PASS information

Title	Multicenter prospective open-label non-interventional uncontrolled Post-Authorisation Safety Study (PASS) to evaluate the safety profile of Polyoxidonium in daily practice
Version identifier of the final study report	Final version 1.0
Date of last version of the final study report	8 May 2017
EU PAS register number	ENCEPP/SDPP/12387 http://www.encepp.eu/encepp/viewResource.htm?id=12388
Active substance	Azoximer bromide Pharmacotherapeutic group: other cytokines and immune modulators ATC code: L03AX
Medicinal product	POLYOXIDONIUM® 6 mg lyophilisate for solution for injection
Product reference	59/0220/02-S (national)
Procedure number	Not applicable
Marketing authorisation holder(s)	MEDIGROUP s.r.o.
Joint PASS	No
Research question and objectives	This PASS aimed to collect data on the safety of Polyoxidonium in patients, for whom Polyoxidonium was prescribed in routine practice in accordance with the terms of the marketing authorisation (MA). The primary objectives were: – to assess the frequency of adverse drug reactions – to estimate the proportion of subjects, who develop signs and symptoms of adverse renal effects associated with the use of Polyoxidonium. Secondary objective was to evaluate the clinical benefit of Polyoxidonium.
Country(-ies) of study	Slovak Republic
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1. Abstract

Title

Multicenter prospective open-label non-interventional uncontrolled Post-Authorisation Safety Study (PASS) to evaluate the safety profile of Polyoxidonium in daily practice

Final version 1.0, 8 May 2017

Author: Natalia V. Chirun, PhD, MD (NPO PETROVAXPHARM)

Keywords

Azoximer bromide, Polyoxidonium, safety, adverse renal effects

Rationale and background

Data from Polyoxidonium acute and sub-acute toxicity studies in rodents and chronic toxicity in dogs showed the potential risk of renal toxicity.

Although no adverse effects on renal system were reported in Polyoxidonium clinical trials development programme and during routine post-authorisation pharmacovigilance activities, the potential renal effects needs to be further investigated.

Research question and objectives

The primary objectives were to assess the frequency of adverse drug reactions and to estimate the proportion of subjects, who develop signs and symptoms of adverse renal effects associated with the use of Polyoxidonium in daily routine practice.

Study design

This was a local, multicenter, prospective, open-label, non-interventional, uncontrolled study. Each subject was observed for the duration of one cycle of Polyoxidonium treatment. Study duration and number of visits for individual subject coincided with routine visits to receive Polyoxidonium injections at the health care centre. Actual assessments undertaken at each visit were determined by clinical practice.

Setting

The study was conducted by 15 physicians (immunologists and allergologists) working in primary and secondary health care setting.

Subjects and study size, including dropouts

Eligible subjects were patients who received Polyoxidonium prescription in accordance to the SmPC currently approved in Slovakia, i.e., for the treatment of any of the following diseases or conditions accompanied by secondary immunodeficiency: chronic recurrent bacterial infection; chronic recurrent viral infection; acute bacterial infection; acute viral infection; allergic disease.

In total, 502 subjects were enrolled into the study. 498 (99.2%) subjects completed the study.

Variables and data sources

Event of interest were signs or symptoms of adverse renal effects.

Data collection was based on the review of medical records and routine examination of subjects. Regular medical records at study sites served as data sources. At the end of study, investigators and subjects rated the overall tolerance of Polyoxidonium treatment

as well as improvement.

Results

Most of subjects were prescribed Polyoxidonium because of chronic recurrent viral or bacterial infections. The mean total Polyoxidonium dose received was 50.64 (±14.35) mg. The mean duration of treatment was 21.79 (±8.26) days.

Out of the 502 subjects, 19 (3.8%) subjects experienced a total of 34 AEs. Only one (0.1%) subject experienced 8 ADRs (i.e., AEs which were assessed by the investigator as related to Polyoxidonium). The overall incidence of ADRs was 1.6/100 subjects. Seven ADRs were mild and one ADR was of moderate severity. There were no renal ADRs and serious ADRs.

At the end of study, both investigators and subjects very positively rated global tolerability and global improvement.

Discussion

Polyoxidonium was well tolerated in the heterogenous population of patients who received Polyoxidonium in accordance with the terms of the marketing authorisation. There were no renal ADRs. Thus, the benefit-risk ration of Polyoxidonium® 6 mg lyophilisate for solution for injection remains positive.

Marketing Authorisation Holder(s)

MEDIGROUP s.r.o

Names and affiliation of coordinating investigator

Peter Pružinec, Prof., MUDr. Csc
MONITOR PLUS, s.r.o.

2. List of abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
CRO	Contract Research Organisation
eCRF	electronic Case Report Form
ECG	electrocardiogram
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
PASS	Post authorization safety study
QPPV	qualified person in pharmacovigilance
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
WBC	white blood cells

3. Investigators

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List of investigators and study sites is presented as a stand-alone document (Annex 1) and is available on request.

4. Other responsible parties

This study was conducted under the sponsorship of NPO PETROVAXPHARM. CRO Biomapas was responsible for central management of study conduct for the local Marketing Authorisation Holder (MAH).

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5. Milestones

Milestone	Planned date	Actual date	Comments
Slovakia State Institute for Drug Control approval	-	28 April 2016	*Study protocol was amended in response to comment of Slovakia State Institute for Drug Control*
Ethics Committee of Bratislava Self-Governing Region approval	-	19 April 2016	*Initial approval (Protocol final version 1.1, dated 25 January 2016) was granted on 1 March 2016*
Start of data collection	May 2016	20 June 2016	*First subject was enrolled on 20 June 2016*
End of data collection	December 2016	10 Feb 2016	Last subject out: 27 December 2016
Registration in the EU PAS register	February 2016	5 April 2016	*Protocol final version 1.1, dated 25 January 2016 was registered on 2 February 2016*
Final report of study results	March 2017	8 May 2017	

6. Rationale and background

Polyoxidonium has been marketed for almost 20 years (it was first launched in 1996 in Russia). In Slovak Republic, Polyoxidonium is available since 2002. It is estimated that during the period from 1996 to 2013 (inclusive) the total number of approximately 1,025,000 patients worldwide have used Polyoxidonium. No adverse effects specifically affecting any of organ systems have been reported in clinical development programme and during routine post-authorisation pharmacovigilance activities.

Data from Polyoxidonium acute and sub-acute toxicity studies in rodents and chronic toxicity studies in dogs showed the potential risk of nephrotoxicity, which occurred at doses well above the therapeutically relevant dose range. Nephrotoxic effect was observed in dogs after 40 daily injections of Polyoxidonium at doses 10 times exceeding the maximum recommended human dose and in rats after 15 daily injections at doses as high as 100 times the maximum recommended human dose. Besides, Polyoxidonium is predominantly excreted by kidneys.

During chronic toxicity research in dogs, the administration of 10 times the therapeutic dose of Polyoxidonium intramuscularly daily for a period of three months did not affect the ECGs, peripheral blood cells, and protein, carbohydrate and lipid metabolism. At the same time, already after two months of administration of Polyoxidonium a moderate increase in transaminase activity, as well as an increase in the alkaline phosphatase, bilirubin, creatinine, and urea concentrations in the blood serum had been observed, all of which became more pronounced after three months of administration. Histopathological examination of internal organs, performed at the end of experiment, had shown that long-term daily administration of Polyoxidonium at 10 times the therapeutic dose (1 mg/kg) led to the development of glomerulitis, changes in renal tubular apparatus, and degeneration of protein and fatty hepatocytes in dogs. Based on the results obtained from the research of systemic toxicity of the drug Polyoxidonium (acute and sub-acute toxicity in rodents and chronic toxicity in dogs), it was possible to conclude that the kidneys are the only target organ of Polyoxidonium. Meanwhile, biochemical and histological studies in rats had shown no damaging effects on the kidneys after 3-month administration of the drug Polyoxidonium 100 times the maximum recommended dose (25 mg/kg) with intervals between injections. The intervals between injections significantly reduce the nephrotoxic effects of the drug Polyoxidonium, moreover there was no nephrotoxic effect was not observed when the drug was temporary withdrawn for up to 7 days.

Although no adverse effects on renal system have been reported in Polyoxidonium clinical development programme and during routine post-authorisation pharmacovigilance activities, the potential adverse renal effects needs to be further investigated.

This non-interventional post-authorisation safety study was conducted to systematically collect safety information under real-life conditions in patients receiving Polyoxidonium therapy. The special focus of this PASS was on signs or symptoms of potential adverse renal effects.

7. Research question and objectives

This PASS aimed to collect data on the safety of Polyoxidonium in patients, for whom Polyoxidonium was prescribed in routine practice in accordance with the terms of the marketing authorisation. This study was a part of a Risk Management Plan (RMP).

The primary objectives were:

a) to assess the frequency of adverse drug reactions
b) to estimate the proportion of subjects, who develop signs and symptoms of adverse renal effects associated with the use of Polyoxidonium.

Secondary objective was to evaluate the clinical benefit of Polyoxidonium by evaluating the

following variables:

a) overall clinical improvement as assessed by investigators and subjects
b) mean duration of primary treatment of disease
c) mean number of days with fever >38°C and (or) disease symptoms
d) change in total and differential white blood cells (WBC) count (blood and urine) from baseline to the end of treatment (if data are available).

8. Amendments and updates

There were no protocol amendments after the start of data collection. The final version of the protocol is included in Annex 1.

9. Research methods

9.1. Study design

This PASS was a local, multicentre, prospective, open-label, non-interventional, uncontrolled study.

Patients for whom Polyoxidonium was prescribed as a part of routine clinical practice were eligible for this study. The decision to prescribe Polyoxidonium was independent of the decision to enrol the subject into the study.

Primary treatment of a disease, Polyoxidonium administration, diagnostic procedures and assessments as well as visits schedule were left at the discretion of investigators, according to local guidelines and routine clinical practices.

The study was explorative in nature. It was undertaken to systematically collect safety information in a community-based sample of subjects receiving Polyoxidonium therapy in routine care setting, to quantify potential risks, investigate potential risk factors and effect modifiers, or to provide evidence about the absence of risks.

9.2. Setting

The study was conducted by 15 physicians (immunologists and allergologists) working in primary and secondary health care setting (refer to Appendix 1 for a list of investigative sites).

