	N/A
2203	R, T	no	29. Aug. 2011	no	no	yes	N/A
2204	T, R	no	25. Oct. 2011	yes	no	yes	N/A
2205	R, T	no	25. Oct. 2011	no	no	yes	N/A
2206	T, R	no	09. Nov. 2011	no	no	yes	N/A
3201	R, T	no	04. Sep. 2011	no	no	yes	N/A
3202	T, R	no	04. Sep. 2011	no	no	yes	N/A
3203	T, R	no	05. Sep. 2011	no	no	yes	N/A
3204	R, T	no	09. Sep. 2011	no	no	yes	N/A
3205	T, R	no	19. Sep. 2011	no	no	yes	N/A
3206	R, T	no	19. Sep. 2011	no	no	yes	N/A
3207	T, R	no	28. Sep. 2011	no	no	yes	N/A
3208	R, T	no	03. Oct. 2011	yes	no	yes	N/A
3209	R, T	no	03. Oct. 2011	no	no	yes	N/A
3210	T, R	no	10. Oct. 2011	yes	no	yes	N/A
4103	R, T	no	04. Oct. 2011	no	no	yes	N/A
4104	T, R	no	04. Oct. 2011	no	no	yes	N/A

4105	T, R	no	04. Oct. 2011	no	no	yes	N/A
4204	R, T	no	21. Nov. 2011	no	no	yes	N/A
4205	R, T	no	21. Nov. 2011	no	no	yes	N/A
4206	T, R	no	21. Nov. 2011	no	no	yes	N/A

N/A = not applicable

14.2 PK and Clinical Efficacy Data Summary

14.2.1 PK Data Summary

Table 34 Deviation of Blood Sampling Time

Enrolment No.	Treatment order	Blood collection for pharmacokinetics									Blood collection for pharmacokinetics								
		Visit 3									Visit 5								
		Sample no.									Sample no.								
		1	2	3	4	5	6	7	8	9	1	2	3	4	5	6	7	8	9
		Time (min)									Time (min)								
		(-)0:30 to (-)0:15	0:30	1:00	1:30	2:00	4:00	6:00	8:00	12:00	(-)0:30 to (-)0:15	0:30	1:00	1:30	2:00	4:00	6:00	8:00	12:00
		Time of sample h:min									Time of sample h:min								
1101	R, T																		
1102	T, R																		
1103	T, R																		
1104	R, T																		
1105	T, R																		
1106	R, T																		
1107	T, R																		
1108	R, T																		
1109	R																		
1110	T, R																		
1111	T, R																		
1112	R, T																		
1113	T, R																		
1114	R, T																		
2101	R, T																		
2102	T, R		3																

2103	T, R		1									1							
2104	R																		
2105	R, T		2																
2106	T, R		2									1							
2107	R, T										2								
2108	T																		
3101	R, T																		
3102	T, R																		
3103	R, T																		
4101	T, R			4	2	8		7					5	1	1				
4102	R, T				4	2	4					2		1					
4106	R, T		6	2								2							
1201	R, T																		
1202	T, R																		
1203	R, T																		
1204	T, R																		
1205	T																		
1206	R, T																		
1207	T, R																		
1208	R, T																		
2201	T, R		1									2							
2202	R, T		2	1								1							
2203	R, T		2		2														
2204	T, R		2									1							
2205	R, T		2																
2206	T, R		1																
3201	R, T		3																
3202	T, R		2																
3203	T, R		4		1	1													
3204	R, T																		
3205	T, R																		
3206	R, T																		
3207	T, R																		

3208	R, T																		
3209	R, T																		
3210	T, R																		
4103	R, T											7							
4104	T, R		-1	2	-2							7							
4105	T, R		-1									1							
4204	R, T		6		1	10		1											
4205	R, T		2																
4206	T, R		5		2	3	1												

Table 35 Deviation of Sputum Sampling Time

Enrolment No.	Treatment order	Sputum collection for pharmacokinetics						Sputum collection for pharmacokinetics					
		Visit 3						Visit 5					
		Sample no.						Sample no.					
		1	2	3	4	5	6	1	2	3	4	5	6
		Time [min]						Time [min]					
		(-)0:30 to (-)0:15	0:10	0:30	1:30	2:00	8:00	(-)0:30 to (-)0:15	0:10	0:30	1:30	2:00	8:00
1101	R, T												
1102	T, R												
1103	T, R												
1104	R, T												
1105	T, R												
1106	R, T												
1107	T, R												
1108	R, T												
1109	R												
1110	T, R												
1111	T, R												
1112	R, T												
1113	T, R												
1114	R, T												
2101	R, T			1	3	1				2			
2102	T, R			4						2			

2103	T, R			2	1	3				3			
2104	R												
2105	R, T			1		1							
2106	T, R			4						2			
2107	R, T	-8											
2108	T												
3101	R, T												
3102	T, R												
3103	R, T	26											
4101	T, R			4				6					
4102	R, T		6					6				-1	
4106	R, T			5									
1201	R, T												
1202	T, R												
1203	R, T												
1204	T, R												
1205	T												
1206	R, T												
1207	T, R												
1208	R, T												
2201	T, R			2							1	2	
2202	R, T			1						1			
2203	R, T	5		1						1			
2204	T, R												
2205	R, T			1									
2206	T, R			2									
3201	R, T			4	3	1							
3202	T, R			7	1								
3203	T, R			5	2	2							
3204	R, T												
3205	T, R			1	1	2							
3206	R, T			2	4	2							
3207	T, R												

3208	R, T												
3209	R, T												
3210	T, R												
4103	R, T			10						2	3	3	
4104	T, R									2			
4105	T, R			6	1								
4204	R, T		6	-		4				2			1
4205	R, T			4									
4206	T, R		1	7						1			

14.2.2 Clinical Efficacy Data Summary

Table 36 CFU Log-Normalized Values Density

Enrolment No.		Treatment order	Visit 2	Visit 3	Visit 4	Visit 5
			log_{10} CFU	log_{10} CFU	log_{10} CFU	log_{10} CFU
1102	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
1103	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
1105	Group 1: 4-13	T, R	0.00	-5.00	-4.10	-0.90
1107	Group 1: 4-13	T, R	0.00	-3.60	-3.60	-3.60
1110	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
1111	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
1113	Group 1: 4-13	T, R	0.00	-0.77	-0.77	-0.77
2102	Group 1: 4-13	T, R	0.00	-1.44	0.74	0.97
2103	Group 1: 4-13	T, R	0.00	-1.14	-0.13	0.02
2106	Group 1: 4-13	T, R	0.00	-1.66	-0.21	-0.79
3102	Group 1: 4-13	T, R	0.00	-7.10	-7.10	-7.10
4101	Group 1: 4-13	T, R	0.00	-3.42	-3.03	-5.28
2108	Group 1: 4-13	T	0.00	-0.46		
1101	Group 1: 4-13	R, T	0.00	-0.42	-4.74	-4.74
1104	Group 1: 4-13	R, T	0.00	0.00	0.00	0.00
1106	Group 1: 4-13	R, T	0.00	0.00	3.00	0.00
1108	Group 1: 4-13	R, T	0.00	-3.90	-3.90	-3.90
1112	Group 1: 4-13	R, T	0.00	0.00	0.00	0.00
1114	Group 1: 4-13	R, T	0.00	-5.44	-4.54	-3.84
2101	Group 1: 4-13	R, T	0.00	-1.76	-2.13	-3.54
2105	Group 1: 4-13	R, T	0.00	0.90	0.84	-0.67
2107	Group 1: 4-13	R, T	0.00	0.07	0.86	-2.88
3101	Group 1: 4-13	R, T	0.00	-8.80	-1.50	-8.80

3103	Group 1: 4-13	R, T	0.00	-9.70	0.00	-1.90
4102	Group 1: 4-13	R, T	0.00	-5.68	-0.16	-5.38
4106	Group 1: 4-13	R, T	0.00	-0.43	0.92	0.48
1202	Group 2: >13	T, R	0.00	0.60	-4.30	-0.30
1204	Group 2: >13	T, R	0.00	-6.77	-6.77	-1.57
1207	Group 2: >13	T, R	0.00	-0.60	0.50	0.10
2201	Group 2: >13	T, R	0.00	-0.05	0.45	0.46
2204	Group 2: >13	T, R	0.00	-0.30	0.26	-0.38
2206	Group 2: >13	T, R	0.00	-0.08	3.51	0.03
3202	Group 2: >13	T, R	0.00	-9.10	-9.10	-9.10
3203	Group 2: >13	T, R	0.00	-2.40	-0.90	-1.60
3205	Group 2: >13	T, R	0.00	-1.40	-0.20	0.30
3207	Group 2: >13	T, R	0.00	0.10	-0.20	0.30
3210	Group 2: >13	T, R	0.00	0.80	1.20	-0.40
4104	Group 2: >13	T, R	0.00	0.25	1.12	1.43
4105	Group 2: >13	T, R	0.00	2.16	0.69	1.41
4206	Group 2: >13	T, R	0.00	-2.29	-0.19	-2.22
1205	Group 2: >13	T	0.00	-5.92		
1201	Group 2: >13	R, T	0.00	1.34	1.60	-1.40
1203	Group 2: >13	R, T	0.00	1.74	0.74	0.16
1206	Group 2: >13	R, T	0.00	-4.11	-4.11	-0.71
1208	Group 2: >13	R, T	0.00	-2.06	-1.26	-1.01
2202	Group 2: >13	R, T	0.00	-0.82	0.08	0.09
2203	Group 2: >13	R, T	0.00	1.36	-0.20	0.20
2205	Group 2: >13	R, T	0.00	0.08	0.21	-0.64
3201	Group 2: >13	R, T	0.00	0.00	0.90	0.10
3204	Group 2: >13	R, T	0.00	-1.70	1.30	-0.40
3206	Group 2: >13	R, T	0.00	-0.30	0.10	-9.00
3208	Group 2: >13	R, T	0.00	-3.30	-0.70	-1.80
3209	Group 2: >13	R, T	0.00	-0.90	-1.00	-1.30
4103	Group 2: >13	R, T	0.00	0.17	1.19	2.37
4204	Group 2: >13	R, T	0.00	0.15	0.15	0.15

4205	Group 2: >13	R, T	0.00	-4.06	-0.79	-1.13

Age 4 - 13 with Drop-outs		**Week**	**2**	**6**	**10**	**14**
SD (±)	T100 (2/3), TOBI (4/5)	SD (±)	0.00	2.25	2.39	2.50
	TOBI (2/3), T100 (4/5)	SD (±)	0.00	3.63	2.35	2.72

Age >13 with Drop-outs		**Week**	**2**	**6**	**10**	**14**
	T100 (2/3), TOBI (4/5)	SD (±)	0.00	3.18	3.40	2.60
	TOBI (2/3), T100 (4/5)	SD (±)	0.00	1.88	1.40	2.44

Both groups with Drop-outs		**Week**	**2**	**6**	**10**	**14**
	T100 (2/3), TOBI (4/5)	SD (±)	0.00	2.74	2.93	2.53
	TOBI (2/3), T100 (4/5)	SD (±)	0.00	2.93	1.90	2.68

Age 4 - 13 with Drop-outs		**Week**	**2**	**6**	**10**	**14**
	T100 (2/3), TOBI (4/5)	Arithmetic mean	0.00	-1.89	-1.52	-1.45
	TOBI (2/3), T100 (4/5)	Arithmetic mean	0.00	-2.70	-0.87	-2.71

Age >13 with Drop-outs		**Week**	**2**	**6**	**10**	**14**
	T100 (2/3), TOBI (4/5)	Arithmetic mean	0.00	-1.67	-0.99	-0.82
	TOBI (2/3), T100 (4/5)	Arithmetic mean	0.00	-0.83	-0.12	-0.95

		Week	2	6	10	14
Both groups with Drop-outs	T100 (2/3), TOBI (4/5)	Arithmetic mean	0.00	-1.77	-1.24	-1.12
	TOBI (2/3), T100 (4/5)	Arithmetic mean	0.00	-1.70	-0.47	-1.77

Age 4 - 13					
N	**26**	**26**	**25**	**25**
Arithmetic mean	**0.00**	**-2.30**	**-1.18**	**-2.10**
SD (±)	**0.000**	**2.984**	**2.345**	**2.641**
CV (%)		**-129.8**	**-198.5**	**-125.5**
Minimum	**0.00**	**-9.70**	**-7.10**	**-8.80**
Maximum	**0.00**	**0.90**	**3.00**	**0.97**
Median	**0.00**	**-0.96**	**-0.13**	**-0.79**

Age >13				
N	**30**	**30**	**29**	**29**
Arithmetic mean	**0.00**	**-1.25**	**-0.54**	**-0.89**
SD (±)	**0.000**	**2.599**	**2.559**	**2.475**
CV (%)		**-208.4**	**-472.5**	**-277.5**
Minimum	**0.00**	**-9.10**	**-9.10**	**-9.10**
Maximum	**0.00**	**2.16**	**3.51**	**2.37**
Median	**0.00**	**-0.30**	**0.10**	**-0.38**

Both groups				
N	**56**	**56**	**54**	**54**
Arithmetic mean	**0.00**	**-1.74**	**-0.84**	**-1.45**
SD (±)	**0.000**	**2.809**	**2.460**	**2.601**
CV (%)		**-161.9**	**-293.7**	**-179.0**
Minimum	**0.00**	**-9.70**	**-9.10**	**-9.10**
Maximum	**0.00**	**2.16**	**3.51**	**2.37**
Median	**0.00**	**-0.53**	**0.00**	**-0.52**

Table 37 CFU Log-Normalized Values Mucoid Biotype

Enrolment No.		Treatment order	Visit 2	Visit 3	Visit 4	Visit 5
			log_{10} CFU mucoid biotype	log_{10} CFU mucoid biotype	log_{10} CFU mucoid biotype	log_{10} CFU mucoid biotype
1102	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
1103	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
1105	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
1107	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
1110	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
1111	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
1113	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
2102	Group 1: 4-13	T, R	0.00	-1.45	0.77	1.00
2103	Group 1: 4-13	T, R	0.00	-0.52	-3.30	-3.30
2106	Group 1: 4-13	T, R	0.00	-1.77	-0.31	-0.83
3102	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
4101	Group 1: 4-13	T, R	0.00	-3.42	-3.03	-5.28
2108	Group 1: 4-13	T	0.00	0.63		
1101	Group 1: 4-13	R, T	0.00	-0.69	-3.69	-3.69
1104	Group 1: 4-13	R, T	0.00	0.00	0.00	0.00
1106	Group 1: 4-13	R, T	0.00	0.00	0.00	0.00
1108	Group 1: 4-13	R, T	0.00	0.00	0.00	0.00
1112	Group 1: 4-13	R, T	0.00	0.00	0.00	0.00
1114	Group 1: 4-13	R, T	0.00	-5.34	-4.44	-3.74
2101	Group 1: 4-13	R, T	0.00	-1.69	-2.06	-3.47
2105	Group 1: 4-13	R, T	0.00	0.00	0.00	0.00
2107	Group 1: 4-13	R, T	0.00	0.00	0.00	0.00
3101	Group 1: 4-13	R, T	0.00	-8.70	-8.70	-8.70
3103	Group 1: 4-13	R, T	0.00	-9.30	0.40	-1.60
4102	Group 1: 4-13	R, T	0.00	-5.65	-0.15	-5.35