Each subject was observed for one cycle of treatment with Polyoxidonium. In accordance with the Summary of Product Characteristics (SmPC), the treatment course consists of 5-10 injections depending on the disease. Thus, study duration and number of visits for individual subject coincided with routine visits to receive Polyoxidonium injections at the health care centre (see Study flow chart in Table 1). At 7 (±1) days after the last injection (this period corresponds to 5 half-lives of Polyoxidonium), a telephone follow-up was conducted. In addition, if any visit (scheduled or unscheduled) occured within 7 days after the last injection of Polyoxidonium as a part of routine practice, information on adverse events was recorded.

Table 1. *Study flow chart*

	Study visits			
Study procedures	**First injection**	**Interim visits** *(3 to 8, depending on indication)*	**Last injection**	**Follow-up***
Day	**Day 1**		**Day 7 to 23**	
Inclusion/exclusion criteria	X			
Informed consent	X			
Demographic data	X			
Height and weight	X			
Medical history	X			
Physical examination**	X	X	X	
Information about relevant infection, allergic condition, etc.	X	X	X	
Vital signs (blood pressure, heart rate, body temperature)**	X	X	X	
Laboratory tests**	X	X	X	
ECG**	X	X	X	
Other diagnostic procedures**	X	X	X	
Polyoxidonium administration	X	X	X	
Concomitant medications	X	X	X	
Adverse events	X	X	X	X
Investigator's and subject's assessment of tolerability and improvement			X	X

**telephone contact at 7 (±1) days after the last injection. In addition, if any visit (scheduled or unscheduled) occurs within 7 days after the last injection of Polyoxidonium as a part of routine clinical practice, information on adverse events was recorded.*
***if undertaken as a part of routine clinical practice. Results of laboratory tests, ECG examinations and other diagnostic procedures were recorded only if performed within 3 days before subject's enrolment and (or) during the study period.*

9.3. Subjects

In order to enrolled subjects who represent the source population (i.e., target patients of Polyoxidonium therapy) in Slovakia, inclusion and exclusion criteria reflected marketing authorisation conditions (i.e., approved therapeutic indications and contraindications).

9.3.1. Inclusion criteria

To be eligible for participation in this study, the patient must:

(a) be male or female at least 18 years of age.

(b) receive Polyoxidonium prescription in accordance to the SmPC currently approved in Slovakia, i.e., for the treatment of any of the following diseases or conditions accompanied by secondary immunodeficiency:
- chronic recurrent bacterial infection;
- chronic recurrent viral infection;
- acute bacterial infection;
- acute viral infection;
- allergic disease (pollinosis, bronchial asthma, atopic dermatitis).

(a) be informed about the study and provide written consent to participate.

9.3.2. Exclusion criteria

The patient couldn't take part in the study if:

(a) Polyoxidonium was contraindicated as per SmPC:
- if there was known hypersensitivity to azoximer bromide or any of the excipients of Polyoxidonium;
- if a woman was pregnant or breast-feeding;
- if a woman of childbearing potential didn't use effective contraception method (acceptable methods of birth control are: intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge, condom, vasectomy, hormonal contraceptive).

(b) investigator deemed necessary to prescribe more than 10 injections of Polyoxidonium per a single treatment course for the given patient.

(c) patient had any clinically significant underlying medical illness, condition or disorder that, in the judgment of the investigator, could interfere with the conduct of the study.

(d) patient was enrolled in any other investigational study or had participated in a interventional study within 4 weeks before enrolment.

9.4. Variables

9.4.1. Event of interest

Event of interest were signs or symptoms of adverse renal effects.

In case of suspected adverse renal effect investigator was encouraged to apply clinical judgement, to perform diagnostic workup and collect as much data as possible to confirm or reject the diagnosis of renal impairment.

9.4.2. Safety variables

Safety variables included:

- proportion of subjects with adverse renal effects
- proportion of subjects, who experienced any AE;
- proportion of subjects with ADRs;
- proportion of subjects experiencing serious adverse events (SAEs);
- proportion of subjects with serious ADRs;

- severity of AEs;
- number of subjects who discontinued the study and the reasons for drop-outs;
- global assessment of tolerability by investigators: very good (no intolerance reactions), good (occasional intolerance reactions), moderate (frequent intolerance reactions), poor (intolerance reactions after every use);
- global assessment of tolerability by subjects: very good, good, moderate and poor.

9.4.3. Clinical benefit variables

Clinical benefit assessment included the following variables:

- global assessment of improvement by subjects score (0 to 4 scale: 0=much worse; 1= somewhat worse; 2=same; 3=somewhat improved; 4 = greatly improved)
- global assessment of improvement by investigators score (0 to 5 scale: 0 = worse; 1 = no appreciable improvement; 2 = slight improvement; 3 = moderate improvement; 4 = marked improvement; 5 = complete resolution)
- mean duration of primary treatment of disease (i.e., days with antibiotic use in case of infection or antiallergic medication in case of allergies),
- days with fever >38°C/days with symptoms,
- total and differential WBC count in blood and urine (if data are available).

9.5. Data sources and measurement

Subjects attended the investigator site for regular visits during their treatment with Polyoxidonium according to local clinical practice. Actual assessments undertaken at each visit were determined by clinical practice. Subjects were not administered any investigational medicinal products and/or medical procedures neither underwent any laboratory evaluations, diagnostic or monitoring procedures specifically for the purposes of this study.

Data collection was based on the review of medical records and routine examination of subjects. Regular medical records at study sites served as data sources. At the end of study, investigators and subjects rated the overall tolerance of Polyoxidonium treatment as well as improvement.

In case of suspected adverse renal effect investigators were encouraged to apply clinical judgement, to perform diagnostic workup and collect as much data as possible to confirm or reject the diagnosis of renal impairment. It was planned that data for each subject for whom adverse renal effect was suspected would be reviewed and adjudicated by an independent assessor. This final adjudicated conclusion was planned to be qualified as event of interest (a case of adverse renal effect) or suspicion about renal toxicity would be rejected.

9.6. Bias

Because of non-randomized design, absence of blinding and control group selection bias and information bias was expected. To mitigate this risk and ensure that study population represented the source population, investigators and study sites were selected randomly from the available list of Slovakian immunologists and allergologists. The investigators were trained and encouraged to enrol all eligible patients consecutively. Since inclusion and exclusion criteria were very limited, it was expected that enrolled subjects would represent the source population (i.e., target patients of Polyoxidonium therapy) in Slovakia.

To mitigate the risk of information bias and misclassification of event of interest, investigators were encouraged to collect as much data concerning the event of interest (adverse renal effects)

as possible within the frame of routine practice. An independent assessor joined the study team to review available clinical data about the event of interest and to make a final conclusion about adverse renal effect.

9.7. Study size

Due to the explorative character of the study and absence of the hypothesis to test, no formal attempt to calculate the sample size and power was made.

A total of 500 subjects were expected to enter the study. It was assumed, that this number of subjects would allow to characterize the safety profile of Polyoxidonium and would be sufficient to identify, quantify and describe statistically the frequency of at least common (≥1/100, <1/10) and uncommon (≥1/1000, <1/100) adverse events and to allow for various subgroup analyses.

9.8. Data transformation

All data were manipulated and analysed using SPSS syntax.

Adverse events were classified on the basis of MedDRA terminology.

Prior and concomitant medications were coded using the International Non-proprietary Names (INN) terminology and Anatomical Therapeutic Chemical (ATC) Classification System levels 2 and 4.

Body mass index (BMI), body temperature, blood pressure, pulse values were categorized into the following categories:

blood pressure <140/90 and >=140/90 mmHg
pulse <50, 50-100 and >100 bpm
temperature <38 and >=38 ^{o}C
BMI <=25, >25 to 30, and >30.0 kg/m^2

9.9. Statistical methods

Statistical analyses have been described in details in the statistical analysis plan (SAP) (see Annex 1. List of stand-alone documents).

9.9.1. Main summary measures

Summary measures included number and percentages of subjects or events and means.

9.9.2. Main statistical methods

Analysis of the subject characteristics was primarily descriptive. Categorical data were summarized in frequency tables, presenting the number and percentage of events. For continuous data, mean, median, minimum, maximum, standard deviation, 5% percentile, 95% percentile, and number of missing values were calculated.

For statistical comparison of categorical data, the chi-square test was used. Parametric Student t-test or nonparametric Wilcoxon rank sum test was used for comparison of continuous data between two independent samples. Parametric paired Student t-test or nonparametric Wilcoxon signed-rank test wasused for comparison of continuous data between two dependent samples. Proportions of two dependent samples was compared using McNemar's test. Statistical tests were interpreted at the 5% significance level (two-sided).

Stratified analysis by therapeutic indication was performed to investigate safety profile and clinical benefit in different subgroups.

SPSS software was used for data analysis.

9.9.3. Missing values

Data were summarized as observed with no imputation for missing values, except partial dates.

For imputation of partial dates, first day, first month approach was used for the start dates and last day, last month approach - for the end dates. In case partial start date of AE falled in the same month as the start of Polyoxidonium treatment, a date equal Polyoxidonium first injection date was set.

9.9.4. Sensitivity analyses

Not applicable. No sensitivity analyses were conducted as part of this study.

9.9.5. Amendments to the statistical analysis plan

A stratified analysis of main event of interest (i.e., adverse renal effect) by prior renal impairment and by use of concomitant nephrotoxic medicines to control confounders was planned. Logistic regression was planned to determine factors as possible predictors of adverse renal effects. During the study only one adverse renal effect occurred, which was not related to Polyoxidonium (refer to Section 10.4.2). Therefore, neither stratified analysis nor logistic regression analysis was performed.

There were no other deviations from the statistical analysis plan.

9.10. Quality control

Data were collected via QCTMS EDC™ using eCRFs. Investigator were responsible for data entry into the QCTMS EDC™ system. Data checks were embedded into the eCRF to remove data entry errors wherever possible. Data were validated throughout the course of the study (raising queries in QCTMS EDC™ if necessary) according a Data Management Plan. In the event of discrepant data, data clarification was requested, which the sites resolveed electronically in the QCTMS EDC™ system. eCRFs and correction documentation were maintained in the QCTMS EDC™ system's audit trail.