4106	Group 1: 4-13	R, T	0.00	-0.39	0.97	0.52
1202	Group 2: >13	T, R	0.00	0.60	-4.30	-5.70
1204	Group 2: >13	T, R	0.00	0.00	0.00	0.00
1207	Group 2: >13	T, R	0.00	0.00	0.00	0.00
2201	Group 2: >13	T, R	0.00	-0.05	0.24	0.25
2204	Group 2: >13	T, R	0.00	0.00	0.00	0.00
2206	Group 2: >13	T, R	0.00	0.00	0.00	0.00
3202	Group 2: >13	T, R	0.00	-8.90	-8.90	-8.90
3203	Group 2: >13	T, R	0.00	-2.40	-0.90	-1.60
3205	Group 2: >13	T, R	0.00	-1.20	0.00	0.30
3207	Group 2: >13	T, R	0.00	0.10	-0.20	0.30
3210	Group 2: >13	T, R	0.00	0.80	1.20	-0.60
4104	Group 2: >13	T, R	0.00	0.25	1.12	1.43
4105	Group 2: >13	T, R	0.00	2.19	0.72	1.44
4206	Group 2: >13	T, R	0.00	-2.29	-0.19	-2.22
1205	Group 2: >13	T	0.00	-5.92		
1201	Group 2: >13	R, T	0.00	0.90	-3.00	-1.40
1203	Group 2: >13	R, T	0.00	1.47	0.70	-4.60
1206	Group 2: >13	R, T	0.00	-4.11	-4.11	-0.71
1208	Group 2: >13	R, T	0.00	4.20	5.00	3.69
2202	Group 2: >13	R, T	0.00	-0.82	0.08	0.09
2203	Group 2: >13	R, T	0.00	0.00	0.00	5.62
2205	Group 2: >13	R, T	0.00	-0.13	-0.07	-1.13
3201	Group 2: >13	R, T	0.00	0.00	0.90	0.10
3204	Group 2: >13	R, T	0.00	0.00	9.60	7.80
3206	Group 2: >13	R, T	0.00	-0.30	0.10	-9.00
3208	Group 2: >13	R, T	0.00	-3.30	-0.70	-1.80
3209	Group 2: >13	R, T	0.00	-0.90	-1.00	-1.30
4103	Group 2: >13	R, T	0.00	4.34	5.36	6.54
4204	Group 2: >13	R, T	0.00	0.00	0.00	0.00
4205	Group 2: >13	R, T	0.00	-3.82	-0.65	-2.23

Age 4 - 13		**Week**	**2**	**6**	**10**	**14**
with Droputs	T100 (2/3), TOBI (4/5)	SD (±)	0.00	1.09	1.27	1.77
SD (±)	TOBI (2/3), T100 (4/5)	SD (±)	0.00	3.52	2.74	2.81

Age >13		**Week**	**2**	**6**	**10**	**14**
with Droputs	T100 (2/3), TOBI (4/5)	SD (±)	0.00	2.85	2.67	2.87
	TOBI (2/3), T100 (4/5)	SD (±)	0.00	2.43	3.43	4.35

Both groups		**Week**	**2**	**6**	**10**	**14**
with Droputs	T100 (2/3), TOBI (4/5)	SD (±)	0.00	2.20	2.11	2.39
	TOBI (2/3), T100 (4/5)	SD (±)	0.00	3.15	3.27	3.80

Age 4 - 13		**Week**	**2**	**6**	**10**	**14**
with Droputs	T100 (2/3), TOBI (4/5)	Arithmetic mean	0.00	-0.50	-0.49	-0.70
	TOBI (2/3), T100 (4/5)	Arithmetic mean	0.00	-2.44	-1.36	-2.00

Age >13		**Week**	**2**	**6**	**10**	**14**
with Droputs	T100 (2/3), TOBI (4/5)	Arithmetic mean	0.00	-1.12	-0.80	-1.09
	TOBI (2/3), T100 (4/5)	Arithmetic mean	0.00	-0.16	0.81	0.11

Both groups		**Week**	**2**	**6**	**10**	**14**
with Droputs	T100 (2/3), TOBI (4/5)	Arithmetic mean	0.00	-0.83	-0.66	-0.91
	TOBI (2/3), T100 (4/5)	Arithmetic mean	0.00	-1.22	-0.19	-0.87

Age 4 - 13

N	**26**	**26**	**25**	**25**
Arithmetic mean	**0.00**	**-1.47**	**-0.94**	**-1.38**
SD (±)	**0.000**	**2.738**	**2.169**	**2.414**
CV (%)		**-185.9**	**-230.5**	**-175.2**
Minimum	**0.00**	**-9.30**	**-8.70**	**-8.70**
Maximum	**0.00**	**0.63**	**0.97**	**1.00**
Median	**0.00**	**0.00**	**0.00**	**0.00**

Age >13

N	**30**	**30**	**29**	**29**
Arithmetic mean	**0.00**	**-0.64**	**0.03**	**-0.47**
SD (±)	**0.000**	**2.649**	**3.145**	**3.695**
CV (%)		**-412.1**	**9108.2**	**-786.2**
Minimum	**0.00**	**-8.90**	**-8.90**	**-9.00**
Maximum	**0.00**	**4.34**	**9.60**	**7.80**
Median	**0.00**	**0.00**	**0.00**	**0.00**

Both groups

N	**56**	**56**	**54**	**54**
Arithmetic mean	**0.00**	**-1.03**	**-0.42**	**-0.89**
SD (±)	**0.000**	**2.698**	**2.756**	**3.171**
CV (%)		**-262.4**	**-660.6**	**-356.3**
Minimum	**0.00**	**-9.30**	**-8.90**	**-9.00**
Maximum	**0.00**	**4.34**	**9.60**	**7.80**
Median	**0.00**	**0.00**	**0.00**	**0.00**

Table 38 CFU Log-Normalized Values Planctonic (dry) Type

Enrolment No.		Treatment order	Visit 2	Visit 3	Visit 4	Visit 5
			log_{10} CFU dry biotype	log_{10} CFU dry biotype	log_{10} CFU dry biotype	log_{10} CFU dry biotype
1102	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
1103	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
1105	Group 1: 4-13	T, R	0.00	-5.00	-4.10	-0.90
1107	Group 1: 4-13	T, R	0.00	-3.60	-3.60	-3.60
1110	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
1111	Group 1: 4-13	T, R	0.00	0.00	0.00	0.00
1113	Group 1: 4-13	T, R	0.00	-0.77	-0.77	-0.77
2102	Group 1: 4-13	T, R	0.00	-1.30	-4.30	-4.30
2103	Group 1: 4-13	T, R	0.00	-1.15	-0.12	0.03
2106	Group 1: 4-13	T, R	0.00	-0.41	0.99	-0.04
3102	Group 1: 4-13	T, R	0.00	-7.10	-7.10	-7.10
4101	Group 1: 4-13	T, R	0.00	-3.70	-3.70	-3.70
2108	Group 1: 4-13	T	0.00	-4.03		
1101	Group 1: 4-13	R, T	0.00	-0.39	-4.69	-4.69
1104	Group 1: 4-13	R, T	0.00	0.00	0.00	0.00
1106	Group 1: 4-13	R, T	0.00	0.00	3.00	0.00
1108	Group 1: 4-13	R, T	0.00	-3.90	-3.90	-3.90

1112	Group 1: 4-13	R, T	0.00	0.00	0.00	0.00
1114	Group 1: 4-13	R, T	0.00	-4.77	-4.77	-4.77
2101	Group 1: 4-13	R, T	0.00	-3.06	-6.95	-6.95
2105	Group 1: 4-13	R, T	0.00	0.90	0.84	-0.67
2107	Group 1: 4-13	R, T	0.00	0.07	0.86	-2.88
3101	Group 1: 4-13	R, T	0.00	-8.30	-1.00	-8.30
3103	Group 1: 4-13	R, T	0.00	-9.50	-9.50	-2.40
4102	Group 1: 4-13	R, T	0.00	-4.48	-0.48	-4.48
4106	Group 1: 4-13	R, T	0.00	-3.60	-0.30	-2.56
1202	Group 2: >13	T, R	0.00	0.00	0.00	5.40
1204	Group 2: >13	T, R	0.00	-6.77	-6.77	-1.57
1207	Group 2: >13	T, R	0.00	-0.60	0.50	0.10
2201	Group 2: >13	T, R	0.00	0.00	-4.60	1.21
2204	Group 2: >13	T, R	0.00	-0.30	0.26	-0.38
2206	Group 2: >13	T, R	0.00	-0.08	3.51	0.03
3202	Group 2: >13	T, R	0.00	-8.60	-8.60	-8.60
3203	Group 2: >13	T, R	0.00	0.00	0.00	0.00
3205	Group 2: >13	T, R	0.00	-8.60	-8.60	0.30
3207	Group 2: >13	T, R	0.00	0.00	0.00	0.00
3210	Group 2: >13	T, R	0.00	0.00	0.00	9.10
4104	Group 2: >13	T, R	0.00	0.00	0.00	0.00
4105	Group 2: >13	T, R	0.00	-300	0.00	-2.52
4206	Group 2: >13	T, R	0.00	0.00	0.00	0.00

1205	Group 2: >13	T	0.00	0.00		
1201	Group 2: >13	R, T	0.00	4.10	4,60	0.00
1203	Group 2: >13	R, T	0.00	1.87	0,70	0.41
1206	Group 2: >13	R, T	0.00	0.00	0,00	0.00
1208	Group 2: >13	R, T	0.00	-2.46	-1,56	-1.02
2202	Group 2: >13	R, T	0.00	0.00	0,00	0.00
2203	Group 2: >13	R, T	0.00	1.36	-0,20	-5.42
2205	Group 2: >13	R, T	0.00	0.66	0,82	0.12
3201	Group 2: >13	R, T	0.00	0.00	0,00	0.00
3204	Group 2: >13	R, T	0.00	-1.70	-8,30	-1.00
3206	Group 2: >13	R, T	0.00	0.00	0,00	0.00
3208	Group 2: >13	R, T	0.00	0.00	0,00	0.00
3209	Group 2: >13	R, T	0.00	0.00	0,00	0.00
4103	Group 2: >13	R, T	0.00	-4.18	-4,18	-4.18
4204	Group 2: >13	R, T	0.00	0.15	0,15	0.15
4205	Group 2: >13	R, T	0.00	-5.11	-1,07	-0.79

Age 4 - 13		**Week**	**2**	**6**	**10**	**14**
with Droputs	T100 (2/3), TOBI (4/5)	SD (±)	0.00	2.34	2.54	2.38
SD (±)	TOBI (2/3), T100 (4/5)	SD (±)	0.00	3.35	3.59	2.66

Age >13		**Week**	**2**	**6**	**10**	**14**
with Droputs	T100 (2/3), TOBI (4/5)	SD (±)	0.00	3.29	3.78	3.88
	TOBI (2/3), T100 (4/5)	SD (±)	0.00	2.29	2.76	1.70

Both groups		**Week**	**2**	**6**	**10**	**14**
with Droputs	T100 (2/3), TOBI (4/5)	SD (±)	0.00	2.84	3.20	3.36
	TOBI (2/3), T100 (4/5)	SD (±)	0.00	3.05	3.20	2.48

Age 4 - 13		**Week**	**2**	**6**	**10**	**14**
with Droputs	T100 (2/3), TOBI (4/5)	Arithmetic mean	0.00	-2.08	-1.89	-1.70
	TOBI (2/3), T100 (4/5)	Arithmetic mean	0.00	-2.85	-2.07	-3.20

Age >13		**Week**	**2**	**6**	**10**	**14**
with Droputs	T100 (2/3), TOBI (4/5)	Arithmetic mean	0.00	-1.86	-1.74	0.22
	TOBI (2/3), T100 (4/5)	Arithmetic mean	0.00	-0.35	-0.60	-0.78

Both groups		**Week**	**2**	**6**	**10**	**14**
with Droputs	T100 (2/3), TOBI (4/5)	Arithmetic mean	0.00	-1.96	-1.81	-0.67
	TOBI (2/3), T100 (4/5)	Arithmetic mean	0.00	-1.51	-1.28	-1.90

Age 4 - 13

N	**26**	**26**	**25**	**25**
Arithmetic mean	**0.00**	**-2.46**	**-1.98**	**-2.48**
SD (±)	**0.000**	**2.861**	**3.068**	**2.594**
CV (%)		**-116.1**	**-154.7**	**-104.6**
Minimum	**0.00**	**-9.50**	**-9.50**	**-8.30**
Maximum	**0.00**	**0.90**	**3.00**	**0.03**
Median	**0.00**	**-1.23**	**-0.48**	**-2.40**

Age >13

N	**30**	**30**	**29**	**29**
Arithmetic mean	**0.00**	**-1.11**	**-1.15**	**-0.30**
SD (±)	**0.000**	**2.886**	**3.282**	**2.949**
CV (%)		**-260.3**	**-285.5**	**-988.4**
Minimum	**0.00**	**-8.60**	**-8.60**	**-8.60**
Maximum	**0.00**	**4.10**	**4.60**	**9.10**
Median	**0.00**	**0.00**	**0.00**	**0.00**

Both groups

N	**56**	**56**	**54**	**54**
Arithmetic mean	**0.00**	**-1.74**	**-1.54**	**-1.31**
SD (±)	**0.000**	**2.928**	**3.182**	**2.975**
CV (%)		**-168.5**	**-207.2**	**-227.4**
Minimum	**0.00**	**-9.50**	**-9.50**	**-8.60**
Maximum	**0.00**	**4.10**	**4.60**	**9.10**
Median	**0,00**	**-0.04**	**0.00**	**0.00**

14.3 Safety Data Summary

14.3.1 Display of AEs

Table 39 Adverse Events: Number observed and Rate, with Patient Identification, stratified into Severity, incl. Related AEs and SAEs

	Mild		Moderate		Severe		Total (N = 76)	
	N (% of AEs)		N (% of AEs)		N (% of AEs)		N (% of AEs)	
	not related	related	not related	related	not related	related	not related	related
Gastrointestinal disorders								
Vomiting			1 (1.3)				1 (1.3)	
Pat. #			2104					
Abdominal pain	1 (1.3)		3 (4.0)				4 (5.3)	
Pat. #	2203		2105					
			3102					
			2201					
			2204					
Abdominal pain aggravated					1 (1.3)		1 (1.3)	
					3201			
General disorders and administration site conditions								
Fever			2 (2.6)				2 (2.6)	
Pat. #			2104					
			2106					
Chest pain		1 (1.3)						1 (1.3)
Pat. #		3103						
Infections and infestations								
Nasopharyngitis	1 (1.3)						1 (1.3)	
Pat. #	1109							
Pharyngitis	2 (2.6)						2 (2.6)	
Pat. #	3102							
	3102							
Cystic fibrosis pulmonary exacerbation	1 (1.3)						1 (1.3)	
Pat. #	1109*)							
Rhinitis	2 (2.6)						2 (2.6)	
Pat. #	2105							
	2106							
Otitis media			1 (1.3)				1 (1.3)	
Pat. #			2108*)					
Mastoiditis*)			1 (1.3)				1 (1.3)	

Pat. #			2108					
Rhinopharyngitis			1 (1.3)				1 (1.3)	
Pat. #			2204					
Common cold	2 (2.6)		1 (1.3)				2 (2.6)	1 (1.3)
Pat. #	3204		3209					
	3209							
Injury, poisoning and procedural complications								
Fracture of humerus			1 (1.3)					1 (1.3)
Pat. #			1106*)					
Respiratory, thoracic andmediastinal disorders								
Coughing after drug inhalation		6 (7.9)						6 (7.9)
Pat. #		2101						
		2101						
		2102						
		2103						
		2103						
		3203						
Haemoptysis	1 (1.3)						1 (1.3)	
Pat. #	2103							
Hoarseness		3 (4.0)		3 (4.0)				6 (7.9)
Pat. #		2101		2107				
		2101		3102				
		3102		4104				
Cough aggravated				1 (1.3)		1 (1.3)		2 (2.6)
Pat. #				2201		2104		
Sputum increased				2 (2.6)		1 (1.4)		3 (4.0)
Pat. #				2106		2104		
				2201				
Cough increased		1 (1.3)		1 (1.3)				2 (2.6)
Pat. #		3208		2106				
Cough	4 (5.3)	5 (6.6)	1 (1.3)	1 (1.3)			5 (6.9)	6 (7.9)
Pat. #	3102	3102	1205	3103				
	3103	3103						
	3103	3103						
	4104	3103						
		4205						
Bronchospasm		1 (1.3)		1 (1.3)				2 (2.6)
Pat. #		3210		4103				
Shortness of breath				1 (1.3)				1 (1.3)

Pat. #				4104				
Dyspnoea		1 (1.3)		1 (1.3)				2 (2.6)
Pat. #		4205		4103				
Pulmonary hemorrhage*)			1 (1.3)				1 (1.3)	
Pat. #			1205*)					
Renal and urinary disorders								
Renal colic			1 (1.3)				1 (1.3)	
Pat. #			2205					
Haematuria	1 (1.3)						1 (1.3)	
Pat. #	3208							
Ear and labyrinth disorders								
Tinnitus		2 (2.6)						2 (2.6)
Pat. #		2101						
		4101						
Vertigo		1 (1.3)		1 (1.3)				2 (2.6)
Pat. #		4101		4101				
Nervous system disorders								
Headache		1 (1.3)	1 (1.3)				1 (1.3)	1 (1.3)
Pat. #		4205	3102					
Taste bitter				1 (1.3)				1 (1.3)
Pat. #				4102				
Investigations								
WBC increased	1 (1.3)						1 (1.3)	
Pat. #	2104							
Neutrophils increased	1 (1.3)						1 (1.3)	
Pat. #	2104							
GGT increase	1 (1.3)						1 (1.3)	
Pat. #	2104							
ALT increased	1 (1.3)						1 (1.3)	
Pat. #	2104							
LDH increased	2 (2.6)						2 (1.3)	
Pat. #	3210							
	3208							
Breath sounds	1 (1.3)						1 (1.3)	
	1203							
Audiometry abnormal		1 (1.3)						1 (1.3)
Pat. #		3203						

* These patients experienced an SAEs (hospitalisation) and stopped the treatment after the first phase, i.e. after Visit 3.

Table 40 Adverse Drug Reactions: Number observed, Rate and Assignment to the Treatment Groups (VANTOBRA / TOBI), with Patient Identiciation

	Mild		Moderate		Severe		Total (N = 33)
	N (%)		N (%)		N (%)		N (%)
	T100 or TOBI	related	T100 or TOBI	related	T100 or TOBI	related	
General disorders and administration site conditions							
Chest pain		1 (3.1)					1 (3.1)
Pat. #	TOBI	3103					
Respiratory, thoracic and mediastinal disorders							
Coughing after drug inhalation		6 (18.8)					6 (18.8)
Pat. #	TOBI	2101					
	T100	2101					
	T100	2102					
	T100	2103					
	TOBI	2103					
	T100	3203					
Hoarseness		3 (9.4)		3 (9.4)			6 (18.8)
Pat. #	TOBI	2101	T100	2107			
	T100	2101	T100	3102			
	TOBI	3102	T100	4104			
Cough increased		1 (3.1)					1 (3.1)
Pat. #	TOBI	3208					
Cough		5 (15.6)		1 (3.1)			6 (18.8)
Pat. #	TOBI	3102	T100	3103			
	TOBI	3103					
	T100	3103					
	T100	3103					
	T100	4205					
Bronchospasm		1 (3.1)		1 (3.1)			2 (6.3)
Pat. #	TOBI	3210	TOBI	4103			
Shortness of breath				2 (3.1)			2 (6.3)
Pat. #			TOBI	4104			
			T100	4103			
Dyspnoea		1 (3.1)					1 (3.1)
Pat. #	T100	4205					
Ear and labyrinth disorders							
Tinnitus		2 (6.3)					2 (6.3)

Pat. #	T100	2101					
	T100	4101					
Vertigo		1 (3.1)		1 (3.1)			2 (6.3)
Pat. #	TOBI	4101	T100	4101			
Nervous system disorders							
Headache		1 (3.1)					1 (3.1)
Pat. #	T100	4205					
Bitter Taste				1 (3.1)			1 (3.1)
Pat. #			T100	4102			
Audiometry abnormal		1 (3.1)					1 (3.1)
Pat. #	T100	3203					

14.3.2 Listing of Deaths, Other Serious and Significant AEs

No deaths occurred in the study. The other SAEs (all not related) were listed already in Table 22.

14.3.3 Narratives of the AEs

Pat. 2108

This report concerns a male patient aged 7 years and was received on 13-Dec-2011 and 19-Dec-2011.

Medical history included bronchopulmonary exacerbation (06-Sep-2011 – 19-Sep-2011). The patient's concurrent conditions included cystic fibrosis, pancreatic insufficiency since Feb-2005, and chronic bronchopulmonary *P. aeruginosa* infection since 22-Oct-2010. Concomitant medications included Atrovent (ipratropium bromide), 5% sodium chloride, Pulmozyme (dornase alfa), colistin, and Tussicom (acetyl cysteine), all for cystic fibrosis, Ursofalk (ursodeoxycholic acid) as liver disease prophylaxis, Kreon (pancreatin), Lipancrea (pancreatin), and multivitamins, all for pancreatic insufficiency.

The patient was treated with T100 from 20-Oct-2011 to 16-Nov-2011 for bronchopulmonary chronic *Pseudomonas aeruginosa* infection. Treatment with TOBI was not yet started.

On 08-Dec-2011, the patient experienced bacterial otitis media and on 09-Dec-2011 mastoiditis, resulting in hospitalisation. Important symptoms were earache, mastoid oedema and fever. Treatment with i.v. Biotaksym (cefotaxime sodium) 500 mg BID was started on 09-Dec-2011. The patient was discharged on an unreported date.

Bacterial otitis media and mastoiditis did not yet resolve.

The reporter considered the causality between bacterial otitis media and mastoiditis and T100 as not related.

Follow-up information was received on 03-Jan-2012.

The patient suffered from earache from 08-Dec-2011 till 21-Dec-2011 and from mastoidalgia, mastoid oedema and fever from 09-Dec-2011 till 21-Dec-2011. Paracentesis was performed on 09-Dec-2011. The patient also received treatment with Zyrtec (cetirizine hydrochloride), xylometazoline and Perfalgan (paracetamol). Intravenous cefotaxime sodium was stopped on 14-Dec-2011 and switched to oral Zinnat [(cefuroxime) 250 mg BID, 15-Dec-2011 – 21-Dec-2011]. The most reasonable cause for the events was unknown. The patient was discharged on 14-Dec-2011 and on 30-Dec-2011 the patient was withdrawn from the study.

Bacterial otitis media and mastoiditis resolved on 21-Dec-2011.

06-Jan-2012: The sponsor assessed the causal relationship of otitis media and mastoiditis with the IMP as unlikely related. The most likely cause is the underlying condition of cystic fibrosis.

Patient 1106

This report concerns a male patient aged 10 years. Information was received on 07-Oct-2011 and 18-Oct-2011.

Medical history was not provided. The patient's concurrent conditions included cystic fibrosis, chronic bronchopulmonary *Pseudomonas aeruginosa* infection since 24-Oct-2002 and bedwetting. Concomitant medication included pancreatin, multivitamins, acetylcysteine, ursodeoxycholic acid, phospholipids, dornase alfa, mometasone furoate and salbutamol, all for cystic fibrosis.

The patient was treated with TOBI from 02-Sep-2011 till 29-Sep-2011 for bronchopulmonary chronic *Pseudomonas aeruginosa* infection. Treatment with T100 was not yet started.

On 06-Oct-2011 the patient experienced a supracondylar fracture of the left humerus and was hospitalized for surgery. Intravenous atropine, propofol, sufentanil and inhaled sevoflurane were administered for general anaesthesia. Intravenous paracetamol, ketoprofen and cefuroxime axetil was started for the injury.

The patient was discharged from the hospital on 08-Oct-2011.

At the time of the report, the supracondylar fracture of the left humerus had not yet resolved.

The reporter considered the causality between supracondylar fracture of the left humerus and TOBI as not related.

Follow-up information was received on 29-Dec-2011.

Upon internal review following correction was made: the reaction onset date was 06-Oct-2011 (previously entered as 07-Oct-2011).

The patient was treated with T100 from 28-Oct-2011 till 24-Nov-2011.

The supracondylar fracture of the left humerus was resolved on 24-Nov-2011.

16-Jan-2012: The sponsor assessed the causal relationship with the IMP as unlikely. The event was most probably caused by an injury. Based on the safety profile of the IMP no impact on central nervous functions that may result in accidents, are suspected. Notably, the MAH's investigational medicinal product was administered after onset of the event.

Patient 1109

This report concerns a male patient aged 12 years. Information was received on 15-Nov-2011.

Medical history was not provided. The patient's concurrent conditions included cystic fibrosis, chronic bronchopulmonary *P. aeruginosa* infection, glucose intolerance and gastrooesophageal reflux (dates not reported). Concomitant medication included pancreatin, multivitamins, tocopherol, ursodeoxycholic acid, azithromycin, formoterol, budesonide, dornase alfa, omeprazole, retinol, all for cystic fibrosis.

The patient was treated with TOBI (dates not reported) for bronchopulmonary chronic *P. aeruginosa* infection.

On 15-Nov-2011 the patient experienced pulmonary exacerbation and was hospitalised. Intravenous Colistin and Imipenem was started. Prior to the event, the patient had a nasopharyngeal infection from 31-Oct-2011 until 15-Nov-2011 which was treated with oral ciprofloxacin (31-Oct-2011 till 14-Nov-2011).

The outcome for pulmonary exacerbation was not provided.

The reporter considered the causality between pulmonary exacerbation and TOBI as not related.

Follow-up information was received on 29-Dec-2011.

This case concerns a patient aged 13 years (previously reported as 12 years).

Medical history included antireflux procedure performed in 2008 and percutaneous endoscopic gastrostomy placement in 2010. The patient's concurrent conditions included exocrine pancreatic insufficiency since an unreported date. Chronic bronchopulmonary *P.aeruginosa* infection was diagnosed on 28-May-2003.

The patient was treated with TOBI from 05-Oct-2011 till 31-Oct-2011. T100 was not started.

The patient was treated ambulatory with ciprofloxacin since 28-Oct-2011 because of intensification of cough. One week before admission he had fever up to 38.5 ºC, vomiting of respiratory tract mucus and lack of appetite. At admission there was marked inspiratory-expiratory dyspnoea, deficiency of body mass, anteversion of shoulders, clubbing of fingers, excessively overt percussion sound and auscultatory many rattles, more intense on the right side. Additional examination showed increased inflammatory state.

Antibiotic therapy with intravenous colistin and Tienam (imipenem / cilastatin sodium) was started, but switched to Meronem (meropenem) because of reported nausea and abdominal pain. During the

stay there was gradual improvement of the general condition and regression of auscultatory changes. The patient was discharged on 30-Nov-2011 in good general condition.

The reporter updated the event term to cystic fibrosis pulmonary exacerbation.

The patient recovered from cystic fibrosis pulmonary exacerbation on 30-Nov-2011.

18-Jan-2012: The sponsor assessed the causal relationship of pulmonary exacerbation with the IMP as unlikely related based on the temporal relationship and the safety profile of the IMP. Study medication was stopped 15 days before occurrence of the event. The most likely cause is the underlying condition of cystic fibrosis.

Patient 1205

This report concerns a male patient aged 18 years. Information was received on 27-Sep-2011 and 04-Oct-2011.

Medical history was not provided. The patient's concurrent conditions included cystic fibrosis and chronic bronchopulmonary *Pseudomonas aeruginosa* infection since Mar-1999. Concomitant medication included pancreatin, multivitamins, tocopherol, phytomenadione, ursodeoxycholic acid, salbutamol, dornase alfa and calcium lactate gluconate, all for cystic fibrosis.

The patient was treated with T100 from 11-Aug-2011 till 07-Sep-2011 for bronchopulmonary chronic *Pseudomonas aeruginosa* infection.

On 26-Sep-2011 the patient experienced cough and pulmonary haemorrhage and was admitted to the hospital. Intravenous treatment with ethamsylate and tranexamic acid was started the same day. On 27-Sep-2011, dornase alfa was stopped and i.v. ceftazidime and ranitidine, and oral ciprofloxacin and codeine were added. At the time of the event, the patient was in the wash-out period and did not yet started to take TOBI.

The patient recovered from pulmonary haemorrhage on 03-Oct-2011 and was discharged.

The reporter considered the causality between pulmonary haemorrhage and T100 as not related.

20-Oct-2011: Sponsor comment: Cystic fibrosis as the relevant medical condition of the patient is likely to have contributed to the occurrence of pulmonary haemorrhage. Since the event started in the wash-out period without administration of any study drug it is very unlikely that the IMP has caused and/or contributed to the pulmonary haemorrhage.

Follow-up information was received on 27-Oct-2011.

The patient was admitted to the hospital with cough with purulent phlegm and haemoptysis.

At the hospital ward there was a massive haemorrhagic episode, controlled by medication.

Based on the clinical picture and examinations, there was an assumption of bronchiectasis. During the admission the patient received broad-spectrum antibiotics, anti-haemorrhagic drugs, inhalations, oxygen, and postural drainages. The patient's clinical state improved and haemoptysis regressed. The patient was discharged from the hospital with the recommendation of further ambulatory treatment.

14.3.4 Abnormal Laboratory Values Listing (each patient)

Table 41 Abnormal Haemoblobin Values per Patient (Visit 1 – 3)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Haemoglobin				Haemoglobin				Haemoglobin			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. Relevance	Unit	Value	Evaluation	Clin. Relevance	Unit	Value	Evaluation	Clin. Relevance
1101	R, T	g/dl	12,0	abnormal low	clin. not relevant	g/dl	11,7	abnormal low	clin. not relevant	g/dl	11,7	abnormal low	clin. not relevant
1102	T, R									g/dl	12,9	abnormal low	clin. not relevant
1109	R	g/dl	12,7	abnormal low	clin. not relevant	g/dl	12,7	abnormal low	clin. not relevant				
2105	R, T	g/dl	11,9	abnormal low	clin. not relevant					g/dl	11,5	abnormal low	clin. not relevant
3101	R, T	g/dl	11,7	abnormal low	clin. not relevant	g/dl	11,2	abnormal low	clin. not relevant	g/dl	11,6	abnormal low	clin. not relevant
4106	R, T					g/dl	14,3	abnormal high	clin. not relevant				
1203	R, T					g/dl	11,6	abnormal low	clin. not relevant				
2201	T, R	g/dl	10,0	abnormal low	clin. not relevant	g/dl	11,3	abnormal low	clin. not relevant	g/dl	11,8	abnormal low	clin. not relevant
3205	T, R	g/dl	16,2	abnormal high	clin. not relevant	g/dl	15,6	abnormal high	clin. not relevant	g/dl	15,7	abnormal high	clin. not relevant

Table 42 Abnormal Haemoglobin Values per Patient (Visit 4 – 6)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Haemoglobin				Haemoglobin				Haemoglobin			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. Relevance	Unit	Value	Evaluation	Clin. Relevance	Unit	Value	Evaluation	Clin. Relevance
1101	R, T	g/dl	11,9	abnormal low	clin. not relevant	g/dl	12,5	abnormal low	clin. not relevant	g/dl	12,0	abnormal low	clin. not relevant
1102	T, R	g/dl	12,8	abnormal low	clin. not relevant					g/dl	12,9	abnormal low	clin. not relevant
1109	R									g/dl	12,9	abnormal low	clin. not relevant
										g/dl	15,6	abnormal high	clin. not relevant
1114	R, T					g/dl	15,7	abnormal high	clin. not relevant	g/dl	15,6	abnormal high	clin. not relevant
3101	R, T	g/dl	11,7	abnormal low	clin. not relevant	g/dl	11,8	abnormal high	clin. not relevant	g/dl	11,6	abnormal low	clin. not relevant
1203	R, T	g/dl	11,2	abnormal low	clin. not relevant	g/dl	11,8	abnormal low	clin. not relevant	g/dl	11,9	abnormal low	clin. not relevant
1208	R, T					g/dl	11,6	abnormal low	clin. not relevant	g/dl	11,6	abnormal low	clin. not relevant
2201	T, R	g/dl	11,2	abnormal low	clin. not relevant	g/dl	11,5	abnormal low	clin. not relevant	g/dl	11,2	abnormal low	clin. not relevant
3205	T, R	g/dl	15,8	abnormal high	clin. not relevant	g/dl	15,8	abnormal high	clin. not relevant				
3206	R, T					g/dl	15,5	abnormal high	clin. not relevant				
3204	R, T									g/dl	10,9	abnormal low	clin. not relevant