Monitoring activities were performed by the CRO, as defined in the Monitoring Plan. Each site was visited at regular intervals by a monitor to ensure compliance with the study protocol and legal aspects. This included on-site checking of eCRFs for completeness and clarity, cross-checking with source documents, and clarification of administrative matters. In addition, the monitor reviewed remotely the data entered into the eCRFs on an ongoing basis.

10. Results

10.1. Participants

In total, 502 subjects were enrolled into the study. 498 (99.2%) subjects completed the study. One subject was enrolled violating one of exclusion criteria (i.e., a woman of childbearing potential doesn't use effective contraception method). Information on the number of subjects enrolled in each study site is presented in Appendix (Table 1).

Four subjects (0.8%) did not complete the study; of them, 2 subjects were withdrawn due to AEs (Table 10.1). A list of all subjects who withdrew from the study after enrolment, including a subject ID, time of withdrawal, and the reason for withdrawal is provided in Appendix (Table 2).

In addition to enrolment visit (i.e., day of the first injection) and study end visit (i.e., day of the last injection), subjects attended few interim visits coinciding with routine visits to receive Polyoxidonium injections. Most of subjects had 3 or 8 interim visits (Table 10.1).

Table 10.1. *Study subjects disposition*

	n (%)
Enrolled subjects	502
Subjects who completed the study	498 (99.2)
Primary reason for early withdrawal	
Adverse event	2 (0.4)
Lost to follow up	1 (0.2)
Subject withdrew consent	1 (0.2)
Number of interim visits	
1	2 (0.4)
3	142 (28.3)
4	11 (2.2)
7	1 (0.2)
8	331 (65.9)
9	15 (3.0)
Follow-up visits	
Phone call	471 (94.0)
successful	425 (90.2)
unsuccessful	46 (9.8)
Office visit*	30 (6.0)
Number of follow-up visits per subject	
1	499 (99.6)
2	2 (0.4)

** reasons for office follow-up visits are provided in Appendix (Table 3).*

10.2. Descriptive data

There were 360 (71.7%) women and 142 (28.3%) men. The mean (±SD) age of subjects was 44.94 (±15.15) years (Table 10.2).

Most of subjects were prescribed Polyoxidonium because of chronic recurrent viral or bacterial infections (Table 10.2). Respiratory tract infections were the most common reason for Polyoxidonium prescriptions. Information on precise diagnoses is provided in Appendix (Table 4).

Half of subjects (50.6%) had at least one concomitant disease. The most common concomitant diseases were asthma (n=74), rhinitis (n=58), allergic rhinitis (n=45), and hypertension (n=44). None of subjects had renal insufficiency. A list of all concomitant diseases and their prevalence among study subjects are provided in Appendix (Table 5). Results of physical examination are presented in Appendix (Table 6), vital signs and ECG – in Appendix Table 7, laboratory tests – in Appendix Table 8.

During the study, 214 (42.6%) subjects took concomitant medications; 69 (13.7%) took medications for the primary treatment of disease of interest (Table 10.2). The most common concomitant medications were systemic antihistamines (taken by 30.7% of subjects), drugs for obstructive airway diseases (21.3%), and nasal preparations (12.9%) (refer to Appendix Table 9 for details).

10.3. Outcome data

Not applicable.

Table 10.2. *Socio-demographic and clinical characteristics at baseline*

Characteristics	
Gender, n (%)	
men	142 (28.3)
women	360 (71.7)
Age, years	
mean ± SD	44.94 ± 15.15
min	18
max	85
≥65 years, n (%)	62 (12.4)
Indications for Polyoxidonium prescription, n (%)	
Chronic recurrent bacterial infection	194 (38.6)
Chronic recurrent viral infection	209 (41.6)
Acute bacterial infection	18 (3.6)
Acute viral infection	23 (4.6)
Allergic disease	58 (11.6)
Time from diagnosis to enrolment (days), mean ± SD	489.35 ± 1230.25
Subjects with any concomitant disease*, n (%)	254 (50.6)
Subjects with any concomitant disease that ended prior the study, n (%)	42 (8.4)
Subjects with any ongoing concomitant disease, n (%)	245 (48.8)
Subjects taking any prior medications**, n (%)	27 (5.4)
Subjects taking any concomitant medications, n (%)	214 (42.6)
Reasons for concomitant treatment, n (%)	
primary treatment of disease of interest	69 (13.7)
chronic recurrent bacterial	30 (6.0)
chronic recurrent viral infection	12 (2.4)
acute bacterial infection	5 (1.0)
acute viral infection	7 (1.4)
allergic disease	15 (3.0)
treatment of concomitant disease	186 (37.1)
treatment of adverse event	1 (0.2)
other	20 (4.0)
Subjects with ongoing primary treatment at the end of study, n (%)	66 (13.1)

**current concomitant disease or any previous clinically relevant disease(s) which occurred within 5 years before enrolment; ** medicines used within 30 days before enrolment*

10.4. Main results

10.4.1. Polyoxidonium exposure

342 (68.1%) of subjects were prescribed 10 injections of Polyoxidonium and 159 (31.7%) were prescribed 5 injections (Table 10.3). Treatment regimens were various (refer to Appendix Table 10 for details).

The mean total Polyoxidonium dose received was 50.64 (±14.35) mg. The mean duration of treatment was 21.79 (±8.26) days. There were no considerable exposure differences in subjects prescribed Polyoxidonium because of different therapeutic indications (Appendix Table 11).

Table 10.3. *Details on previous treatment with Polyoxidonium and Polyoxidonium exposure during the study*

Previous and current prescriptions	
Previous Polyoxidonium prescriptions	
Subjects who previously received Polyoxidonium, n (%)	86 (17.1)
Number of previous treatment cycles	
mean±SD	2.91±2.22
min	1
max	10
Current Polyoxidonium prescription	
Number of injections	
mean±SD	8.40±2.35
min	1
max	10
Subjects prescribed different number of injections, n (%)	
1	1 (0.2)
5	159 (31.7)
10	342 (68.1)
Daily dose	
mean±SD	5.99±0.22
min	1
max	6
Polyoxidonium exposure	
Treatment duration, days	
mean±SD	21.79±8.26
min	4
max	57
Number of doses taken	
mean±SD	8.47±2.35
min	1
max	11
Total dose, mg	
mean±SD	50.64±14.35
min	6
max	66
Subjects with dosage changes*, n (%)	
not changed	470 (93.6)
reduced	6 (1.2)
increased	26 (5.2)

** difference in number of doses (i.e., injections) prescribed and received*

10.4.2. Safety evaluation

10.4.2.1 Adverse drug reactions/renal ADRs

Polyoxidonium was well tolerated. Only one (0.1%) subject experienced 8 ADRs (i.e., AEs which were assessed by the investigator as related to Polyoxidonium) (Table 10.4). The overall incidence of ADRs was 1.6/100 subjects. Seven ADRs were mild and one ADR was of moderate severity.

Elevated body temperature and restlessness are listed in the current Summary of Product

Characteristics of Polyoxidonium as very rare adverse effects. Fatigue, asthenia and feeling hot are not listed in the SmPC.

There were no renal ADRs.

All other safety information is presented and analysed in Section 10.6.

Table 10.4. *Number, rate of occurrence and severity of ADRs in SOCs*

Adverse Drug Reaction (ADR)	n	Severity
Psychiatric disorders		
Restlessness	1 (0.2%)	mild
General disorders and administration site conditions		
Fatigue	1 (0.2%)	moderate
Feeling hot	2 (0.4%)	mild
Pyrexia	3 (0.6%)	mild
Asthenia	1 (0.2%)	mild

10.4.2.2 Global tolerability

Investigators as well as subjects were asked to assess global tolerability at the end of and at the follow-up).

According investigators' assessment, global tolerability of Polyoxidonium was very good in 80% of subjects (Table 10.5). Proportion of subjects with at least moderate tolerability ("very good", "good", or "moderate") were not different at Study end and Follow-up visits (McNemar test's p=1.000).

Table 10.5. *Global tolerability assessment by investigators at the end of study, n (%)*

Investigators' assessment of tolerability	Study end visit	Follow-up
Very good	400 (79.7)	406 (80.9)
Good	97 (19.3)	87 (17.3)
Moderate	2 (0.4)	7 (1.4)
Poor	1 (0.2)	1 (0.2)
Missing data	2 (0.4)	1 (0.2)

Almost all subjects positively assessed global tolerability of Polyoxidonium (Table 10.6). Proportion of subjects who positively rated the tolerability ("very good", "good", or "moderate") was not significantly different at Study end and Follow-up visits (McNemar test's p=1.000).

Table 10.6. *Global tolerability assessment by subjects at the end of study, n (%)*

Subjects' assessment of tolerability	Study end visit	Follow-up
Very good	378 (75.3)	374 (74.5)
Good	106 (21.1)	89 (17.7)
Moderate	1 (0.2)	2 (0.4)
Poor	1 (0.2)	1 (0.2)
Missing data	16 (3.2)	36 (7.2)

Stratified analysis by therapeutic indications showed that there were numerically less subjects with global tolerability assessment score "very good" among subjects with acute infections or allergic diseases to compare to those with chronic infections (Appendix Table 12). 2

10.4.3. Clinical benefit evaluation

10.4.3.1 Global improvement

According to the opinion of investigators, complete resolution occurred in 26.1% of subjects, marked improvement was observed in 56.0% of subjects (Table 10.7). Proportion of subjects, for whom investigators noted the improvement ("slight improvement", "moderate improvement", "marked improvement", or "complete resolution") were not different at Study End and Follow-up visits (McNemar test's p=0.500).

Subjects also assessed their own improvement very positively – over 90% of subjects reported improvement (Table 10.8). Proportion of subjects with self-reported improvement decreased from 96.8% at Study End visit to 92.2% at Follow-up visit (McNemar test's p=0.007).