Table 43 Abnormal Haematocrit Values per Patient (Visit 1 – 3)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Haematocrit				Haematocrit				Haematocrit			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1101	TOBI, T100	%	37,3	abnormal low	clin. not relevant	%	36,1	abnormal low	clin. not relevant	%	36,4	abnormal low	clin. not relevant
1102	T100, TOBI									%	39,5	abnormal low	clin. not relevant
1106	TOBI, T100					%	45,1	abnormal high	clin. not relevant	%	44,4	abnormal high	clin. not relevant
1109	TOBI					%	38,9	abnormal low	clin. not relevant				
1110	T100, TOBI	%	46,5	abnormal high	clin. not relevant	%	44,8	abnormal high	clin. not relevant	%	46,3	abnormal high	clin. not relevant
1112	TOBI, T100	%	44,1	abnormal high	clin. not relevant	%	45,0	abnormal high	clin. not relevant	%	45,0	abnormal high	clin. not relevant
1114	TOBI, T100	%	44,3	abnormal high	clin. not relevant	%	45,2	abnormal high	clin. not relevant				
2105	TOBI, T100	%	35,9	abnormal low	clin. not relevant					%	35,5	abnormal low	clin. not relevant
2107	TOBI, T100	%	44,1	abnormal high	clin. not relevant	%	44,2	abnormal high	clin. not relevant				
2108	T100					%	36,9	abnormal low	clin. not relevant				
3101	TOBI, T100					%	37,0	abnormal low	clin. not relevant	%	38,9	abnormal low	clin. not relevant
2201	T100, TOBI	%	30,8	abnormal low	clin. not relevant								
3205	T100, TOBI	%	49,4	abnormal high	clin. not relevant	%	47,7	abnormal high	clin. not relevant	%	48,4	abnormal high	clin. not relevant
3208	R, T									%	47,3	abnormal high	clin. not relevant
3210	T, R									%	47,7	abnormal high	clin. not relevant

Table 44 Abnormal Haemotocrit Values per Patient (Visit 4 – 6)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Haematocrit				Haematocrit				Haematocrit			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1101	TOBI, T100	%	36,8	abnormal low	clin. not relevant	%	38,8	abnormal low	clin. not relevant	%	36,2	abnormal low	clin. not relevant
1102	T100, TOBI	%	38,3	abnormal low	clin. not relevant	%	39,8	abnormal low	clin. not relevant	%	38,0	abnormal low	clin. not relevant
1106	TOBI, T100	%	46,8	abnormal high	clin. not relevant	%	46,7	abnormal high	clin. not relevant	%	45,0	abnormal high	clin. not relevant
1109	TOBI									%	39,5	abnormal low	clin. not relevant
1110	T100, TOBI	%	44,5	abnormal high	clin. not relevant	%	44,2	abnormal high	clin. not relevant	%	47,4	abnormal high	clin. not relevant
1114	TOBI, T100					%	47,5	abnormal high	clin. not relevant	%	46,7	abnormal high	clin. not relevant
2107	TOBI, T100	%	44,6	abnormal high	clin. not relevant								
3101	TOBI, T100	%	38,7	abnormal low	clin. not relevant					%	38,7	abnormal low	clin. not relevant
1208	TOBI, T100					%	35,9	abnormal low	clin. not relevant	%	35,8	abnormal low	clin. not relevant
2201	T100, TOBI	%	33,9	abnormal low	clin. not relevant					%	34,5	abnormal low	clin. not relevant
3205	T100, TOBI	%	48,7	abnormal high	clin. not relevant	%	49,1	abnormal high	clin. not relevant				
3206	TOBI, T100					%	48,0	abnormal high	clin. not relevant				
3208	TOBI, T100	%	47,5	abnormal high	clin. not relevant	%	48,3	abnormal high	clin. not relevant	%	47,5	abnormal high	clin. not relevant
3210	T100, TOBI	%	48,0	abnormal high	clin. not relevant	%	48,7	abnormal high	clin. not relevant	%	47,1	abnormal high	clin. not relevant

4204	TOBI, T100									%	34,7	abnormal low	clin. not relevant

Table 45 Abnormal Erythrocyte (RBC) Values per Patient (Visit 1 – 3)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Red blood cell count				Red blood cell count				Red blood cell count			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1110	T, R	10^6/µl	5,54	abnormal high	clin. not relevant					10^6/µl	5,54	abnormal high	clin. not relevant
2104	R	TI/l	5,21	abnormal high	clin. not relevant	TI/l	5,29	abnormal high	clin. not relevant				
3101	R, T	10^6/µl	5,42	abnormal high	clin. not relevant					10^6/µl	5,33	abnormal high	clin. not relevant
3102	T, R									10^6/µl	5,17	abnormal high	clin. not relevant
4101	T, R									TI/l	5,23	abnormal high	clin. not relevant
4106	R, T	TI/l	5,45	abnormal high	clin. not relevant	TI/l	5,29	abnormal high	clin. not relevant	TI/l	5,25	abnormal high	clin. not relevant
2201	T, R	TI/l	3,67	abnormal low	clin. not relevant								
2203	R, T									TI/l	5,08	abnormal high	clin. not relevant
2205	R, T					TI/l	5,30	abnormal high	clin. not relevant				
3205	T, R	10^6/µl	5,55	abnormal high	clin. not relevant	10^6/µl	5,35	abnormal high	clin. not relevant	10^6/µl	5,40	abnormal high	clin. not relevant
3206	R, T	10^6/µl	5,44	abnormal high	clin. not relevant	10^6/µl	5,43	abnormal high	clin. not relevant	10^6/µl	5,28	abnormal high	clin. not relevant
3210	T, R	10^6/µl	5,23	abnormal high	clin. not relevant	10^6/µl	5,18	abnormal high	clin. not relevant	10^6/µl	5,39	abnormal high	clin. not relevant
4105	T, R	TI/l	5,33	abnormal high	clin. not relevant	TI/l	5,34	abnormal high	clin. not relevant				

Table 46 Abnormal Erythrocyte (RBC) Values per Patient (Visit 4 – 6)

		Haematology				Haematology				Haematology			
		Red blood cell count				Red blood cell count				Red blood cell count			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1110	T, R									10^6/µl	5,62	abnormal high	clin. not relevant
3101	R, T	10^6/µl	5,37	abnormal high	clin. not relevant	10^6/µl	5,52	abnormal high	clin. not relevant	10^6/µl	5,33	abnormal high	clin. not relevant
4101	T, R	TI/l	5,53	abnormal high	clin. not relevant	TI/l	5,46	abnormal high	clin. not relevant				
4106	R, T	TI/l	5,57	abnormal high	clin. not relevant	TI/l	5,44	abnormal high	clin. not relevant	TI/l	5,50	abnormal high	clin. not relevant
2205	R, T	TI/l	5,21	abnormal high	clin. not relevant								
2206	T, R					TI/l	5,01	abnormal high	clin. not relevant				
3205	T, R	10^6/µl	5,44	abnormal high	clin. not relevant	10^6/µl	5,39	abnormal high	clin. not relevant				
3206	R, T	10^6/µl	5,50	abnormal high	clin. not relevant	10^6/µl	5,63	abnormal high	clin. not relevant	10^6/µl	5,15	abnormal high	clin. not relevant
3208	R, T	10^6/µl	5,17	abnormal high	clin. not relevant	10^6/µl	5,28	abnormal high	clin. not relevant	10^6/µl	5,24	abnormal high	clin. not relevant
3210	T, R	10^6/µl	5,46	abnormal high	clin. not relevant	10^6/µl	5,48	abnormal high	clin. not relevant	10^6/µl	5,30	abnormal high	clin. not relevant

Table 47 Abnormal Leukocyte (WBC) Values per Patient (Visit 1 – 3)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		White cell count				White cell count				White cell count			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1101	R, T	$10^3/\mu l$	10,27	abnormal high	clin. not relevant								
1104	R, T	$10^3/\mu l$	11,22	abnormal high	clin. not relevant	$10^3/\mu l$	15,49	abnormal high	clin. not relevant				
1113	T, R	$10^3/\mu l$	10,20	abnormal high	clin. not relevant								
2103	T, R									GI/l	15,52	abnormal high	clin. not relevant
2104	R	GI/l	11,75	abnormal high	clin. not relevant	GI/l	14,94	abnormal high	clin. not relevant				
3101	R, T									$10^3/\mu l$	13,80	abnormal high	clin. not relevant
4106	R, T	GI/l	11,60	abnormal high	clin. not relevant	GI/l	10,50	abnormal high	clin. not relevant	GI/l	11,60	abnormal high	clin. not relevant
1203	R, T					$10^3/\mu l$	11,03	abnormal high	clin. not relevant	$10^3/\mu l$	13,65	abnormal high	clin. not relevant
1204	T, R	$10^3/\mu l$	13,69	abnormal high	clin. not relevant	$10^3/\mu l$	13,94	abnormal high	clin. not relevant				
1206	R, T	$10^3/\mu l$	12,61	abnormal high	clin. not relevant	$10^3/\mu l$	15,56	abnormal high	clin. not relevant				
1208	R, T	$10^3/\mu l$	11,11	abnormal high	clin. not relevant	$10^3/\mu l$	12,91	abnormal high	clin. not relevant	$10^3/\mu l$	11,64	abnormal high	clin. not relevant
2205	R, T	GI/l	14,05	abnormal high	clin. not relevant	GI/l	14,45	abnormal high	clin. not relevant				

3206	R, T	$10^3/\mu l$	13,40	abnormal high	clin. not relevant								
3210	T, R	$10^3/\mu l$	15,90	abnormal high	clin. not relevant	$10^3/\mu l$	15,20	abnormal high	clin. not relevant				
4104	T, R	GI/l	11,50	abnormal high	clin. not relevant								
4105	T, R	GI/l	11,20	abnormal high	clin. not relevant								

Table 48 Abnormal Leukocyte (WBC) Values per Patient (Visit 4 – 6)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		White cell count				White cell count				White cell count			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1104	R, T	$10^3/\mu l$	16,03	abnormal high	clin. not relevant					$10^3/\mu l$	13,81	abnormal high	clin. not relevant
1110	T, R									$10^3/\mu l$	3,90	abnormal low	clin. not relevant
1112	R, T									$10^3/\mu l$	12,80	abnormal high	clin. not relevant
1113	T, R					$10^3/\mu l$	3,80	abnormal low	clin. not relevant				
2101	R, T					GI/l	10,28	abnormal high	clin. not relevant				
2103	T, R					GI/l	12,60	abnormal high	clin. not relevant				
2104	R									GI/l	16,89	abnormal high	clin. relevant
2107	R, T									GI/l	12,05	abnormal high	clin. not relevant
3101	R, T	$10^3/\mu l$	12,80	abnormal high	clin. not relevant	$10^3/\mu l$	12,70	abnormal high	clin. not relevant				
4102	R, T									GI/l	10,60	abnormal high	clin. not relevant
4106	R, T	GI/l	13,30	abnormal high	clin. not relevant	GI/l	11,90	abnormal high	clin. not relevant	GI/l	15,50	abnormal high	clin. not relevant
1203	R, T	$10^3/\mu l$	12,11	abnormal high	clin. not relevant					$10^3/\mu l$	15,28	abnormal high	clin. not relevant
1204	T, R									$10^3/\mu l$	10,83	abnormal high	clin. not relevant

1206	R, T	$10^3/\mu l$	12,77	abnormal high	clin. not relevant								
1207	T, R									$10^3/\mu l$	10,69	abnormal high	clin. not relevant
1208	R, T	$10^3/\mu l$	11,00	abnormal high	clin. not relevant					$10^3/\mu l$	12,20	abnormal high	clin. not relevant
2205	R, T	GI/l	10,27	abnormal high	clin. not relevant								
3209	R, T					$10^3/\mu l$	13,70	abnormal high	clin. not relevant				
3210	T, R	$10^3/\mu l$	14,10	abnormal high	clin. not relevant					$10^3/\mu l$	13,80	abnormal high	clin. not relevant
4104	T, R					GI/l	13,20	abnormal high	clin. not relevant	GI/l	10,80	abnormal high	clin. not relevant
4105	T, R									GI/l	10,50	abnormal high	clin. not relevant
4205	R, T									GI/l	10,10	abnormal high	clin. not relevant

Table 49 Abnormal Neutrophil Values per Patient (Visit 1 – 3)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Neutrophils				Neutrophils				Neutrophils			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1104	R, T					$10^3/\mu l$	11,76	abnormal high	clin. not relevant				
1113	T, R									$10^3/\mu l$	1,33	abnormal low	clin. not relevant
2103	T, R									GI/l	10,60	abnormal high	clin. not relevant
2104	R					GI/l	11,39	abnormal high	clin. not relevant				
2106	T, R					GI/l	1,40	abnormal low	clin. not relevant				
3102	T, R									%	31,00	abnormal low	clin. not relevant
4106	R, T	GI/l	7,75	abnormal high	clin. not relevant					GI/l	5,81	abnormal high	clin. not relevant
1203	R, T									$10^3/\mu l$	8,05	abnormal high	clin. not relevant
1204	T, R	$10^3/\mu l$	9,25	abnormal high	clin. not relevant	$10^3/\mu l$	9,51	abnormal high	clin. not relevant	$10^3/\mu l$			
1206	R, T	$10^3/\mu l$	9,80	abnormal high	clin. not relevant	$10^3/\mu l$	12,18	abnormal high	clin. not relevant	$10^3/\mu l$			
1208	R, T					$10^3/\mu l$	9,36	abnormal high	clin. not relevant	$10^3/\mu l$			
2205	R, T	GI/l	9,74	abnormal high	clin. not relevant	GI/l	9,68	abnormal high	clin. not relevant	GI/l			
3202	T, R					%	59,00	abnormal high	clin. not relevant	%			
3206	R, T	%	80,00	abnormal high	clin. not relevant								

3207	T, R	%	77,00	abnormal high	clin. not relevant	%	78,00	abnormal high	clin. not relevant				
3208	R, T					%	77,00	abnormal high	clin. not relevant				
3209	R, T					%	82,00	abnormal high	clin. not relevant				
3210	T, R	%	79,00	abnormal high	clin. not relevant	%	83,00	abnormal high	clin. not relevant				
4104	T, R	GI/l	6,62	abnormal high	clin. not relevant	GI/l	7,91	abnormal high	clin. not relevant				
4105	T, R	GI/l	9,13	abnormal high	clin. not relevant	GI/l	5,87	abnormal high	clin. not relevant				
4204	R, T					Gl/l	6,26	abnormal high	clin. not relevant	GI/l	6,34	abnormal high	clin. not relevant
4205	R, T	GI/l	6,24	abnormal high	clin. not relevant								

Table 50 Abnormal Neutrophil Values per Patient (Visit 4 – 6)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Neutrophils				Neutrophils				Neutrophils			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1104	R, T	$10^3/\mu l$	12,01	abnormal high	clin. not relevant					$10^3/\mu l$	9,93	abnormal high	clin. not relevant
1113	T, R					$10^3/\mu l$	1,17	abnormal low	clin. not relevant				
2103	T, R					GI/l	8,11	abnormal high	clin. not relevant				
2104	R									GI/l	13,01	abnormal high	clin. relevant
2106	T, R					GI/l	0,79	abnormal low	clin. not relevant				
2107	R, T					GI/l	1,77	abnormal low	clin. not relevant	GI/l	8,43	abnormal high	clin. not relevant
3101	R, T									%	73,00	abnormal high	clin. not relevant
4102	R, T	GI/l	2,92	abnormal low	clin. not relevant	GI/l	6,01	abnormal high	clin. not relevant	GI/l	6,04	abnormal high	clin. not relevant
4106	R, T	GI/l	8,58	abnormal high	clin. not relevant	GI/l	7,03	abnormal high	clin. not relevant	GI/l	11,01	abnormal high	clin. not relevant
1203	R, T									$10^3/\mu l$	9,42	abnormal high	clin. not relevant
1206	R, T	$10^3/\mu l$	9,98	abnormal high	clin. not relevant								
1207	T, R									$10^3/\mu l$	8,90	abnormal high	clin. not relevant
1208	R, T									$10^3/\mu l$	8,19	abnormal high	clin. not relevant
3202	T, R					%	77,00	abnormal high	clin. not relevant				

3206	R, T					%	39,00	abnormal low	clin. not relevant				
3208	R, T					%	78,00	abnormal high	clin. not relevant				
3209	R, T	%	78,00	abnormal high	clin. not relevant								
3210	T, R	%	77,00	abnormal high	clin. not relevant								
4103	R, T									GI/l	6,82	abnormal high	clin. not relevant
4104	T, R					GI/l	9,49	abnormal high	clin. not relevant	GI/l	8,15	abnormal high	clin. not relevant
4105	T, R	GI/l	7,09	abnormal high	clin. not relevant					GI/l	8,28	abnormal high	clin. not relevant

Table 51 Abnormal Lymphocyte Values per Patient (Visit 1 – 3)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Lymphocytes				Lymphocytes				Lymphocytes			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1110	T, R									$10^3/\mu l$	2,35	abnormal low	clin. not relevant
1111	T, R									$10^3/\mu l$	3,74	abnormal low	clin. not relevant
1112	R, T									$10^3/\mu l$	3,97	abnormal low	clin. not relevant
1113	T, R									$10^3/\mu l$	2,03	abnormal low	clin. not relevant
1114	R, T					$10^3/\mu l$	3,55	abnormal low	clin. not relevant				
3102	T, R									%	67,00	abnormal high	clin. not relevant
4106	R, T					GI/l	3,36	abnormal high	clin. not relevant	GI/l	3,96	abnormal high	clin. not relevant
3205	T, R	%	23,00	abnormal low	clin. not relevant								
3206	R, T	%	20,00	abnormal low	clin. not relevant	%	24,00	abnormal low	clin. not relevant				
3207	T, R	%	20,00	abnormal low	clin. not relevant	%	15,00	abnormal low	clin. not relevant				
3208	R, T	%	22,00	abnormal low	clin. not relevant	%	19,00	abnormal low	clin. not relevant				
3209	R, T					%	16,00	abnormal low	clin. not relevant				
3210	T, R	%	21,00	abnormal low	clin. not relevant	%	12,00	abnormal low	clin. not relevant				

4104	T, R	GI/l	3,92	abnormal high	clin. not relevant	GI/l	2,21	abnormal low	clin. not relevant				
4105	T, R	GI/l	1,20	abnormal low	clin. not relevant	GI/l	1,38	abnormal low	clin. not relevant				
4204	R, T									GI/l	1,48	abnormal low	clin. not relevant
4205	R, T									GI/l	3,15	abnormal high	clin. not relevant

Table 52 Abnormal Lymphocyte Values per Patient (Visit 4 – 6)

		Haematology				Haematology				Haematology			
		Lymphocytes				Lymphocytes				Lymphocytes			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1110	T, R					10^3/µl	3,86	abnormal low	clin. not relevant	10^3/µl	2,56	abnormal low	clin. not relevant
1111	T, R	10^3/µl	2,26	abnormal low	clin. not relevant	10^3/µl	2,33	abnormal low	clin. not relevant				
1112	R, T	10^3/µl	3,62	abnormal low	clin. not relevant								
1113	T, R	10^3/µl	3,30	abnormal low	clin. not relevant	10^3/µl	3,89	abnormal low	clin. not relevant				
1114	R, T	10^3/µl	2,31	abnormal low	clin. not relevant								
4106	R, T									%	21,00	abnormal low	clin. not relevant
3206	R, T					GI/l	3,09	abnormal high	clin. not relevant				
3207	T, R									GI/l	3,32	abnormal high	clin. not relevant
3208	R, T	GI/l	3,19	abnormal high	clin. not relevant	GI/l	3,41	abnormal high	clin. not relevant				
3209	R, T	10^3/µl	0,77	abnormal low	clin. not relevant								
4104						%	58,00	abnormal high	clin. not relevant				
4105										%	23,00	abnormal low	clin. not relevant
4204						%	16,00	abnormal low	clin. not relevant	%	24,00	abnormal low	clin. not relevant

4205	R, T	%	18,00	abnormal low	clin. not relevant								

Table 53 Abnormal Monocyte Values per Patient (Visit 1 – 3)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Monocytes				Monocytes				Monocytes			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1109	R	10^3/µl	1,29	abnormal high	clin. not relevant	10^3/µl	1,00						
2101	R, T					GI/l	1,10	abnormal high	clin. not relevant				
2104	R	GI/l	1,20	abnormal high	clin. not relevant	GI/l	1,55	abnormal high	clin. not relevant				
1203	R, T									10^3/µl	1,50	abnormal high	clin. not relevant
1206	R, T					10^3/µl	1,35	abnormal high	clin. not relevant				
2204	T, R									GI/l	1,09	abnormal high	clin. not relevant
2205	R, T	GI/l	1,02	abnormal high	clin. not relevant	GI/l	1,01	abnormal high	clin. not relevant				

Table 54 Abnormal Monocyte Values per Patient (Visit 4 – 6)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Monocytes				Monocytes				Monocytes			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1104	R, T	10^3/µl	1,25	abnormal high	clin. not relevant					10^3/µl	1,32	abnormal high	clin. not relevant
2101	R, T					GI/l	1,60	abnormal high	clin. not relevant				
2104	R									GI/l	1,40	abnormal high	clin. not relevant
2107	R, T									GI/l	1,02	abnormal high	clin. not relevant
1203	R, T	10^3/µl	1,35	abnormal high	clin. not relevant					10^3/µl	1,73	abnormal high	clin. not relevant
1206	R, T	10^3/µl	1,33	abnormal high	clin. not relevant								
2203	R, T									GI/l	1,17	abnormal high	clin. not relevant
2205	R, T	GI/l	1,05	abnormal high	clin. not relevant								

Table 55 Abnormal Basophil Values per Patient (Visit 1 – 3)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Eosinophils				Eosinophils				Eosinophils			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1109	R	$10^3/\mu l$	0,00	abnormal low	clin. not relevant								
3101	R, T					%	8,00	abnormal high	clin. not relevant				
3201	R, T	%	7,00	abnormal high	clin. not relevant	%	9,00	abnormal high	clin. not relevant				

Table 56 Abnormal Basophil Values per Patient (Visit 4 – 6)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Eosinophils				Eosinophils				Eosinophils			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1114	R, T									$10^3/\mu l$	1,10	abnormal high	clin. not relevant
3101	R, T	%	7,00	abnormal high	clin. not relevant	%	6,00	abnormal high	clin. not relevant	%	2,00	normal	
1206	R, T	$10^3/\mu l$	0,00	abnormal low	clin. not relevant					$10^3/\mu l$	0,00	abnormal low	clin. not relevant
3208	R, T	%	6,00	abnormal high	clin. not relevant								

Table 57 Abnormal Eosinophil Values per Patient (Visit 1 – 3)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Eosinophils				Eosinophils				Eosinophils			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1109	R	$10^3/\mu l$	0,00	abnormal low	clin. not relevant								
3101	R, T					%	8,00	abnormal high	clin. not relevant				
3201	R, T	%	7,00	abnormal high	clin. not relevant	%	9,00	abnormal high	clin. not relevant				

Table 58 Abnormal Eosinophil values per Patient (Visit 4 – 6)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Eosinophils				Eosinophils				Eosinophils			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1114	R, T									$10^3/\mu l$	1,10	abnormal high	clin. not relevant
3101	R, T	%	7,00	abnormal high	clin. not relevant	%	6,00	abnormal high	clin. not relevant				
1206	R, T	$10^3/\mu l$	0,00	abnormal low	clin. not relevant					$10^3/\mu l$	0,00	abnormal low	clin. not relevant
3208	R, T	%	6,00	abnormal high	clin. not relevant								

Table 59 Abnormal Platelet Values per Patient (Visit 1 – 3)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Platelet cell count				Platelet cell count				Platelet cell count			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1110	T, R	$10^3/\mu l$	91	abnormal low	clin. not relevant	$10^3/\mu l$	107	abnormal low	clin. not relevant	$10^3/\mu l$	93	abnormal low	clin. not relevant
1114	R, T	$10^3/\mu l$	452	abnormal high	clin. not relevant								
3101	R, T	$10^3/\mu l$	586	abnormal high	clin. not relevant	$10^3/\mu l$	516	abnormal high	clin. not relevant	$10^3/\mu l$	626	abnormal high	clin. not relevant
3102	T, R	$10^3/\mu l$	439	abnormal high	clin. not relevant	$10^3/\mu l$	491	abnormal high	clin. not relevant	$10^3/\mu l$	499	abnormal high	clin. not relevant
4106	R, T	Gl/l	388	abnormal high	clin. not relevant	Gl/l	406	abnormal high	clin. not relevant				
1203	R, T	$10^3/\mu l$	469	abnormal high	clin. not relevant					$10^3/\mu l$	496	abnormal high	clin. not relevant
1207	T, R	$10^3/\mu l$	134	abnormal low	clin. not relevant					$10^3/\mu l$	137	abnormal low	clin. not relevant
3206	R, T									$10^3/\mu l$	123	abnormal low	clin. not relevant
3210	T, R	$10^3/\mu l$	390	abnormal high	clin. not relevant	$10^3/\mu l$	354	abnormal high	clin. not relevant				
4104	T, R	Gl/l	363	abnormal high	clin. not relevant								
4205	R, T	Gl/l	360	abnormal high	clin. not relevant								

Table 60 Abnormal Platelet Values per Patient (Visit 4 – 6)

Enrolment No.	Treatment order	Haematology				Haematology				Haematology			
		Platelet cell count				Platelet cell count				Platelet cell count			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1103	T, R	$10^3/\mu l$	142	abnormal low	clin. not relevant								
1104	R, T	$10^3/\mu l$	508	abnormal high	clin. not relevant	$10^3/\mu l$	451	abnormal high	clin. not relevant	$10^3/\mu l$	459	abnormal high	clin. not relevant
1110	T, R	$10^3/\mu l$	102	abnormal low	clin. not relevant	$10^3/\mu l$	88	abnormal low	clin. not relevant	$10^3/\mu l$	95	abnormal low	clin. not relevant
3101	R, T	$10^3/\mu l$	589	abnormal high	clin. not relevant	$10^3/\mu l$	508	abnormal high	clin. not relevant	$10^3/\mu l$	493	abnormal high	clin. not relevant
3102	T, R	$10^3/\mu l$	518	abnormal high	clin. not relevant	$10^3/\mu l$	444	abnormal high	clin. not relevant	$10^3/\mu l$	502	abnormal high	clin. not relevant
4106	R, T	GI/l	403	abnormal high	clin. not relevant	GI/l	380	abnormal high	clin. not relevant				
1203	R, T	$10^3/\mu l$	507	abnormal high	clin. not relevant								
1207	T, R	$10^3/\mu l$	109	abnormal low	clin. not relevant	$10^3/\mu l$	114	abnormal low	clin. not relevant	$10^3/\mu l$	127	abnormal low	clin. not relevant
1208	R, T									$10^3/\mu l$	510	abnormal high	clin. not relevant
2205	R, T	GI/l	452	abnormal high	clin. not relevant								
3209	R, T					$10^3/\mu l$	414	abnormal high	clin. not relevant	$10^3/\mu l$	405	abnormal high	clin. not relevant
3210	T, R	$10^3/\mu l$	356	abnormal high	clin. not relevant								
4204	R, T	GI/l	376	abnormal high	clin. not relevant								
4205	R, T	GI/l	376	abnormal high	clin. not relevant								

Table 61 Abnormal Alkaline Phosphatase Values per Patient (Visit 1 – 3)

Enrolment No.	Treatment order	Biochemistry				Biochemistry				Biochemistry			
		Alk. Phosphatase				Alk. Phosphatase				Alk. Phosphatase			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1101	R, T	U/l	454,0	abnormal high	clin. not relevant	U/l	411,8	abnormal high	clin. not relevant	U/l	396,1	abnormal high	clin. not relevant
1102	T, R	U/l	529,2	abnormal high	clin. not relevant	U/l	537,7	abnormal high	clin. not relevant	U/l	478,9	abnormal high	clin. not relevant
1103	T, R	U/l	332,7	abnormal high	clin. not relevant	U/l	344,9	abnormal high	clin. not relevant	U/l	327,7	abnormal high	clin. not relevant
1106	R, T					U/l	304,8	abnormal high	clin. not relevant				
1107	T, R	U/l	330,0	abnormal high	clin. not relevant	U/l	353,4	abnormal high	clin. not relevant	U/l	382,6	abnormal high	clin. not relevant
1108	R, T									U/l	319,2	abnormal high	clin. not relevant
1110	T, R	U/l	373,7	abnormal high	clin. not relevant	U/l	341,0	abnormal high	clin. not relevant	U/l	323,6	abnormal high	clin. not relevant
1112	R, T	U/l	332,4	abnormal high	clin. not relevant	U/l	351,7	abnormal high	clin. not relevant	U/l	346,1	abnormal high	clin. not relevant
1113	T, R	U/l	308,3	abnormal high	clin. not relevant								
2107	R, T	U/l	387,0	abnormal high	clin. not relevant	U/l	421,0	abnormal high	clin. not relevant	U/l	421,0	abnormal high	clin. not relevant
2108	T	U/l	371,0	abnormal high	clin. not relevant	U/l	364,0	abnormal high	clin. not relevant	U/l	388,0	abnormal high	clin. not relevant
3101	R, T	U/l	428,0	abnormal high	clin. not relevant	U/l	373,0	abnormal high	clin. not relevant	U/l	325,0	abnormal high	clin. not relevant
3103	R, T					U/l	319,0	abnormal high	clin. not relevant	U/l	381,0	abnormal high	clin. not relevant
1202	T, R	U/l	188,1	abnormal high	clin. not relevant								

1203	R, T	U/l	242,6	abnormal high	clin. not relevant	U/l	229,0	abnormal high	clin. not relevant	U/l	219,5	abnormal high	clin. not relevant
1204	T, R	U/l	143,7	abnormal high	clin. not relevant	U/l	149,4	abnormal high	clin. not relevant	U/l	125,0	abnormal high	clin. not relevant
1205	T	U/l	184,5	abnormal high	clin. not relevant	U/l	198,3	abnormal high	clin. not relevant	U/l	188,3	abnormal high	clin. not relevant
1208	R, T					U/l	193,7	abnormal high	clin. not relevant	U/l	235,4	abnormal high	clin. not relevant
2201	T, R	U/l	171,0	abnormal high	clin. not relevant	U/l	183,0	abnormal high	clin. not relevant	U/l	158,0	abnormal high	clin. not relevant
2202	R, T	U/l	106,0	abnormal high	clin. not relevant	U/l	110,0	abnormal high	clin. not relevant				
2205	R, T	U/l	188,0	abnormal high	clin. not relevant	U/l	204,0	abnormal high	clin. not relevant	U/l	198,0	abnormal high	clin. not relevant
2206	T, R	U/l	21,0	abnormal low	clin. not relevant	U/l							
3201	R, T	U/l	159,0	abnormal high	clin. not relevant	U/l	207,0	abnormal high	clin. not relevant	U/l	215,0	abnormal high	clin. not relevant
3202	T, R	U/l	162,0	abnormal high	clin. not relevant	U/l	172,0	abnormal high	clin. not relevant				
3205	T, R									U/l	153,0	abnormal high	clin. not relevant
3206	R, T	U/l	158,0	abnormal high	clin. not relevant	U/l	155,0	abnormal high	clin. not relevant	U/l	208,0	abnormal high	clin. not relevant
3207	T, R	U/l	133,0	abnormal high	clin. not relevant	U/l	137,0	abnormal high	clin. not relevant	U/l	161,0	abnormal high	clin. not relevant
3208	R, T									U/l	130,0	abnormal high	clin. not relevant

Table 62 Abnormal Alkaline Phosphatase Values per Patient (Visit 4 – 6)