Table 10.7. *Investigators' assessment of global improvement at the end of study, n (%)*

Investigators' assessment	Study end visit	Follow-up
Complete resolution	131 (26.1)	145 (28.9)
Marked improvement	281 (56.0)	268 (53.4)
Moderate improvement	73 (14.5)	68 (13.5)
Slight improvement	11 (2.2)	12 (2.4)
No appreciable improvement	4 (0.8)	8 (1.6)
Missing data	2 (0.4)	1 (0.2)

Table 10.8. *Subjects' assessment of global improvement at the end of study, n (%)*

Subjects' assessment	Study end visit	Follow-up
Greatly improved	180 (35.9)	191 (38.0)
Somewhat improved	304 (60.6)	272 (54.2)
Same	5 (1.0)	16 (3.2)
Somewhat worse	2 (0.4)	0
Much worse	1 (0.2)	0
Missing data	10 (2.0)	23 (4.6)

Global tolerability assessment in therapeutic indications subgroups are presented in Appendix Table 13.

10.4.3.2 Duration of primary treatment of disease

Only 69 (13.7%) subjects received other medicines than Polyoxidonium for the treatment of disease of interest, and almost all of them (n=66) continued this treatment at the end of study (Table 10.2). Since the date of the last visit was considered as stop date for treatments which were ongoing at the end of study, no conclusion can be made regarding the effect of Polyoxidonium on the duration of primary treatment.

Duration of primary treatment of disease of interest (days) in all subjects and in therapeutic indication subgroups are presented in Appendix (Table 14).

10.4.3.3 Days with fever and (or) disease symptoms

A quarter of subjects (24.9%) had ongoing symptoms of disease of interest at the time Polyoxidonium was prescribed (Table 10.9). A large variety of symptoms were reported, the most common being cough (5.4%), oropharyngeal pain (2.2%) and fatigue (2.6%). Symptoms and their prevalence in the whole study population as well as in therapeutic indication subgroups are presented in Appendix (Table 15). New symptoms which occurred during the study are listed in Appendix (Table 16).

Out of 343 symptoms reported, 155 (45.2%) symptoms resolved, 186 (54.2%) - improved and only 2 (0.6%) symptoms worsened during the study period (Table 10.9). On average, disease symptoms lasted for 14.58 (± 9.62) days. Table 10.10 presents data on the duration of disease symptoms reported by at least 5 subjects.

Only 3 (0.6%) subjects had ongoing fever episodes at enrolment and 2 (0.4%) subjects experienced fever while participating in the study (Table 10.8). The mean duration of fever episodes was 4.67 (±2.50) days (Table 10.9).

Table 10.9. *Clinical characteristics of disease of interest (i.e., disease due to which Polyoxidonium was prescribed)*

Disease symptoms and fever episodes	
Subjects with disease symptoms within 7 days before enrolment, n (%)	126 (25.1)
Subjects with disease symptoms ongoing at enrolment, n (%)	125 (24.9)
Subjects with new symptoms during the study, n (%)	8 (1.2)
Subjects with the dynamics of disease symptoms during the study	85 (16.9)
Dynamics of disease symptoms during the study	
resolved	155 (45.2)
improved	186 (54.2)
worsened	2 (0.6)
Duration of symptoms, days	
mean ± SD	14.58 ± 9.62
min	1
max	65
Subjects with fever within 7 days before enrolment, n (%)	3 (0.6)
Subjects with ongoing fever episode at enrolment, n (%)	3 (0.6)
Subjects with new fever episodes during the study, n (%)	2 (0.4)
Subjects with fever episodes, n (%)	
chronic recurrent bacterial infection	3
acute bacterial infection	1
acute viral infection	1

Table 10.10. *Mean duration (days) of fever episodes and most commonly reported symptoms of disease of interest*

Symptom	**All subjects**	**Chronic recurrent bacterial infection**	**Chronic recurrent viral infection**	**Acute bacterial infection**	**Acute viral infection**	**Allergic disease**
Fever						
n*	6	4	0	1	1	0
mean±SD	4.67±2.50	6.00±1.83		2	2	
Symptoms						
Cough						
n**	27	9	14	3	1	0
mean±SD	16.48±9.71	22.00±10.28	15.43±8.70	9.00±1.73	4	
Fatigue						
n**	13	3	8	0	0	2
mean±SD	18.85±7.06	20.67±9.29	19.50±6.87			13.50±4.95
Oropharyngeal pain						
n**	11	4	5	2	0	0
mean±SD	18.85±10.60	20.00±9.06	20.00±13.82	12.00±2.83		

** number of fever episodes; **number of subjects with a given symptom*

Table 10.10. *continued*

Symptom	All subjects	Chronic recurrent bacterial infection	Chronic recurrent viral infection	Acute bacterial infection	Acute viral infection	Allergic disease
Pruritus						
n**	9	3	0	1	1	4
mean±SD	14.11±9.52	25.33±6.66		8	2	10.25±2.22
Upper-airway cough syndrome						
n**	9	3	1	2	2	1
mean±SD	8.78±3.67	6.67±3.22	4	13.00±2.83	9.50±2.12	10
Nasal congestion						
n**	8	3	3	0	0	2
mean±SD	19.88±8.31	19.00±9.64	26.00±5.00			12.00±2.83
Secretion discharge						
n**	8	1	7	0	0	0
mean±SD	11.88±6.56	5	12.86±6.41			
Headache						
n**	7	1	1	0	2	3
mean±SD	5.43±2.64	3	7		5.00±2.83	6.00±3.46
Erythema						
n**	6	2	0	0	0	4
mean±SD	13.83±6.34	18.00±7.01				11.75±5.74
Herpes virus infection						
n**	6	1	5	0	0	0
mean±SD	19.50±23.12	7	22.00±24.93			
Purulent discharge						
n**	6	3	0	3	0	0
mean±SD	15.17±9.99	18.33±14.57		12.00±2.65		
Rhinorrhea						
n**	5	3	0	0	0	2
mean±SD	14.40±2.30	15.67±2.08				12.50±0.71
Pelvic pain						
n**	5	5	0	0	0	0
mean±SD	10.80±4.09	10.80±4.09				
Speech disorder						
n**	9	6	0	1	0	2
mean±SD	11.22±5.22	10.50±6.29		14		12.00±2.83

** number of fever episodes; **number of subjects with a given symptom*

10.4.3.4 Change in blood and urine WBC

At enrolment, mean blood WBC was 7.62 (±2.12)×10^9/L (range, 4.60 to 14.03 × 10^9/L). At the study end, mean blood WBC was 6.77 (±1.48) (range, 4.90 to 10.10) (refer to Appendix Table 8 for more detailed data). None of subjects had clinically significant abnormalities, as judged by investigators.

Mean urine WBC was 4.55 (±8.15) /µl and 2.33 (±6.63) /µl at enrolment and study end, respectively. At study end, one subject (0.2%) had abnormal urine WBC value, which was considered as clinically significant.

Only few subjects had at least two blood and urine WBC measurements available. The mean duration of period between the two measurements was 14.77 (±6.64) days for blood WBC (range, 6 to 26 days) and 24.00 (±4.36) for urine WBC (range, 21 to 29 days). There were no significant differences between mean blood WBC (total and differential) and urine WBC values on two occasions (Table 10.11).

Table 10.11. *Mean blood and urine WBC values at two time points (i.e., the first and the last measurements for a given subject), $\times 10^9$/L*

Laboratory parameter	First measurement	Last measurement	p*
Total WBC (blood)			
n	23	23	
Mean± SD	7.05±2.67	6.43±1.33	0.194
WBC differential			
Neutrophils, x10^9/L			
n	10	10	0.575
mean±SD	4.57±1.26	4.39±0.80	
Neutrophils, %			
n	7	7	0.866
mean±SD	58.61±7.07	56.39±9.35	
Lymphocytes, x10^9/L			
n	9	9	0.678
mean±SD	1.95±0.91	2.00±0.73	
Lymphocytes, %			
n	7	7	0.397
mean±SD	30.39±6.64	32.77±9.98	
Monocytes, %			
n	2	2	0.655
mean±SD	4.31±5.65	7.20±0.14	
Eosinophils, x10^9/L			
n	2	2	0.180
mean±SD	0.18±0.09	0.26±0.13	
Eosinophils, %			
n	2	2	0.655
mean±SD	2.15±0.49	2.10±1.13	
Basophils, %			
n	2	2	0.655
mean±SD	0.21±0.28	0.35±0.07	
Urine WBC			
n	2	2	
Mean± SD	12.50±17.68	0.50±0.71	0.655

n, number of subjects with data available
** Wilcoxon Signed Ranks Test*

10.5. Other analyses

Not applicable

10.6. Adverse events/adverse reactions

Out of the 502 subjects, 19 (3.8%) subjects experienced a total of 34 AEs. Most AEs occurred in subjects with chronic recurrent viral infections (Table 10.12). There were 23 mild and 3 moderate AEs (Table 10.13).

Eight AEs (all occurred in the same subject) were related to Polyoxidonium as judged by the investigator (refer to Section 10.4.2 for more detailed information).

There was 1 renal AE (renal failure). This AEs was reported at enrolment visit, in a subject who had not previously received Polyoxidonium. The intensity of this event was considered as mild. Investigator assessed it as not related to Polyoxidonium treatment (refer to Section 10.6.1 for a narrative of this AE).

In total, 2 SAEs (liver function test increased and vertigo) were reported in 2 (0.4%) subjects. None of SAEs were related to Polyoxidonium treatment. 2 AEs caused early withdrawal from the study (Table 10.13). None of these AEs were related to Polyoxidonium.

Polyoxidonium treatment was discontinued due to AE in 2 subjects. These AEs were liver function test increased and vertigo. 2 AEs (bronchitis and vertigo) led to Polyoxidonium treatment interruption (Table 10.14). None of these AEs was evaluated by investigators as related to Polyoxidonium treatment (refer to Appendix Table 17 *Adverse events listing* for more information).