Enrolment No.	Treatment order	Biochemistry				Biochemistry				Biochemistry			
		Alk. Phosphatase				Alk. Phosphatase				Alk. Phosphatase			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1101	R, T	U/l	436,2	abnormal high	clin. not relevant	U/l	372,1	abnormal high	clin. not relevant	U/l	392,5	abnormal high	clin. not relevant
1102	T, R	U/l	470,6	abnormal high	clin. not relevant	U/l	494,4	abnormal high	clin. not relevant	U/l	472,9	abnormal high	clin. not relevant
1103	T, R	U/l	371,3	abnormal high	clin. not relevant	U/l	351,7	abnormal high	clin. not relevant	U/l	363,8	abnormal high	clin. not relevant
1104	R, T					U/l	237,0	abnormal high	clin. not relevant	U/l	214,9	abnormal high	clin. not relevant
1107	T, R	U/l	349,0	abnormal high	clin. not relevant	U/l	373,8	abnormal high	clin. not relevant	U/l	349,8	abnormal high	clin. not relevant
1108	R, T					U/l	342,3	abnormal high	clin. not relevant				
1110	T, R	U/l	322,8	abnormal high	clin. not relevant	U/l	313,5	abnormal high	clin. not relevant	U/l	338,3	abnormal high	clin. not relevant
1112	R, T	U/l	320,0	abnormal high	clin. not relevant	U/l	327,0	abnormal high	clin. not relevant	U/l	309,2	abnormal high	clin. not relevant
1113	T, R	U/l	318,8	abnormal high	clin. not relevant	U/l	311,3	abnormal high	clin. not relevant	U/l	331,2	abnormal high	clin. not relevant
2107	R, T	U/l	370,0	abnormal high	clin. not relevant	U/l	464,0	abnormal high	clin. not relevant	U/l	425,0	abnormal high	clin. not relevant
2108	T									U/l	360,0	abnormal high	clin. not relevant
3101	R, T	U/l	315,0	abnormal high	clin. not relevant					U/l	305,0	abnormal high	clin. not relevant
3103	R, T	U/l	361,0	abnormal high	clin. not relevant	U/l	383,0	abnormal high	clin. not relevant	U/l	350,0	abnormal high	clin. not relevant
1203	R, T	U/l	180,3	abnormal high	clin. not relevant	U/l	213,5	abnormal high	clin. not relevant	U/l	195,9	abnormal high	clin. not relevant

1204	T, R	U/l	143,4	abnormal high	clin. not relevant	U/l	121,8	abnormal high	clin. not relevant	U/l	120,0	abnormal high	clin. not relevant
1205	T									U/l	179,4	abnormal high	clin. not relevant
1208	R, T	U/l	232,9	abnormal high	clin. not relevant								
2201	T, R	U/l	190,0	abnormal high	clin. not relevant	U/l	180,0	abnormal high	clin. not relevant	U/l	183,0	abnormal high	clin. not relevant
2202	R, T	U/l	111,0	abnormal high	clin. not relevant	U/l	115,0	abnormal high	clin. not relevant	U/l	105,0	abnormal high	clin. not relevant
2206	T, R					U/l	107,0	abnormal high	clin. not relevant				
3201	R, T	U/l	127,0	abnormal high	clin. not relevant	U/l	125,0	abnormal high	clin. not relevant				
3202	T, R	U/l	135,0	abnormal high	clin. not relevant					U/l	143,0	abnormal high	clin. not relevant
3205	T, R	U/l	170,0	abnormal high	clin. not relevant	U/l	162,0	abnormal high	clin. not relevant	U/l	152,0	abnormal high	clin. not relevant
3206	R, T	U/l	224,0	abnormal high	clin. not relevant	U/l	169,0	abnormal high	clin. not relevant	U/l	169,0	abnormal high	clin. not relevant
3207	T, R	U/l	202,0	abnormal high	clin. not relevant	U/l	161,0	abnormal high	clin. not relevant	U/l	180,0	abnormal high	clin. not relevant

Table 63 Abnormal GGT Values per Patient (Visit 1 – 3)

Enrolment No.	Treatment order	Biochemistry				Biochemistry				Biochemistry			
		GGT				GGT				GGT			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1101	R, T	U/l	100,0	abnormal high	clin. not relevant	U/l	87,0	abnormal high	clin. not relevant	U/l	98,0	abnormal high	clin. not relevant
1107	T, R	U/l	7,0	abnormal low	clin. not relevant	U/l	8,0						
2105	R, T	U/l	7,0	abnormal low	clin. not relevant	U/l	7,0	abnormal low	clin. not relevant	U/l	7,0	abnormal low	clin. not relevant
2107	R, T	U/l	7,0	abnormal low	clin. not relevant					U/l	6,0	abnormal low	clin. not relevant
3101	R, T	U/l	8,0	abnormal low	clin. not relevant	U/l	7,0	abnormal low	clin. not relevant				
3103	R, T					U/l	57,0	abnormal high	clin. not relevant	U/l	70,0	abnormal high	clin. not relevant
2205	R, T					U/l	37,0	abnormal high	clin. not relevant				
3201	R, T	U/l	76,0	abnormal high	clin. not relevant	U/l	95,0	abnormal high	clin. not relevant	U/l	178,0	abnormal high	clin. not relevant
3204	R, T					U/l	5,0	abnormal low	clin. not relevant				
3208	R, T	U/l	91,0	abnormal high	clin. not relevant	U/l	90,0	abnormal high	clin. not relevant	U/l	95,0	abnormal high	clin. not relevant
3209	R, T	U/l	9,0	abnormal low	clin. not relevant	U/l	9,0	abnormal low	clin. not relevant				
4105	T, R	U/l	41,8	abnormal high	clin. not relevant					U/l	64,1	abnormal high	clin. not relevant

Table 64 Abnormal GGT Values per Patient (Visit 4 – 6)

Enrolment No.	Treatment order	Biochemistry				Biochemistry				Biochemistry			
		GGT				GGT				GGT			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1101	R, T	U/l	93,0	abnormal high	clin. not relevant	U/l	72,0	abnormal high	clin. not relevant	U/l	75,0	abnormal high	clin. not relevant
2101	R, T					U/l	6,0	abnormal low	clin. not relevant	U/l	7,0	abnormal low	clin. not relevant
2105	R, T	U/l	6,0	abnormal low	clin. not relevant	U/l	7,0	abnormal low	clin. not relevant	U/l	7,0	abnormal low	clin. not relevant
3103	R, T	U/l	78,0	abnormal high	clin. not relevant	U/l	69,0	abnormal high	clin. not relevant	U/l	65,0	abnormal high	clin. not relevant
2203	R, T									U/l	38,0	abnormal high	clin. not relevant
2205	R, T	U/l	37,0	abnormal high	clin. not relevant								
3201	R, T	U/l	64,0	abnormal high	clin. not relevant								
3207	T, R	U/l	40,0	abnormal high	clin. not relevant								
3208	R, T	U/l	109,0	abnormal high	clin. not relevant	U/l	101,0	abnormal high	clin. not relevant	U/l	121,0	abnormal high	clin. not relevant
4105	T, R	U/l	62,0	abnormal high	clin. not relevant	U/l	46,7	abnormal high	clin. not relevant	U/l	57,0	abnormal high	clin. not relevant

Table 65 Abnormal ASAT Values per Patient (Visit 1 – 3)

Enrolment No.	Treatment order	Biochemistry				Biochemistry				Biochemistry			
		ASAT				ASAT				ASAT			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1101	R, T	U/l	84,0	abnormal high	clin. not relevant								
1106	R, T	U/l	42,0	abnormal high	clin. not relevant								
1108	R, T					U/l	44,0	abnormal high	clin. not relevant				
1110	T, R	U/l	49,0	abnormal high	clin. not relevant	U/l	48,0	abnormal high	clin. not relevant				
2105	R, T	U/l	42,0	abnormal high	clin. not relevant	U/l	38,0	abnormal high	clin. not relevant	U/l	62,0	abnormal high	clin. not relevant
2108	T	U/l	40,0	abnormal high	clin. not relevant	U/l	38,0	abnormal high	clin. not relevant	U/l	58,0	abnormal high	clin. not relevant
3101	R, T	U/l	48,0	abnormal high	clin. not relevant								
3102	T, R	U/l	46,0	abnormal high	clin. not relevant								
3103	R, T	U/l	56,0	abnormal high	clin. not relevant	U/l	53,0	abnormal high	clin. not relevant	U/l	71,0	abnormal high	clin. not relevant
1201	R, T	U/l	54,0	abnormal high	clin. not relevant	U/l	60,0	abnormal high	clin. not relevant	U/l	49,0	abnormal high	clin. not relevant
2202	R, T	U/l	35,0	abnormal high	clin. not relevant								
2203	R, T	U/l	33,0	abnormal high	clin. not relevant								
2206	T, R									U/l	69,0	abnormal high	clin. not relevant
3201	R, T					U/l	50,0	abnormal high	clin. not relevant				

3207	T, R									U/l	39,0	abnormal high	clin. not relevant
3208	R, T	U/l	42,0	abnormal high	clin. not relevant	U/l	43,0	abnormal high	clin. not relevant				

Table 66 Abnormal ASAT Values per Patient (Visit 4 – 6)

Enrolment No.	Treatment order	Biochemistry				Biochemistry				Biochemistry			
		ASAT				ASAT				ASAT			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1101	R, T	U/l	47,0	abnormal high	clin. not relevant	U/l	47,0	abnormal high	clin. not relevant	U/l	42,0	abnormal high	clin. not relevant
1105	T, R									U/l	44,0	abnormal high	clin. not relevant
1106	R, T					U/l	41,0	abnormal high	clin. not relevant	U/l	66,0	abnormal high	clin. not relevant
1110	T, R	U/l	45,0	abnormal high	clin. not relevant					U/l	48,0	abnormal high	clin. not relevant
1113	T, R	U/l	44,0	abnormal high	clin. not relevant								
2102	T, R					U/l	48,0	abnormal high	clin. not relevant				
2105	R, T	U/l	39,0	abnormal high	clin. not relevant	U/l	41,0	abnormal high	clin. not relevant	U/l	41,0	abnormal high	clin. not relevant
2108	T									U/l	51,0	abnormal high	clin. not relevant
3101	R, T	U/l	46,0	abnormal high	clin. not relevant	U/l	50,0	abnormal high	clin. not relevant				
3103	R, T	U/l	69,0	abnormal high	clin. not relevant	U/l	62,0	abnormal high	clin. not relevant	U/l	62,0	abnormal high	clin. not relevant
1201	R, T	U/l	47,0	abnormal high	clin. not relevant	U/l	51,0	abnormal high	clin. not relevant	U/l	52,0	abnormal high	clin. not relevant
2206	T, R					U/l	34,0	abnormal high	clin. not relevant				
3207	T, R	U/l	45,0	abnormal high	clin. not relevant					U/l	61,0	abnormal high	clin. not relevant
3208	R, T					U/l	50,0	abnormal high	clin. not relevant				

Table 67 Abnormal ALAT Values per Patient (Visit 1 – 3)

Enrolment No.	Treatment order	Biochemistry				Biochemistry				Biochemistry			
		ALAT				ALAT				ALAT			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1101	R, T	U/l	56,0	abnormal high	clin. not relevant								
1102	T, R									U/l	42,0	abnormal high	clin. not relevant
1110	T, R	U/l	62,0	abnormal high	clin. not relevant	U/l	56,0	abnormal high	clin. not relevant	U/l	48,0	abnormal high	clin. not relevant
1112	R, T									U/l	42,0	abnormal high	clin. not relevant
2108	T									U/l	60,0	abnormal high	clin. not relevant
3102	T, R	U/l	59,0	abnormal high	clin. not relevant	U/l	47,0	abnormal high	clin. not relevant				
3103	R, T	U/l	61,0	abnormal high	clin. not relevant	U/l	59,0	abnormal high	clin. not relevant	U/l	75,0	abnormal high	clin. not relevant
2205	R, T	U/l	46,0	abnormal high	clin. not relevant	U/l	44,0	abnormal high	clin. not relevant				
2206	T, R	U/l	35,0	abnormal high	clin. not relevant	U/l	44,0	abnormal high	clin. not relevant				
3201	R, T	U/l	47,0	abnormal high	clin. not relevant	U/l	59,0	abnormal high	clin. not relevant	U/l	117,0	abnormal high	clin. not relevant
3207	T, R									U/l	53,0	abnormal high	clin. not relevant
3208	R, T					U/l	60,0	abnormal high	clin. not relevant				

Table 68 Abnormal ALAT Values per Patient (Visit 4 – 6)

		Biochemistry				Biochemistry				Biochemistry			
		ALAT				ALAT				ALAT			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1110	T, R	U/l	46,0	abnormal high	clin. not relevant					U/l	46,0	abnormal high	clin. not relevant
3103	R, T	U/l	81,0	abnormal high	clin. not relevant	U/l	65,0	abnormal high	clin. not relevant	U/l	71,0	abnormal high	clin. not relevant
2205	R, T	U/l	32,0	abnormal high	clin. not relevant					U/l	32,0	abnormal high	clin. not relevant
3207	T, R	U/l	73,0	abnormal high	clin. not relevant	U/l	53,0	abnormal high	clin. not relevant	U/l	68,0	abnormal high	clin. not relevant
3208	R, T									U/l	49,0	abnormal high	clin. not relevant

Table 69 Abnormal Glucose Values per Patient (Visits 1 – 3)

Enrolment No.	Treatment order	Biochemistry				Biochemistry				Biochemistry			
		Glucose				Glucose				Glucose			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1110	T, R	mg/dl	66,00	abnormal low	clin. not relevant								
2102	T, R					mg/dl	110,00	abnormal high	clin. not relevant				
2103	T, R	mg/dl	107,00	abnormal high	clin. not relevant	mg/dl	116,00	abnormal high	clin. not relevant	mg/dl	126,00	abnormal high	clin. not relevant
2106	T, R					mg/dl	127,00	abnormal high	clin. not relevant				
2107	R, T					mg/dl	100,00	abnormal high	clin. not relevant				
1204	T, R	mg/dl	65,00	abnormal low	clin. not relevant								
2201	T, R	mg/dl	100,00	abnormal high	clin. not relevant								
2205	R, T									mg/dl	102,00	abnormal high	clin. not relevant
3204	R, T					mmol/l	5,88	abnormal high	clin. not relevant				
3206	R, T					mmol/l	3,38	abnormal low	clin. not relevant				
3208	R, T	mmol/l	3,70	abnormal low	clin. not relevant					mmol/l	3,32	abnormal low	clin. not relevant
3210	T, R	mmol/l	6,48	abnormal high	clin. not relevant					mmol/l	6,37	abnormal high	clin. not relevant
4104	T, R									mmol/l	7,10	abnormal high	clin. not relevant
4204	R, T					mmol/l	9,00	abnormal high	clin. not relevant	mmol/l	7,50	abnormal high	clin. not relevant

4206	T, R									mmol/l	3,00	abnormal low	clin. not relevant

Table 70 Abnormal Glucose Values per Patient (Visits 4 – 6)

		Biochemistry				Biochemistry				Biochemistry			
		Glucose				Glucose				Glucose			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1105	T, R									mg/dl	66,00	abnormal low	clin. not relevant
2101	R, T	mg/dl	103,00	abnormal high	clin. not relevant					mg/dl	100,00	abnormal high	clin. not relevant
2103	T, R	mg/dl	120,00	abnormal high	clin. not relevant	mg/dl	130,00	abnormal high	clin. not relevant	mg/dl	120,00	abnormal high	clin. not relevant
2106	T, R	mg/dl	162,00	abnormal high	clin. not relevant	mg/dl	102,00	abnormal high	clin. not relevant				
3103	R, T	mmol/l	5,92	abnormal high	clin. not relevant	mmol/l	3,42	abnormal low	clin. not relevant	mmol/l	7,17	abnormal high	clin. not relevant
4101	T, R					mmol/l	6,60	abnormal high	clin. not relevant				
1201	R, T									mg/dl	118,00	abnormal high	clin. not relevant
1202	T, R									mg/dl	53,00	abnormal low	clin. not relevant
1204	T, R									mg/dl	63,00	abnormal low	clin. not relevant
2201	T, R					mg/dl	101,00	abnormal high	clin. not relevant				

2203	R, T	mg/dl	100,00	abnormal high	clin. not relevant	mg/dl	116,00	abnormal high	clin. not relevant				
2206	T, R					mg/dl	114,00	abnormal high	clin. not relevant	mg/dl	165,00	abnormal high	clin. not relevant
3204	R, T	mmol/l	5,96	abnormal high	clin. not relevant					mmol/l	2,99	abnormal low	clin. not relevant
3205	T, R					mmol/l	3,50	abnormal low	clin. not relevant				
3206	R, T					mmol/l	3,80	abnormal low	clin. not relevant				
3207	T, R	mmol/l	3,34	abnormal low	clin. not relevant								
3208	R, T	mmol/l	3,73	abnormal low	clin. not relevant								
4103	R, T									mmol/l	3,30	abnormal low	clin. not relevant
4104	T, R					mmol/l	6,80	abnormal high	clin. not relevant				
4105	T, R									mmol/l	3,60	abnormal low	clin. not relevant
4205	R, T									mmol/l	3,40	abnormal low	clin. not relevant
4206	T, R									mmol/l	6,70	abnormal high	clin. not relevant

Table 71 Abnormal LDH Values per Patient (Visits 1 – 6)

Enrolment No.	Treatment order	Biochemistry LDH Visit 1	Biochemistry LDH Visit 2	Biochemistry LDH Visit 3	Biochemistry LDH Visit 4	Biochemistry LDH Visit 5	Biochemistry LDH Visit 6
1106	R, T		LDH, U/l 223, abnormal low, clin. not relevant	LDH, U/l 234, abnormal low, clin. not relevant	LDH, U/l 228, abnormal low, clin. not relevant	LDH, U/l 237, abnormal low, clin. not relevant	
2101	R, T			LDH, U/l 325, abnormal high, clin. not relevant			
2102	T, R		LDH, U/l 134, abnormal low, clin. not relevant			LDH, U/l 443, abnormal high, clin. not relevant	
2103	T, R					LDH, U/l 347, abnormal high, clin. not relevant	
2105	R, T	LDH, U/l 233, abnormal high, clin. not relevant		LDH, U/l 406, abnormal high, clin. not relevant			
2106	T, R			LDH, U/l 240, abnormal high, clin. not relevant	LDH, U/l 254, abnormal high, clin. not relevant		
2108	T	LDH, U/l 232, abnormal high, clin. not relevant		LDH, U/l 245, abnormal high, clin. not relevant			LDH, U/l 251, abnormal high, clin. not relevant
3101	R, T				LDH, U/l 976, abnormal high, clin. not relevant	LDH, U/l 971, abnormal high, clin. not relevant	

3103	R, T			LDH, U/l 899, abnormal high, clin. not relevant		LDH, U/l 742, abnormal high, clin. not relevant	LDH, U/l 823, abnormal high, clin. not relevant
4101	T, R			LDH, U/l 470.44, abnormal high, clin. not relevant			
4102	R, T			LDH, U/l 528.91, abnormal high, clin. not relevant		LDH, U/l 452.39, abnormal high, clin. not relevant	LDH, U/l 478.71, abnormal high, clin. not relevant
1204	T, R			LDH, U/l 233, abnormal high, clin. not relevant			
1205	T						LDH, U/l 238, abnormal low, clin. not relevant
2201	T, R			LDH, U/l 314, abnormal high, clin. not relevant		LDH, U/l 240, abnormal high, clin. not relevant	
2202	R, T			LDH, U/l 426, abnormal high, clin. not relevant			
2203	R, T	LDH, U/l 295, abnormal high, clin. not relevant		LDH, U/l 423, abnormal high, clin. not relevant		LDH, U/l 408, abnormal high, clin. not relevant	
2206	T, R			LDH, U/l 717, abnormal high, clin. not relevant			
3201	R, T		LDH, U/l 592, abnormal high, clin. not relevant	LDH, U/l 560, abnormal high, clin. not relevant			LDH, U/l 514, abnormal high, clin. not relevant
3202	T, R	LDH, U/l 543, abnormal high, clin. not relevant		LDH, U/l 550, abnormal high, clin. not relevant		LDH, U/l 219, abnormal low, clin. not relevant	

3203	T, R	LDH, U/l 465, abnormal high, clin. not relevant	LDH, U/l 440, abnormal high, clin. not relevant	LDH, U/l 657, abnormal high, clin. not relevant			LDH, U/l 573, abnormal high, clin. not relevant
3204	R, T	LDH, U/l 533, abnormal high, clin. not relevant			LDH, U/l 439, abnormal high, clin. not relevant		LDH, U/l 463, abnormal high, clin. not relevant
3205	T, R	LDH, U/l 542, abnormal high, clin. not relevant					LDH, U/l 772, abnormal high, clin. not relevant
3207	T, R	LDH, U/l 519, abnormal high, clin. not relevant					
3208	R, T		LDH, U/l 603, abnormal high, clin. not relevant	LDH, U/l 502, abnormal high, clin. not relevant		LDH, U/l 1137, abnormal high, clin. relevant	LDH, U/l 586, abnormal high, clin. not relevant
3209	R, T			LDH, U/l 652, abnormal high, clin. not relevant	LDH, U/l 509, abnormal high, clin. not relevant	LDH, U/l 486, abnormal high, clin. not relevant	LDH, U/l 1217, abnormal high, clin. not relevant
3210	T, R	LDH, U/l 519, abnormal high, clin. not relevant			LDH, U/l 549, abnormal high, clin. not relevant	LDH, U/l 1066, abnormal high, clin. relevant	

3210	T, R	LDH, U/l 519, abnormal high, clin. not relevant	LDH, U/l 442, normal	LDH, U/l 360, normal	LDH, U/l 549, abnormal high, clin. not relevant	LDH, U/l 1066, abnormal high, clin. relevant	LDH, U/l 312, normal

Table 72 Abnormal Creatinine Values per Patient (Visits 1 – 3)

Enrolment No.	Treatment order	Biochemistry				Biochemistry				Biochemistry			
		Creatinine				Creatinine				Creatinine			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. Relevance
1101	R, T	µmol/l	25,00	abnormal low	clin. not relevant					µmol/l	25,00	abnormal low	clin. not relevant
1102	T, R	µmol/l	29,00	abnormal low	clin. not relevant	µmol/l	32,00	abnormal low	clin. not relevant	µmol/l	30,00	abnormal low	clin. not relevant
1103	T, R					µmol/l	32,00	abnormal low	clin. not relevant	µmol/l	34,00	abnormal low	clin. not relevant
1104	R, T									µmol/l	34,00	abnormal low	clin. not relevant
1105	T, R	µmol/l	26,00	abnormal low	clin. not relevant	µmol/l	27,00	abnormal low	clin. not relevant	µmol/l	26,00	abnormal low	clin. not relevant
1108	R, T	µmol/l	29,00	abnormal low	clin. not relevant	µmol/l	30,00	abnormal low	clin. not relevant	µmol/l	30,00	abnormal low	clin. not relevant
1109	R	µmol/l	31,00	abnormal low	clin. not relevant	µmol/l	31,00	abnormal low	clin. not relevant				
1112	R, T									µmol/l	33,00	abnormal low	clin. not relevant
1113	T, R	µmol/l	34,00	abnormal low	clin. not relevant								
1114	R, T									µmol/l	27,00	abnormal low	clin. not relevant
2101	R, T	mg/dl	0,48	abnormal low	clin. not relevant					mg/dl	0,47	abnormal low	clin. not relevant
2102	T, R	mg/dl	0,31	abnormal low	clin. not relevant	mg/dl	0,32	abnormal low	clin. not relevant	mg/dl	0,30	abnormal low	clin. not relevant
2104	R	mg/dl	0,36	abnormal low	clin. not relevant								

2105	R, T					mg/dl	0,38	abnormal low	clin. not relevant	mg/dl	0,38	abnormal low	clin. not relevant
2106	T, R	mg/dl	0,36	abnormal low	clin. not relevant	mg/dl	0,31	abnormal low	clin. not relevant	mg/dl	0,34	abnormal low	clin. not relevant
4106	R, T	µmol/l	51,93	abnormal low	clin. not relevant	µmol/l	52,34	abnormal low	clin. not relevant	µmol/l	45,09	abnormal low	clin. not relevant
1201	R, T					µmol/l	48,00	abnormal low	clin. not relevant	µmol/l	51,00	abnormal low	clin. not relevant
1202	T, R	µmol/l	42,00	abnormal low	clin. not relevant	µmol/l	37,00	abnormal low	clin. not relevant				
1205	T	µmol/l	51,00	abnormal low	clin. not relevant	µmol/l	56,00	abnormal low	clin. not relevant	µmol/l	59,00	abnormal low	clin. not relevant
1206	R, T	µmol/l	54,00	abnormal low	clin. not relevant	µmol/l	57,00	abnormal low	clin. not relevant				
1207	T, R	µmol/l	55,00	abnormal low	clin. not relevant	µmol/l	57,00	abnormal low	clin. not relevant	µmol/l	56,00	abnormal low	clin. not relevant
1208	R, T	µmol/l	31,00	abnormal low	clin. not relevant					µmol/l	34,00	abnormal low	clin. not relevant
2201	T, R					mg/dl	0,49	abnormal low	clin. not relevant				
4104	T, R	µmol/l	77,96	abnormal low	clin. not relevant	µmol/l	66,38	abnormal low	clin. not relevant	µmol/l	62,45	abnormal low	clin. not relevant

Table 73 Abnormal Creatinine Values per Patient (Visits 4 – 6)

		Biochemistry				Biochemistry				Biochemistry			
		Creatinine				Creatinine				Creatinine			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1101	R, T	µmol/l	27,00	abnormal low	clin. not relevant	µmol/l	27,00	abnormal low	clin. not relevant	µmol/l	29,00	abnormal low	clin. not relevant
1102	T, R	µmol/l	32,00	abnormal low	clin. not relevant	µmol/l	31,00	abnormal low	clin. not relevant				
1105	T, R	µmol/l	26,00	abnormal low	clin. not relevant	µmol/l	29,00	abnormal low	clin. not relevant	µmol/l	29,00	abnormal low	clin. not relevant
1106	R, T	µmol/l	34,00	abnormal low	clin. not relevant								
1107	T, R	µmol/l	25,00	abnormal low	clin. not relevant								
1108	R, T	µmol/l	31,00	abnormal low	clin. not relevant					µmol/l	33,00	abnormal low	clin. not relevant
1109	R									µmol/l	27,00	abnormal low	clin. not relevant
1110	T, R					µmol/l	27,00	abnormal low	clin. not relevant	µmol/l	27,00	abnormal low	clin. not relevant
1112	R, T									µmol/l	30,00	abnormal low	clin. not relevant
1113	T, R									µmol/l	93,00	abnormal high	clin. not relevant
1114	R, T	µmol/l	26,00	abnormal low	clin. not relevant								
2101	R, T	mg/dl	0,45	abnormal low	clin. not relevant	mg/dl	0,53	abnormal low	clin. not relevant	mg/dl	0,55	abnormal low	clin. not relevant
2102	T, R	mg/dl	0,28	abnormal low	clin. not relevant	mg/dl	0,31	abnormal low	clin. not relevant	mg/dl	0,31	abnormal low	clin. not relevant
2105	R, T	mg/dl	0,34	abnormal low	clin. not relevant	mg/dl	0,37	abnormal low	clin. not relevant				

2106	T, R	mg/dl	0,35	abnormal low	clin. not relevant					mg/dl	0,32	abnormal low	clin. not relevant
4106	R, T	µmol/l	45,71	abnormal low	clin. not relevant	µmol/l	39,80	abnormal low	clin. not relevant				
1201	R, T	µmol/l	48,00	abnormal low	clin. not relevant	µmol/l	55,00	abnormal low	clin. not relevant	µmol/l	53,00	abnormal low	clin. not relevant
1202	T, R	µmol/l	37,00	abnormal low	clin. not relevant	µmol/l	43,00	abnormal low	clin. not relevant	µmol/l	39,00	abnormal low	clin. not relevant
1203	R, T	µmol/l	41,00	abnormal low	clin. not relevant					µmol/l	43,00	abnormal low	clin. not relevant
1205	T									µmol/l	59,00	abnormal low	clin. not relevant
1206	R, T	µmol/l	56,00	abnormal low	clin. not relevant								
1207	T, R					µmol/l	52,00	abnormal low	clin. not relevant	µmol/l	59,00	abnormal low	clin. not relevant
1208	R, T	µmol/l	32,00	abnormal low	clin. not relevant	µmol/l	33,00	abnormal low	clin. not relevant	µmol/l	34,00	abnormal low	clin. not relevant
2201	T, R									mg/dl	0,49	abnormal low	clin. not relevant
2203	R, T									mg/dl	0,46	abnormal low	clin. not relevant
4104	T, R	µmol/l	73,03	abnormal low	clin. not relevant	µmol/l	67,15	abnormal low	clin. not relevant	µmol/l	66,47	abnormal low	clin. not relevant
4105	T, R	µmol/l	76,56	abnormal low	clin. not relevant	µmol/l	70,19	abnormal low	clin. not relevant	µmol/l	77,24	abnormal low	clin. not relevant

Table 74 Abnormal Blood Urea Nitrogen (BUN) Values per Patient (Visits 4 – 6)

Enrolment No.	Treatment order	Biochemistry				Biochemistry				Biochemistry			
		BUN				BUN				BUN			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
4206	T, R	mg/dl	8,68	abnormal low	clin. not relevant								

BUN values at Visits 1-3 were all normal (compare **Appendix 16.2.10**).

Table 75 Abnormal Total Bilirubin Values per Patient (Visits 1 – 3)

		Biochemistry				Biochemistry				Biochemistry			
Enrolment No.	Treatment order	Total Bilirubin				Total Bilirubin				Total Bilirubin			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1103	T, R					µmol/l	21,30	abnormal high	clin. not relevant	µmol/l	26,70	abnormal high	clin. not relevant
1106	R, T	µmol/l	21,00	abnormal high	clin. not relevant								
1107	T, R					µmol/l	19,10	abnormal high	clin. not relevant				
2101	R, T	mg/dl	1,71	abnormal high	clin. not relevant					mg/dl	1,86	abnormal high	clin. not relevant
1207	T, R	µmol/l	59,30	abnormal high	clin. not relevant	µmol/l	72,90	abnormal high	clin. not relevant	µmol/l	38,20	abnormal high	clin. not relevant
2202	R, T									mg/dl	1,30	abnormal high	clin. not relevant
2206	T, R	mg/dl	2,08	abnormal high	clin. not relevant					mg/dl	2,05	abnormal high	clin. not relevant
3205	T, R	µmol/l	20,26	abnormal high	clin. not relevant	µmol/l	26,85	abnormal high	clin. not relevant	µmol/l	25,45	abnormal high	clin. not relevant
4103	R, T	µmol/l	4,98	abnormal low	clin. not relevant	µmol/l	3,33	abnormal low	clin. not relevant				
4104	T, R									µmol/l	4,75	abnormal low	clin. not relevant
4105	T, R	µmol/l	21,75	abnormal high	clin. not relevant								
4204	R, T					µmol/l	6,95				18,22	abnormal high	clin. not relevant
4206	T, R					µmol/l	5,94				4,91	abnormal low	clin. not relevant

Table 76 Abnormal Total Bilirubin Values per Patient (Visits 4 – 6)