Table 10.12. *Subjects with adverse events in different therapeutic indication subgroups, n (%)*

	All subjects	**Chronic recurrent bacterial infection**	**Chronic recurrent viral infection**	**Acute bacterial infection**	**Acute viral infection**	**Allergic disease**
Subjects with at least one AE	19 (3.8)	5 (2.6)	13 (6.2)	0	1 (4.3)	0
Subjects with at least one AE related to Polyoxidonium	1 (0.2)	0	1	0	0	0
Subjects with at least one adverse renal effect	1 (0.2)	0	1	0	0	0
Subjects with at least one SAE	2 (0.4)	1	1	0	0	0
Subjects with at least one SAE related to Polyoxidonium	0	0	0	0	0	0

Table 10.13. *Summary of adverse events*

Adverse events characteristics	n
Total number of AEs	34
related to Polyoxidonium (ADRs)	8
not related to Polyoxidonium	26
Severity of AEs	
mild	23
moderate	3
severe	0
Severity of ADRs	
mild	7
moderate	1
severe	0
Total number of SAEs	2
Total number of serious ADRs	0
Total number of renal AEs	1
Total number of renal ADRs	0
AEs which led to early withdrawal	
liver function test increased	1
vertigo	1

Table 10.14. *Subjects with actions taken with Polyoxydonium due to AE, n (%)*

Actions taken with Polyoxydonium	n (%)
Subjects with Polyoxidonium withdrawn due to an AE	2 (0.4)
Subjects with Polyoxidonium dose reduced due to an AE	0
Subjects with Polyoxidonium interrupted due to an AE	2 (0.4)

All AEs, described both the original term reported by the investigator and by the preferred term, are provided for each subject in Appendix Table 17.

Appendix Table 18 lists AEs grouped by System Organ Class (SOC) and divided into severity categories (mild, moderate, severe), relatedness to Polyoxidonium treatment, the number of subjects in whom the event occurred and the rate of occurrence.

10.6.1 Narrative of renal adverse event

A male subject (ID 1537) with recurrent viral infection reported dry skin and eyelid oedema as disease symptoms at enrolment visit. He had no concomitant diseases and took no other medicines. On the same day, samples were taken for clinical biochemistry and urine analysis. Serum creatinine was 129 μmol/L, which was considered by the investigator as clinically significant abnormality. All other laboratory parameters (urea, AST, urine WBC) were within normal ranges. The subject did not receive Polyoxidonium treatment earlier. The investigator recorded mild renal insufficiency as an adverse event (resolving), not related to Polyoxidonium. During the subsequent study visits, no new disease symptoms were reported. Laboratory tests (clinical haematology, biochemistry, urine analysis) were repeated after 20 days. Serum

creatinine was 135μmol/L which was assessed by the investigator as not clinically significant. All other laboratory parameters were within normal ranges. The subject had not experienced other adverse events during the study, he completed the cycle of Polyoxidonium treatment as prescribed (10 injections given every second day).

11. Discussion

11.1. Key results

Polyoxidonium was well tolerated in the heterogenous population of patients who received Polyoxidonium in accordance with the terms of the marketing authorisation. Of 502 subjects who participated in this study, only one (0.1%) subject experienced 8 ADRs. These ADRs were restlessness, fatigue, feeling hot (n=2), pyrexia (n=3), and asthenia. The overall incidence of ADRs was 1.6/100 subjects. Seven ADRs were mild and one ADR was of moderate severity. None of subjects experiences any renal ADR.

At the end of study, both investigators and subjects very positively rated global tolerability. According investigators' assessment, global tolerability of Polyoxidonium was very good in 80% of subjects. Global tolerability was assessed as very good by 75% of subjects and as good – by 21% of subjects.

Global improvement was also highly rated. According to the opinion of investigators, complete resolution occurred in 26% of subjects, marked improvement was observed in 56% of subjects. Subjects also assessed their own improvement very positively – over 90% of subjects reported improvement.

At enrolment, 125 subjects reported experiencing at least one disease symptom and dynamics of symptoms during the study was observed in 85 subjects. High variety of disease symptoms were reported at baseline, almost all of the symptoms resolved (45%) or improved (54%) during the study. Taking into consideration that only 69 (13.7%) subjects received primary treatment of disease of interest (i.e., other medicines than Polyoxidonium), symptomatic improvement might be attributed to the effectiveness of Polyoxidonium.

11.2. Limitations

This PASS aimed to collect data on the safety of Polyoxidonium in patients receiving the treatment in routine clinical practice. Most of enrolled subjects (80%) received Polyoxidonium prescription because of chronic recurrent bacterial or viral infections. The rest of subjects had acute bacterial or viral infections or allergic disease. There are no data available on Polyoxidonium prescriptions according therapeutic indications in Slovakia, thus, it is unknown if the studied population represented target patient population.

This study reached no clear clinical benefit results due to inherent methodological problems which are common to all observational uncontrolled studies.

11.3. Interpretation

Stratified analysis by therapeutic indications showed that there were numerically less subjects with global tolerability assessment score "very good" among subjects with acute infections or allergic diseases to compare to those with chronic infections. Due to small number of subjects with these indications, it remains unclear whether such results were due to selection bias, chance or whether Polyoxidonium tolerability indeed depends on disease or some clinical conditions. Nevertheless, the differences observed relates only to the proportion of subjects with tolerability scores "very good" and "good". None of subjects with acute infections or allergic diseases had "moderate" or "poor" tolerability scores.

Due to characteristics of study population, no definite conclusions can be made with regard to other secondary endpoints of clinical benefit (i.e., duration of primary treatment of disease, days with disease symptoms and change in blood and urine WBC). 66 out of 69 (13.7%) subjects receiving primary treatment continued this treatment at the end of study, therefore meaningful estimates of treatment duration could not be done. Due to heterogeneity of study population, various disease symptoms were recorded and very few of individual symptoms were reported by at least 5 subjects. None of subjects with WBC measurements available had clinically significant abnormalities; therefore no changes in WBC values could have been expected during the treatment.

11.4. Generalisability

Most of enrolled subjects (80%) had chronic recurrent bacterial or viral infections. Due to small number of subjects with other therapeutic indications, it is unknown whether study results can be generalized to patients with acute bacterial or viral infections.

Subjects were observed for one cycle of treatment with Polyoxidonium (mean treatment duration was 21.79 days). 17% of subjects received at least one treatment cycle previously. Thus, the results obtained in this study cannot be generalized to long-term or repetitive treatment.

There were no subjects with a diagnosis of renal insufficiency in the study population, thus no conclusions can be drawn regarding the safety of Polyoxidonium in patients with impaired renal function.

12. Other information

Not applicable

13. Conclusion

Polyoxidonium was well tolerated in the heterogenous population of patients who received Polyoxidonium in accordance with the terms of the marketing authorisation. No renal ADRs were reported in this PASS, which was designed with a special focus on identifying potential adverse renal effects. The risk of nephrotoxicity observed in preclinical studies has not be confirmed in patients receiving short-term treatment with Polyoxidonium. Thus, the benefit-risk ratio of Polyoxidonium® 6 mg lyophilisate for solution for injection remains positive and no additional safety surveillance is required.

14. References

None

Appendix. *Tables referred to but not included in the text*

Table 1. *Number of subjects enrolled in each study site*

Study site No	Site name	Enrolled subjects n (%)
01	RAFMED s.r.o.	31 (6.2)
02	Analyticko-diagnostické laboratórium a ambulancie s.r.o.	31 (6.2)
03	IMUNOSPOL s.r.o	39 (7.8)
04	Spimal s.r.o	11 (2.2)
05	Alfa El, spol s.r.o.	9 (1.8)
06	Stalerg s.r.o.	27 (5.4)
07	Zoll-Med s.r.o	30 (6.0)
08	Milrea s.r.o.	71 (14.1)
09	Alersa s.r.o.	14 (2.8)
10	Pollex s.r.o.	30 (6.0)
11	Imuno s.r.o.	80 (15.9)
12	Imunoalergy s.r.o.	11 (2.2)
13	IMUNO - ALERGO JB, s.r.o.	43 (8.6)
14	Albatros K+K s.r.o.	33 (6.6)
15	Specialized St.Svorad Hospital Nitra Zobor, Nonprofit Org.	42 (8.4)
Total		**502 (100.0)**

Table 2. *Listing of subjects who withdrew from the study*

Subject ID	Primary reason for early withdrawal	Last visit before withdrawal
0506	subject withdrew consent	interim visit 1
0807	adverse event	interim visit 4
1203	lost to follow-up	interim visit 1
1340	adverse event	interim visit 7

Table 3. *The distribution of subjects according to reasons of office follow-up visits*

Reported reason*	n (%)
Agreement with patient	2 (0.4)
Cystitis	1 (0.2)
Controll examination	2 (0.4)
Yes, reccurent adverse event	1 (0.2)
Lab tests	3 (0.6)
Routine control	1 (0.2)
Routine control of the patients	1 (0.2)
Scheduled visit	1 (0.2)
Subject prefers to visit PI	1 (0.2)
Unknown**	17 (3.4)

**the exact wording entered by investigators is presented*
***the wording entered was meaningless (i.e., „very", „very good"*

Table 4. *Clinical diagnoses because of which Polyoxidonium was prescribed to subjects*

Clinical diagnosis	**n (%)**
Abscess	1 (0.2)
Acne	1 (0.2)
Anal abscess	1 (0.2)
Anogenital warts	2 (0.4)
Aphthous ulcer	2 (0.4)
Arthritis reactive	1 (0.2)
Asthma	22 (4.4)
Bacterial infection	20 (4.0)
Bacterial infection & Viral infection	2 (0.4)
Balanoposthitis	1 (0.2)
Bronchitis	19 (3.8)
Bronchitis & Pneumonia	1 (0.2)
Cellulitis	2 (0.4)
Chronic fatigue syndrome	1 (0.2)
Chronic fatigue syndrome & Lymphadenopathy & Oral herpes	1 (0.2)
Chronic obstructive pulmonary disease	1 (0.2)
Chronic tonsillitis	4 (0.8)
Cystitis	7 (1.4)
Conjunctivitis	6 (1.2)
Conjunctivitis & Abscess of eyelid	1 (0.2)
Conjunctivitis allergic	2 (0.4)
Dermatitis	4 (0.8)
Dermatitis atopic	11 (2.2)
Dermatitis bullous	1 (0.2)
Dermatitis contact	1 (0.2)
Eczema	1 (0.2)
Fungal infection	1 (0.2)
Fungal infection & Viral infection	1 (0.2)
Furuncle	4 (0.8)
Gastroenteritis	1 (0.2)
Genital herpes	3 (0.6)
Genital infection female	3 (0.6)
Genitourinary chlamydia infection	1 (0.2)