Enrolment No.	Treatment order	Biochemistry				Biochemistry				Biochemistry			
		Total Bilirubin				Total Bilirubin				Total Bilirubin			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1103	T, R	µmol/l	20,70	abnormal high	clin. not relevant	µmol/l	21,00	abnormal high	clin. not relevant	µmol/l	26,80	abnormal high	clin. not relevant
1106	R, T	µmol/l	20,30	abnormal high	clin. not relevant	µmol/l	18,00	abnormal high	clin. not relevant	µmol/l	25,70	abnormal high	clin. not relevant
1107	T, R	µmol/l	19,60	abnormal high	clin. not relevant								
2101	R, T									mg/dl	1,57	abnormal high	clin. not relevant
4102	R, T					µmol/l	4,18	abnormal low	clin. not relevant	µmol/l	2,52	abnormal low	clin. not relevant
1207	T, R	µmol/l	60,50	abnormal high	clin. not relevant	µmol/l	24,20	abnormal high	clin. not relevant	µmol/l	57,80	abnormal high	clin. not relevant
2202	R, T					mg/dl	1,71	abnormal high	clin. not relevant				
2206	T, R	mg/dl	1,38	abnormal high	clin. not relevant	mg/dl	1,79	abnormal high	clin. not relevant				
3203	T, R	µmol/l	20,96	abnormal high	clin. not relevant	µmol/l	22,58	abnormal high	clin. not relevant	µmol/l	22,10	abnormal high	clin. not relevant
3205	T, R	µmol/l	40,43	abnormal high	clin. not relevant	µmol/l	20,25	abnormal high	clin. not relevant				
4103	R, T									µmol/l	3,51	abnormal low	clin. not relevant
4104	T, R					µmol/l	4,80	abnormal low	clin. not relevant	µmol/l	2,39	abnormal low	clin. not relevant
4105	T, R					µmol/l	18,02	abnormal high	clin. not relevant				
4204	R, T					µmol/l	19,49	abnormal high	clin. not relevant				
4205	R, T	µmol/l	2,26	abnormal low	clin. not relevant	µmol/l	3,26	abnormal low	clin. not relevant	µmol/l	2,94	abnormal low	clin. not relevant
4206	T, R			l		µmol/l	4,83	abnormal low	clin. not relevant	µmol/l	5,00	abnormal low	clin. not relevant

Table 77 Abnormal Total Protein Values per Patient (Visits 4 – 6)

Enrolment No.	Treatment order	Biochemistry				Biochemistry				Biochemistry			
		Total Protein				Total Protein				Total Protein			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1110	T, R					G/l	57,60	abnormal low	clin. not relevant				

NOTE: All other values were within the reference range or not determined. (See Raw Data Listings, **Appendix 16.2.10**)

Table 78 Abnormal Albumin Values per Patient (Visits 1 – 3)

Enrolment No.	Treatment order	Biochemistry				Biochemistry				Biochemistry			
		Albumin				Albumin				Albumin			
		Visit 1				Visit 2				Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1207	T, R	G/l	49,00	abnormal high	clin. not relevant	G/l	51,00	abnormal high	clin. not relevant				

Table 79 Abnormal Albumin Values per Patient (Visits 4 – 6)

Enrolment No.	Treatment order	Biochemistry				Biochemistry				Biochemistry			
		Albumin				Albumin				Albumin			
		Visit 4				Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1201	R, T	G/l	52,00	abnormal high	clin. not relevant	G/l	49,00	abnormal high	clin. not relevant	G/l	49,00	abnormal high	clin. not relevant

Table 80 Urinalysis: Abnormal pH Values per Patient (Visits 1 – 3)

Enrolment No.	Treatment order	Urinalysis			Urinalysis			Urinalysis		
		pH			pH			pH		
		Visit 1			Visit 2			Visit 3		
		Value	Evaluation	Clin. relevance	Value	Evaluation	Clin. relevance	Value	Evaluation	Clin. relevance
1102	T, R							5,00	abnormal low	clin. not relevant
1105	T, R				7,50	abnormal high	clin. not relevant			
1108	R, T	7,50	abnormal high	clin. not relevant						
2102	T, R	9,00	abnormal high	clin. not relevant						
3101	R, T	8,00	abnormal high	clin. not relevant						

Table 81 Urinalysis: Abnormal pH Values per Patient (Visits 4 – 6)

Enrolment No.	Treatment order	Urinanlysis			Urinanlysis			Urinanlysis		
		pH			pH			pH		
		Visit 4			Visit 5			Visit 6		
		Value	Evaluation	Clin. relevance	Value	Evaluation	Clin. relevance	Value	Evaluation	Clin. relevance
1102	T, R	5,00	abnormal low	clin. not relevant						
1103	T, R							7,50	abnormal high	clin. not relevant
1110	T, R							7,50	abnormal high	clin. not relevant
3101	R, T	7,00	abnormal high	clin. not relevant				8,00	abnormal high	clin. not relevant
4106	R, T							8,00	abnormal high	clin. not relevant

Table 82 Urinalysis: Values of abnormal Specific Gravity per Patient (Visits 1 – 3)

Enrolment No.	Treatment order	Urinanalysis				Urinanalysis				Urinanalysis			
		Spec. gravity				Spec. gravity				Spec. gravity			
		Visit 1				Visit 2				Visit 3			
		Unit [1/1]	Value	Evaluation	Clin. relevance	Unit [1/1]	Value	Evaluation	Clin. relevance	Unit [1/1]	Value	Evaluation	Clin. relevance
1101	R, T						1,030	abnormal high	clin. not relevant				
1102	T, R										1,030	abnormal high	clin. not relevant
1105	T, R		1,030	abnormal high	clin. not relevant								
1106	R, T		1,030	abnormal high	clin. not relevant						1,005	abnormal low	clin. not relevant
1107	T, R		1,030	abnormal high	clin. not relevant								
1108	R, T										1,005	abnormal low	clin. not relevant
1109	R										1,030	abnormal high	clin. not relevant
1111	T, R										1,010	abnormal low	clin. not relevant
1114	R, T		1,030	abnormal high	clin. not relevant						1,030	abnormal high	clin. not relevant
2103	T, R		1,010	abnormal low	clin. not relevant								
2108	T		1,005	abnormal low	clin. not relevant		1,010	abnormal low	clin. not relevant				
4106	R, T						1,010	abnormal low	clin. not relevant				
1202	T, R		>1.030	abnormal high	clin. not relevant								
1203	R, T		1,030	abnormal high	clin. not relevant						1,030	abnormal high	clin. not relevant

1205	T										1,010	abnormal low	clin. not relevant
1206	R, T		1,030	abnormal high	clin. not relevant		1,030	abnormal high	clin. not relevant		1,030	abnormal high	clin. not relevant
1207	T, R						1,030	abnormal high	clin. not relevant				
1208	R, T										1,030	abnormal high	clin. not relevant
4104	T, R		1,005	abnormal low	clin. not relevant								
4105	T, R		1,005	abnormal low	clin. not relevant		1,005	abnormal low	clin. not relevant				
4204	R, T						1,005	abnormal low	clin. not relevant		1,005	abnormal low	clin. not relevant
4205	R, T		1,005	abnormal low	clin. not relevant		1,005	abnormal low	clin. not relevant		1,005	abnormal low	clin. not relevant
4206	T, R		1,010	abnormal low	clin. not relevant						1,005	abnormal low	clin. not relevant

Table 83 Urinalysis: Values of abnormal Specific Gravity per Patient (Visits 4 – 6)

Enrolment No.	Treatment order	Urinanalysis				Urinanalysis				Urinanalysis			
		Spec. gravity				Spec. gravity				Spec. gravity			
		Visit 4				Visit 5				Visit 6			
		Unit [1/1]	Value	Evaluation	Clin. relevance	Unit [1/1]	Value	Evaluation	Clin. relevance	Unit [1/1]	Value	Evaluation	Clin. relevance
1101	R, T		1,030	abnormal high	clin. not relevant								
1102	T, R		1,030	abnormal high	clin. not relevant								
1104	R, T						1,010	abnormal low	clin. not relevant				
1106	R, T		1,005	abnormal low	clin. not relevant		1,010	abnormal low	clin. not relevant		1,010	abnormal low	clin. not relevant
1107	T, R						1,030	abnormal high	clin. not relevant				
1108	R, T						1,005	abnormal low	clin. not relevant				
1111	T, R						1,010	abnormal low	clin. not relevant				
1112	R, T		1,030	abnormal high	clin. not relevant								
1113	T, R						1,005	abnormal low	clin. not relevant		1,010	abnormal low	clin. not relevant
1114	R, T										1,030	abnormal high	clin. not relevant
4101	T, R						1,005	abnormal low	clin. not relevant		1,040	abnormal low	clin. not relevant
4102	R, T		1,005	abnormal low	clin. not relevant								
1203	R, T						1,030	abnormal high	clin. not relevant				
1204	T, R						1,005	abnormal low	clin. not relevant				

1206	R, T		1,030	abnormal high	clin. not relevant		1,030	abnormal high	clin. not relevant				
1207	T, R						1,030	abnormal high	clin. not relevant		1,030	abnormal high	clin. not relevant
1208	R, T						-				1,030	abnormal high	clin. not relevant
4104	T, R										1,010	abnormal low	clin. not relevant
4105	T, R		1,005	abnormal low	clin. not relevant						1,005	abnormal low	clin. not relevant
4204	R, T		1,005	abnormal low	clin. not relevant								
4205	R, T					g/l	1,005	abnormal low	clin. not relevant		1,010	abnormal low	clin. not relevant

Table 84 Urinalysis: Abnormal Blood per Patient (Visits 1 – 2)

Enrolment No.	Treatment order	Urinalysis					Urinalysis				
		Blood					Blood				
		Visit 1					Visit 2				
		Unit	Value	Evaluation	Clin. relevance	Comment	Unit	Value	Evaluation	Clin. relevance	Comment
1204	T, R	Ery/µl	1+	abnormal high	clin. not relevant	menstruation					
2205	R, T	Ery/µl	5-10	abnormal high	clin. not relevant	menstruation	Ery/µl	a lot of erytr. in the area	abnormal high	clin. not relevant	menstruation
3207	T, R						Ery/µl	25,00	abnormal high	clin. not relevant	

Table 85 Urinalysis: Abnormal Blood per Patient (Visits 3 – 4)

Enrolment No.	Treatment order	Urinalysis					Urinalysis				
		Blood					Blood				
		Visit 3					Visit 4				
		Unit	Value	Evaluation	Clin. relevance	Comment	Unit	Value	Evaluation	Clin. relevance	Comment
2107	R, T	Ery/µl	positive	abnormal high	clin. not relevant						
1204	T, R	Ery/µl	+/-	abnormal high	clin. not relevant	menstruation	Ery/µl	+	abnormal high	clin. not relevant	menstruation
2205	R, T	Ery/µl	-			menstruation	Ery/µl	2-5	abnormal high	clin. not relevant	

Table 86 Urinalysis: Abnormal Blood per Pateint (Visits 5 – 6)

Enrolment No.	Treatment order	Urinalysis				Urinalysis			
		Blood				Blood			
		Visit 5				Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
2107	R, T	Ery/µl	0-2	abnormal high	clin. not relevant	Ery/µl	1-3	abnormal high	clin. not relevant
3208	R, T	Ery/µl	250,00	abnormal high	clin. not relevant				

Table 87 Urinalysis: Abnormal Protein Values per Patient (Visits 1 – 3)

Enrolment No.	Treatment order	Urinalysis				Urinalysis					Urinalysis			
		Protein				Protein					Protein			
		Visit 1				Visit 2					Visit 3			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Comment	Unit	Value	Evaluation	Clin. relevance
1101	R, T					g/l	1,00	abnormal high	clin. not relevant					
1102	T, R					g/l	0,30	abnormal high	clin. not relevant					
1105	T, R	-	trace	abnormal high	clin. not relevant									
1109	R	-	trace	abnormal high	clin. not relevant	-	trace	abnormal high	clin. not relevant					
1110	T, R										-	trace	abnormal high	clin. not relevant
2107	R, T										-	positive	abnormal high	clin. not relevant
1201	R, T					g/l	1,00	abnormal high	clin. not relevant					
1206	R, T					+	positive	abnormal high	clin. not relevant	trace				
2205	R, T					mg/dl	91,00	abnormal high	clin. not relevant					

Table 88 Urinalysis: Abnormal Protein values per Patient (Visits 4 – 6)

Enrolment No.	Treatment order	Urinalysis				Urinalysis					Urinalysis			
		Protein				Protein					Protein			
		Visit 4				Visit 5					Visit 6			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance	Comment	Unit	Value	Evaluation	Clin. relevance
2106	T, R					mg/dl	24,00	abnormal high	clin. not relevant		mg/dl	18,00	abnormal high	clin. not relevant
1206	R, T	-	trace	abnormal high	clin. not relevant									
2206	T, R										mg/dl	9,00	abnormal high	clin. not relevant

Table 89 Urinalysis: Abnormal Glucose Values per Patient (Visits 1 – 2)

Enrolment No.	Treatment order	Urinanalysis				Urinanalysis			
		Glucose				Glucose			
		Visit 1				Visit 2			
		Unit	Value	Evaluation	Clin. relevance	Unit	Value	Evaluation	Clin. relevance
1101	R, T					mmol/l	5,60	abnormal high	clin. not relevant
1102	T, R					mmol/l	5,60	abnormal high	clin. not relevant
1105	T, R	mmol/l	5,60	abnormal high	clin. not relevant				
1108	R, T					mmol/l	5,60	abnormal high	clin. not relevant
1201	R, T					mmol/l	5,60	abnormal high	clin. not relevant
1206	R, T	mmol/l	5,60	abnormal high	clin. not relevant				

NOTE: Values of glucose in urine at Visits 3-6 were normal.

14.3.5 Changes in Vital Signs

Table 90 Vital Signs pre- and post-Study of All Patients

	Age	Resp.Rate pre	Resp.Rate post	Heart Rate pre	Heart Rate post	Resting O_2 saturation pre	Resting O_2 saturation post
N	58	58	58	58	58	58	58
units	years	1/min	1/min	BPM	BPM	%	%
Minimum		16	16	54	63	90	97
Maximum		32	32	90	120	99	99
Mean		**23**	**22**	**85**	**87**	**96**	**96**
SD		3.9	3.9	11.3	9.9	2.3	2.6

Table 91 Vital Signs pre- and post-study of Age Group 4 to 13 Years

	Age	Resp.Rate pre	Resp.Rate post	Heart Rate pre	Heart Rate post	Resting O_2 saturation pre	Resting O_2 saturation post
units	years	1/min	1/min	BPM	BPM	%	%
N	28	28	28	28	28	28	28
Minimum		16	18	67	67	89	90
Maximum		32	30	120	109	99	99
Mean		**23**	**22**	**89**	**89**	**96**	**96**
±SD		4.2	3.8	11.1	10.9	2.6	2.2

Table 92 Vital Signs pre- and post-study of Age Group> 13 Years

	Resp.Rate pre	**Resp.Rate post**	**Heart Rate pre**	**Heart Rate post**	**Resting O_2 saturation pre**	**Resting O_2 saturation post**
units	1/min	1/min	BPM	BPM	%	%
N	30	30	30	30	30	30
Minimum	18	16	63	63	90	87
Maximum	32	32	101	120	99	98
Mean	**23**	**22**	**83**	**85**	**96**	**96**
±SD	3.7	4.1	11.6	8.6	2.0	2.9

Table 93 Blood Pressure pre-and post-study of All Patients

	RR syst. pre	**RR syst. post**	**RR diast. pre**	**RR diast. post**
units	mmHg	mmHg	mmHg	mmHg
N	58	58	58	58
Minimum	69	78	48	51
Maximum	135	138	80	90
Mean	**104**	**107**	**65**	**67**
±SD	13.7	12.8	8.2	8.8

Table 94 Blood Pressure pre- and post-study of Age Group 4 to 13 Years

	RR syst. pre	**RR syst. post**	**RR diast. pre**	**RR diast. post**
units	mmHg	mmHg	mmHg	mmHg
N	28	28	28	28
Minimum	78	78	48	51
Maximum	130	120	80	71
Mean	**103**	**103**	**61**	**62**
±SD	12.7	10.8	8.5	5.3

Table 95 Blood Pressure pre- and post-study of Age Group >13 Years

	RR syst. Pre	**RR syst. Post**	**RR diast. Pre**	**RR diast. Post**
units	mmHg	mmHg	mmHg	mmHg
N	30	30	30	30
Minimum	93	90	60	56
Maximum	135	138	80	90
Mean	**108**	**110**	**68**	**71**
±SD	10.4	13.4	6.7	9.1

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