Table 4. *continued*

Clinical diagnosis	n (%)
Gynaecological chlamydia infection	1 (0.2)
Herpes simplex	15 (3.0)
Herpes virus infection	10 (2.0)
Herpes virus infection & Bacterial infection	1 (0.2)
Herpes virus infection & Bronchitis	1 (0.2)
Herpes virus infection & Viral infection	1 (0.2)
Herpes zoster	11 (2.2)
Herpes zoster & Rhinitis	1 (0.2)
Hypersensitivity	2 (0.4)
Immunodeficiency	6 (1.2)
Impetigo	1 (0.2)
Infectious mononucleosis	1 (0.2)
Intestinal cyst	1 (0.2)
Keratitis	1 (0.2)
Leukoplakia	1 (0.2)
Lyme disease	4 (0.8)
Lymphadenopathy	1 (0.2)
Nasopharyngitis	8 (1.6)
Ophthalmic herpes simplex	2 (0.4)
Ophthalmic herpes zoster	1 (0.2)
Oral herpes	12 (2.4)
Oral herpes & Asthma	1 (0.2)
Oral herpes & Nasal herpes	1 (0.2)
Osteomyelitis	1 (0.2)
Pemphigus	1 (0.2)
Pharyngitis	25 (5.0)
Pharyngotonsillitis	23 (4.6)
Pharyngotonsillitis & Stomatitis	1 (0.2)
Pilonidal cyst	1 (0.2)
Pneumonia	1 (0.2)
Pneumonia & Primary ciliary dyskinesia	1 (0.2)
Prostatitis	4 (0.8)
Psoriasis	1 (0.2)

Table 4. *continued*

Clinical diagnosis	**n (%)**
Rash papulosquamous	1 (0.2)
Respiratory tract infection	22 (4.4)
Respiratory tract infection & Urinary tract infection bacterial	4 (0.8)
Respiratory tract infection bacterial	2 (0.4)
Respiratory tract infection viral	49 (9.8)
Rhinitis	4 (0.8)
Rhinitis allergic	11 (2.2)
Seasonal allergy	9 (1.8)
Seasonal allergy & Urinary tract infection	1 (0.2)
Seborrhoeic dermatitis	1 (0.2)
Secondary immunodeficiency & Viral infection	1 (0.2)
Sinobronchitis	1 (0.2)
Sinusitis	52 (10.4)
Skin bacterial infection	1 (0.2)
Skin infection	1 (0.2)
Skin papilloma	4 (0.8)
Stomatitis	9 (1.8)
Subcutaneous abscess	4 (0.8)
Tracheitis	3 (.6)
Urinary tract infection	7 (1.4)
Urinary tract infection bacterial	4 (0.8)
Urticaria chronic	1 (0.2)
Vaginal infection	2 (0.4)
Varicose vein	1 (0.2)
Viral infection	28 (5.6)
Viral infection & Aphthous ulcer	2 (0.4)
Viral infection & Candida infection	3 (0.6)
Vulvovaginitis	1 (0.2)

Table 5. *Prevalence of concomitant diseases among study subjects*

Concomitant disease	**n (%)**
Abscess drainage	1 (0.2)
Acne	3 (0.6)
Adenovirus infection	1 (0.2)
Alopecia	1 (0.2)
Anaemia	6 (1.2)
Angina pectoris	1 (0.2)
Aphthous ulcer	4 (0.8)
Arthroscopy	1 (0.2)
Asthma	74 (14.7)
Atypical benign partial epilepsy	1 (0.2)
Autoimmune thyroiditis	6 (1.2)
Back pain	1 (0.2)
Balanoposthitis	1 (0.2)
Benign prostatic hyperplasia	1 (0.2)
Bone neoplasm	1 (0.2)
Breast cancer	2 (0.4)
Breast neoplasm	1 (0.2)
Bronchial hyperreactivity	1 (0.2)
Bronchitis	8 (1.6)
Bronchitis chronic	1 (0.2)
Carpal tunnel syndrome	2 (0.4)
Cerebral palsy	1 (0.2)
Cervical polypectomy	1 (0.2)
Cervicobrachial syndrome	1 (0.2)
Chlamydial infection	1 (0.2)
Cholecystectomy	1 (0.2)
Chronic fatigue syndrome	2 (0.4)
Chronic gastritis	2 (0.4)
Chronic obstructive pulmonary disease	3 (0.6)
Cyst drainage	1 (0.2)
Cyst removal	1 (0.2)
Cystitis	1 (0.2)
Cytomegalovirus test positive	1 (0.2)

Table 5. *continued*

Concomitant disease	n (%)
Coeliac disease	3 (0.6)
Conjunctivitis	2 (0.4)
Conjunctivitis allergic	4 (0.8)
Cough	2 (0.4)
Cow's milk intolerance	2 (0.4)
Depression	9 (1.8)
Dermatitis atopic	3 (0.6)
Dermatitis contact	2 (0.4)
diabetes mellitus	3 (0.6)
Diabetic neuropathy	1 (0.2)
Diverticulum	2 (0.4)
Dyslipidaemia	1 (0.2)
Dyspepsia	1 (0.2)
Dry eye	1 (0.2)
Eczema	3 (0.6)
Eye disorder	1 (0.2)
Embolism	1 (0.2)
Eosinophilic oesophagitis	1 (0.2)
Epilepsy	2 (0.4)
Epstein-Barr virus infection	1 (0.2)
Face oedema	1 (0.2)
Food allergy	5 (1.0)
Foot deformity	1 (0.2)
Fungal infection	1 (0.2)
Gastric disorder	1 (0.2)
Gastritis	1 (0.2)
Gastrooesophageal reflux disease	7 (1.4)
Glaucoma	2 (0.4)
Goitre	1 (0.2)
Granuloma annulare	1 (0.2)
Haemorrhage	1 (0.2)
Headache	4 (0.8)
Hepatic steatosis	2 (0.4)

Table 5. *continued*

Concomitant disease	n (%)
Herpes simplex	1 (0.2)
Herpes simplex test positive	1 (0.2)
Herpes virus infection	2 (0.4)
Herpes zoster	3 (0.6)
Hiatus hernia	2 (0.4)
Histamine intolerance	12 (2.4)
Hyperchlorhydria	1 (0.2)
Hypercholesterolaemia	10 (2.0)
Hypercoagulation	1 (0.2)
Hyperlipidaemia	6 (1.2)
Hypersensitivity	11 (2.2)
Hypertension	44 (8.8)
Hypertriglyceridaemia	1 (0.2)
Hyperuricaemia	3 (0.6)
Hypogammaglobulinaemia	3 (0.6)
Hypothyroidism	14 (2.8)
Hysterectomy	1 (0.2)
Hodgkin's disease	1 (0.2)
Immune system disorder	1 (0.2)
Immunodeficiency	2
Infectious mononucleosis	1 (0.2)
Insomnia	3 (0.6)
Iron deficiency anaemia	3 (0.6)
Ischaemic heart disease prophylaxis	1 (0.2)
Ischaemic stroke	1 (0.2)
Yersinia infection	1 (0.2)
Lacrimation increased	1 (0.2)
Lactose intolerance	1 (0.2)
Leukocytosis	1 (0.2)
Leukopenia	1 (0.2)
Limb injury	1 (0.2)
Liver disorder	7 (1.4)
Lyme disease	5 (1.0)

Table 5. *continued*

Concomitant disease	n (%)
Metrorrhagia	1 (0.2)
Microcytic anaemia	1 (0.2)
Migraine	1 (0.2)
Myocardial ischaemia	5 (1.0)
Nasal polyps	3 (0.6)
Nasal septum deviation	1 (0.2)
Nasopharyngitis	4 (0.8)
Nephrocalcinosis	1 (0.2)
Nephrolithiasis	1 (0.2)
Onychomycosis	1 (0.2)
Oral candidiasis	1 (0.2)
Oral herpes	7 (1.4)
Osteoarthritis	3 (0.6)
Osteochondrosis	1 (0.2)
Osteopenia	5 (1.0)
Osteoporosis	4 (0.8)
Otitis externa	1 (0.2)
Pain	1 (0.2)
Patellofemoral pain syndrome	1 (0.2)
Peptic ulcer	1 (0.2)
Periodontitis	2 (0.4)
Peripheral venous disease	2 (0.4)
Pernicious anaemia	1 (0.2)
Pneumonia	2 (0.4)
Post herpetic neuralgia	1 (0.2)
Postoperative hernia	1 (0.2)
Premature menopause	1 (0.2)
Primary ciliary dyskinesia	1 (0.2)
Prostatitis	1 (0.2)
Pruritus	1 (0.2)
Psoriasis	1 (0.2)
pulmonary embolism	1 (0.2)
Rash	1 (0.2)

Table 5. *continued*

Concomitant disease	n (%)
Respiratory tract infection	2 (0.4)
Rheumatoid arthritis	1 (0.2)
Rhinitis	58 (11.6)
Rhinitis allergic	45 (9.0)
Rosacea	1 (0.2)
Rotator cuff repair	1 (0.2)
Seasonal allergy	26 (5.2)
Secondary immunodeficiency	20 (4.0)
Selective IgM immunodeficiency	1 (0.2)
Sinus tachycardia	1 (0.2)
Sinusitis	7 (1.4)
Spinal pain	3 (0.6)
Splenomegaly	1 (0.2)
Sticky platelet syndrome	1 (0.2)
Tetany	1 (0.2)
Thyroid cancer	1 (0.2)
Thyroid disorder	1 (0.2)
Thyroiditis chronic	2 (0.4)
Thrombocytopenic purpura	1 (0.2)
Thrombosis	1 (0.2)
Type 2 diabetes mellitus	3 (0.6)
Type I hypersensitivity	1 (0.2)
Tonsillitis	1 (0.2)
Tracheitis	2 (0.4)
Tracheobronchitis	2 (0.4)
Trigeminal neuralgia	1 (0.2)
Urinary tract infection	5 (1.0)
Urticaria	4 (0.8)
Uterine dilation and curettage	1 (0.2)
Vaginal infection	2 (0.4)
Varicose vein	2 (0.4)
Varicose vein operation	1 (0.2)
Vertigo	1 (0.2)

Table 5. *continued*

Concomitant disease	**n (%)**
Vitamin D deficiency	2 (0.4)
Vitiligo	1 (0.2)
Vocal cord paralysis	1 (0.2)
Vulvovaginitis	1 (0.2)

Table 6. *Physical examination findings, n (%)*

Organ systems	Enrolment visit	Interim visits									Study end visit
		1	2	3	4	5	6	7	8	9	
	N=502	N=502	N=499	N=499	N=358	N=346	N=347	N=347	N=345	N=15	N=500
Subjects with physical examination performed	391 (77.9)	152 (30.3)	150 (30.1)	141 (28.3)	76 (21.2)	72 (20.8)	67 (19.3)	70 (20.2)	68 (19.7)	3 (20.0)	209 (41.8)
Abdomen											
normal	231 (46.0)	64 (12.7)	53 (10.6)	46 (9.2)	35 (9.8)	31 (9.0)	27 (7.8)	27 (7.8)	24 (7.0)	2 (13.3)	50 (10.0)
abnormal ncs	0	0	0	0	0	0	0	0	0	0	0
abnormal cs	0	0	0	0	0	0	0	0	0	0	0
Anorectal											
normal	51 (10.2)	7 (1.4)	2 (0.4)	3 (0.6)	2 (0.6)	0	2 (0.6)	0	61 (17.7)	0	1 (0.2)
abnormal ncs	0	0	0	0	0	0	0	0	0	0	0
abnormal cs	0	0	0	0	0	0	0	0	0	0	0
Cardiovascular System											
normal	308 (61.4)	96 (19.1)	89 (17.8)	78 (15.6)	58 (16.2)	54 (15.6)	51 (14.7)	52 (15.0)	49 (14.2)	3 (20.0)	125 (25.0)
abnormal ncs	0	0	0	0	0	0	0	0	0	0	0
abnormal cs	3 (0.6)	0	0	0	0	0	0	0	0	0	0
Eyes Ear Nose Throat											
normal	330 (65.7)	83 (16.5)	89 (17.8)	85 (17.0)	45 (12.6)	41 (11.8)	37(10.7)	38 (11.0)	37 (10.7)	2 (20.0)	156 (31.2)
abnormal ncs	21 (4.2)	6 (1.2)	7 (1.4)	9 (1.8)	1 (0.3)	0	0	0	0	0	4 (0.8)
abnormal cs	21 (4.2)	11 (2.2)	6 (1.2)	3 (6)	0	0	0	0	1 (0.3)	0	1 (0.2)
Extremities											
normal	199 (39.6)	57 (11.4)	50 (10.0)	42 (8.4)	33 (9.2)	28 (8.1)	26 (7.5)	25 (7.2)	22 (6.4)	2 (13.3)	51 (10.2)
abnormal ncs	1 (0.2)	0	0	0	0	0	0	0	0	0	0
abnormal cs	2 (0.4)	1 (0.2)	0	0	0	0	0	0	0	0	0
General appearance											
normal	369 (73.5)	120 (23.9)	111 (22.2)	101 (20.2)	61 (17.0)	56 (16.2)	54 (15.6)	55 (15.9)	53 (15.4)	2 (20.0)	161 (32.2)
abnormal ncs	2 (0.4)	1 (0.2)	2 (0.4)	2 (0.4)	1 (0.3)	1 (0.3)	1 (0.3)	0	0	0	1 (0.2)
abnormal cs	6 (1.2)	5 (1.0)	2 (0.4)	1 (0.2)	0	0	0	0	0	0	1 (0.2)

ncs, not clinically significant; cs, clinically significant

Table 6. *continued*

Organ systems	Enrolment visit	Interim visits 1	2	3	4	5	6	7	8	9	Study end visit
	N=502	N=502	N=499	N=499	N=358	N=346	N=347	N=347	N=345	N=15	N=500
Genitalia											
normal	49 (9.8)	7 (1.4)	2 (0.4)	3 (0.6)	2 (0.6)	0	1 (0.3)	0	61 (17.7)	0	1 (0.2)
abnormal ncs	0	0	0	0	0	0	0	0	0	0	0
abnormal cs	3 (0.6)	0	0	0	0	1 (0.3)	0	0	0	0	1 (0.2)
Head Neck Thyroid											
normal	310 (61.8)	75 (14.9)	64 (12.8)	53 (10.6)	37 (10.3)	29 (8.4)	28 (8.1)	30 (8.6)	25 (7.2)	2 (13.3)	87 (17.4)
abnormal ncs	1 (0.2)	0	0	0	0	0	0	0	0	1 (6.7)	0
abnormal cs	3 (0.6)	1 (0.2)	2 (0.4)	1 (0.2)	0	0	0	0	0	0	0
Lymph Nodes											
normal	231 (46.0)	85 (16.9)	75 (15.0)	69 (13.8)	32 (8.9)	28 (8.1)	24 (6.9)	26 (7.5)	23 (6.7)	2 (13.3)	78 (15.6)
abnormal ncs	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0	0	0	0	0	0
abnormal cs	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)	0	0	0	0	0	0	0
Muscular-Skeletal											
normal	166 (33.1)	58 (11.6)	48 (9.6)	42 (8.4)	33 (9.2)	28 (8.1)	24 (6.9)	25 (7.2)	22 (6.4)	2 (13.3)	43 (8.6)
abnormal ncs		0	0	0	0	0	0	0	0	0	0
abnormal ncs	01 (0.2)	1 (0.2)	0	0	0	0	0	0	0	0	0
Neurological											
normal	178 (35.5)	56 (11.2)	49 (9.8)	42 (8.4)	32 (8.9)	27 (7.8)	24 (6.9)	25 (7.2)	22 (6.4)	2 (13.3)	50 (10.0)
abnormal ncs	0	0	0	0	0	0	0	0	0	0	0
abnormal cs	0	0	0	0	0	0	0	0	0	0	0
Respiratory System											
normal	333 (66.3)	138 (27.5)	129 (25.9)	123 (24.6)	70 (19.6)	62 (17.9)	60 (17.3)	62 (17.9)	59 (17.1)	3 (20.0)	190 (38.0)
abnormal ncs	2 (0.4)	1 (0.2)	0	2 (0.4)	0	0	1 (0.3)	0	0	0	2 (0.4)
abnormal cs	36 (7.2)	3 (0.6)	2 (0.4)	2 (0.4)	0	0	0	0	0	0	0
Skin											
normal	278 (55.4)	96 (19.1)	90 (18.0)	78 (15.6)	54 (15.1)	54 (15.6)	50 (14.4)	50 (14.4)	50 (14.5)	2 (20.0)	100 (20.0)
abnormal ncs	23 (4.6)	6 (1.2)	7 (1.4)	13 (2.6)	3 (0.8)	3 (0.9)	3 (0.9)	2 (0.6)	1 (0.3)	0	15 (3.0)
abnormal cs	37 (7.4)	16 (3.2)	16 (3.2)	12 (2.4)	4 (1.1)	2 (0.6)	1 (0.3)	3 (0.9)	2 (0.6)	0	5 (1.0)
Other Body System											
normal	37 (7.4)	4 (0.8)	0	0	1 (0.3)	0	0	0	0	0	0
abnormal ncs	0	0	0	0	0	0	0	0	0	0	0
abnormal cs	1 (0.2)	0	0	0	0	0	0	0	0	0	0

Table 7. *Vital signs and electrocardiogram (ECG) resuls*

Parameter	Enrolment visit	Interim visits 1	2	3	4	5	6	7	8	9	Study end visit
	N=502	N=502	N=499	N=499	N=358	N=346	N=347	N=347	N=345	N=15	N=500
BMI, kg/m^2											
n	476	-	-	-	-	-	-	-	-	-	-
mean±SD	25.11±4.54										
min	16.2										
max	42.8										
BMI groups, N (%)											
≤25 kg/m^2	253 (50.4)	-	-	-	-	-	-	-	-	-	-
>25-30 kg/m^2	164 (32.7)										
>30.0 kg/m^2	59 (11.8)										
Body temperature (T), ^{o}C											
n	236	74	57	44	19	16	15	14	14	1	63
mean±SD	36.33±0.33	36.37±0.27	36.37±0.27	36.35±0.27	36.51±0.16	36.46±0.21	36.50±0.16	36.46±0.17	36.45±0.15	36.5	36.38±0.23
min	35.9	36.0	36.0	36.0	36.0	36.0	36.0	36.0	36.0		36.0
max	38.0	37.0	36.8	36.8	36.8	36.7	36.7	36.7	36.6		36.8
T>=38, N (%)	2 (0.4)	0	0	0	0	0	0	0	0	0	0
Systolic blood pressure (SBP), mmHg											
n	380	88	66	58	21	20	15	17	16	2	135
mean±SD	121.13±12.05	122.94±10.22	122.98±9.24	124.36±9.09	122.33±8.00	121.50±11.32	121.33±7.19	123.82±9.67	121.63±8.85	122.00±16.97	119.83±11.6
min	89	100	100	110	110	97	110	110	110	110	1
max	157	173	145	145	140	145	130	140	141	134	94
											148
Diastolic blood pressure (DBP), mmHg											
n	380	88	66	58	21	20	15	17	16	2	135
mean±SD	78.12±8.23	77.88±6.67	77.44±5.95	78.03±7.08	77.62±7.07	77.45±7.44	76.67±6.99	77.00±7.87	75.25±6.35	68.00±4.24	77.51±8.10
min	45	59	60	60	65	64	65	65	65	65	57
max	108	99	90	95	90	95	90	90	85	71	101
SBP/DBP >=140/90, N (%)											
	62 (12.4)	6 (1.2)	4 (0.8)	9 (1.8)	2 (0.6)	3 (0.9)	1 (0.3)	4 (1.2)	1 (0.3)	0	19 (3.8)

n, number of subjects with assessments performed; ncs, not clinically significant; cs, clinically significant

Table 7. *continued*

Parameter	Enrolment visit	Interim visits									Study end visit
		1	2	3	4	5	6	7	8	9	
	N=502	N=502	N=499	N=499	N=358	N=346	N=347	N=347	N=345	N=15	N=500
Heart rate (HR), bpm											
n	404	92	70	62	21	20	15	17	16	2	135
mean±SD	74.55±8.46	72.82±8.14	72.34±8.21	71.47±7.32	72.33±5.34	73.05±5.53	72.13±5.36	71.88±5.17	71.63±5.57	71.00±1.41	73.79±8.98
min	47	52	50	54	60	62	62	60	58	70	52
max	101	96	96	86	80	82	80	80	80	72	100
HR categories, N (%)											
<50 bpm	1 (0.2)	0	0	0	0	0	0	0	0	0	0
50-100 bpm	398 (79.3)	92 (18.3)	70 (14.0)	62 (12.4)	21 (5.9)	20 (5.8)	15 (4.3)	17 (4.9)	16 (4.6)	2 (13.3)	135 (27.0)
>100 bpm	5 (1.0)	0	0	0	0	0	0	0	0	0	0
ECG											
normal	5 (1.0)	3 (0.6)	0	2 (0.4)	0	0	0	0	0	0	7 (1.4)
abnormal ncs	0	0		0							0
abnormal cs	0	1 (0.2)		0							0

n, number of subjects with assessments performed; ncs, not clinically significant; cs, clinically significant

Table 8. *Results of laboratory tests and other diagnostic procedures*

	Enrolment visit	Interim visits								Study end visit	Follow-up
		1	2	3	4	5	6	7	8	9		
	N=502	N=502	N=499	N=499	N=358	N=346	N=347	N=347	N=345	N=15	N=500	501
Clinical haematology parameters												
Subjects with tests performed, n (%)	33 (6.6)	24 (4.8)	3 (0.6)	2 (0.4)	0	1(0.3)	0	1 (0.3)	3 (0.9)	0	14 (2.8)	17 (3.4)
White blood cell count (WBC), $\times 10^9$/L												
n	32	24	3	2	0	1	0	1	3	0	14	17
mean±SD	7.62±2.12	6.90±2.61	6.75±1.85	5.85±0.07		5.60		4.46	7.23±1.67		6.77±1.48	6.13±1.39
min	4.60	2.93	5.20	5.80		5.60		4.46	5.90		4.90	3.23
max	14.03	15.39	8.80	5.90		5.60		4.46	9.10		10.10	9.42
abnormal cs	0	0	0	0		0		0	0		0	0
Red blood cell count (RBC), $\times 10^{12}$/L												
n	31	17	0	0	0	0	0	0	3	0	11	6
mean±SD	4.76±0.52	4.52±0.57							4.88±0.49		4.55±0.61	4.69±0.54
min	3.65	3.42							4.32		3.70	3.99
max	5.94	5.96							5.24		5.78	5.33
abnormal cs	0	1 (0.2)							0		0	0
Hemoglobin (Hb), g/L												
n	31	20	0	0	0	0	0	0	3	0	12	7
mean±SD	144.42±14.99	133.85±14.76							162.67±19.30		138.83±14.22	138.86±18.20
min	122.00	108.00							141.00		116.00	114.00
max	174.00	170.00							178.00		164.00	165.00
abnormal cs	0	1 (0.2)							0		0	0
Mean corpuscular volume(MCV), fl												
n	21	0	0	0	0	0	0	0	0	0	0	0
mean±SD	89.09±6.10											
min	75.12											
max	98.90											
abnormal cs	0											
Mean corpuscular haemoglobin (MCH), pg												
n	21	0	0	0	0	0	0	0	0	0	0	0
mean±SD	30.62±2.08											
min	24.12											
max	33.40											
abnormal cs	0											

Table 8. *continued*

	Enrolment visit	Interim visits									Study end visit	Follow-up
		1	2	3	4	5	6	7	8	9		
	N=502	N=502	N=499	N=499	N=358	N=346	N=347	N=347	N=345	N=15	N=500	501
Platelets (PLT), $\times 10^9$/L												
n	27	14	0	0	0	0	0	0	3	0	12	5
mean±SD	261.98±58.12	281.93±88.63							185.67±40.02		221.83±51.31	225.60±41.99
min	182.00	203.00							145.00		132.00	183.00
max	425.00	489.00							225.00		318.00	272.00
abnormal cs	0	0							0		0	0
Hematocrit (HCT), absol.												
n	25	10	1	2	0	1	0	0	3	0	10	2
mean±SD	0.42±0.04	0.40±0.05	0.36	0.41±0.05		0.37			0.46±0.04		0.42±0.05	0.41±0.02
min	0.34	0.33	0.36	0.37		0.37			0.42		0.35	0.40
max	0.50	0.51	0.36	0.44		0.37			0.48		0.50	0.42
abnormal cs	0	0	0	0		0			0		0	0
Neutrophils, $x10^9$/L												
n	9	11	3	0	0	0	0	0	0	0	1	10
mean±SD	4.96±2.13	4.88±2.77	3.71±1.51								4.00	4.39±0.80
min	2.62	2.30	2.49									2.61
max	9.44	12.39	5.39									5.79
abnormal cs	0	0	0								0	0
Neutrophils, %												
n	10	9	0	0	0	1	0	0	3	0	8	4
mean±SD	60.23±5.85	63.06±7.59				41.70			50.77±7.35		56.15±5.70	57.48±4.50
min	50.10	52.20				41.70			42.70		49.80	52.30
max	69.20	74.50				41.70			57.10		63.80	62.20
abnormal cs	0	0				0			0		0	0
Lymphocytes, $x10^9$/L												
n	9	9	2	0	0	0	0	0	0	0	1	11
mean±SD	2.59±0.68	1.87±0.96	1.86±0.23								2.00	2.08±0.71
min	1.51	0.62	1.70								2.00	0.66
max	3.66	4.04	2.02								2.00	3.01
abnormal cs	0	0	0								0	0

n, number of subjects with laboratory tests performed; cs, clinically significant

Table 8. *continued*

	Enrolment visit	Interim visits									Study end visit	Follow-up
		1	2	3	4	5	6	7	8	9		
	N=502	N=502	N=499	N=499	N=358	N=346	N=347	N=347	N=345	N=15	N=500	501
Lymphocytes, %												
n	9	9	0	0	0	1	0	0	3	0	8	4
mean±SD	26.77±6.04	25.60±7.98				42.80			37.67±4.45		36.11±5.34	60.68±3.51
min	19.50	14.40				42.80			33.30		27.40	27.30
max	37.60	37.90				42.80			42.20		42.60	34.40
abnormal cs	0	0				0			0		0	0
Monocytes, $x10^9$/L												
n	5	3	1	0	0	0	0	0	0	0	0	0
mean±SD	0.69±0.24	0.51±0.25	0.46									
min	0.42	0.33	0.46									
max	1.07	0.80	0.46									
abnormal cs	0	0	0									
Monocytes, %												
n	6	7	0	0	0	0	0	0	0	0	1	2
mean±SD	8.13±1.65	7.19±3.30									7.10	8.50±1.70
min	5.20	0.31									7.10	7.30
max	9.60	10.50									7.10	9.70
abnormal cs	0	0									0	0
Eosinophils, $x10^9$/L												
n	8	6	2	0	0	0	0	0	0	0	0	2
mean±SD	0.18±0.08	0.19±0.11	0.51±0.08									0.26±0.13
min	0.09	0.08	0.45									0.16
max	0.29	0.38	0.57									0.35
abnormal cs	0	0	0									0
Eosinophils, %												
n	5	5	0	0	0	0	0	0	0	0	1	2
mean±SD	4.76±3.92	2.20±1.35									1.30	2.30±0.85
min	0.80	0.20									1.30	1.70
max	10.60	3.90									1.30	2.90
abnormal cs	0	0									0	0

n, number of subjects with laboratory tests performed; cs, clinically significant

Table 8. *continued*

	Enrolment visit	Interim visits									Study end visit	Follow-up
		1	2	3	4	5	6	7	8	9		
	N=502	N=502	N=499	N=499	N=358	N=346	N=347	N=347	N=345	N=15	N=500	501
Basophils, x10^9/L												
n	5	1	1	0	0	0	0	0	0	0	0	0
mean±SD	0.05±0.03	0.07	0.00									
min	0.02											
max	0.09											
abnormal cs	0	0	0									
Basophils, %												
n	5	7	0	0	0	0	0	0	0	0	1	2
mean±SD	0.24±0.17	0.29±0.30									0.40	0.35±0.07
min	0.10	0.01									0.40	0.30
max	0.50	0.90									0.40	0.40
abnormal cs	0	0									0	0
Clinical biochemistry parameters												
Subjects with tests performed, n (%)	39 (7.8)	17 (3.4)	4 (0.8)	3 (0.6)	0	1 (0.3)	0	1 (0.3)	3 (0.9)	0	18 (3.6)	27 (5.4)
Urea, mmol/L												
n	35	6	2	0	0	0	0	0	2	0	17	11
mean±SD	4.41±1.26	4.67±1.79	5.30±0.85						5.30±0.85		4.38±1.14	5.01±2.46
min	1.90	3.40	4.70						4.30		2.90	1.90
max	8.10	8.20	5.90						5.90		7.80	11.00
abnormal cs	0	0	0						0		0	0
Creatinine, µmol/L												
n	38	17	4	0	0	0	0	0	4	0	18	27
mean±SD	87.74±14.82	74.54±11.91	75.28±19.66						75.28±19.66		84.81±16.92	81.35±17.93
min	60.00	55.00	56.00						56.00		49.50	57.00
max	129.00	102.80	102.10						135.10		114.00	120.00
abnormal cs	1 (0.2)	0	0						0		0	0

n, number of subjects with laboratory tests performed; cs, clinically significant

Table 8. *continued*

	Enrolment visit	Interim visits								Study end visit	Follow-up
		1	2	3	4	5	6	7	8	9		
	N=502	N=502	N=499	N=499	N=358	N=346	N=347	N=347	N=345	N=15	N=500	501
Alkaline phosphatase (ALP), U/L												
n	11	0	0	0	0	0	0	0	0	0	4	4
mean±SD	1.27±0.51										1.05±0.49	1.13±0.60
min	0.66										0.68	0.37
max	2.00										1.77	1.77
abnormal cs	0										0	0
Alanine aminotransferase (ALT), U/L												
n	19	15	4	0	0	0	0	0	4	0	6	21
mean±SD	0.42±0.16	0.43±0.29	0.57±0.38						0.57±0.38		0.45±0.22	0.55±0.25
min	0.21	0.16	0.19						0.19		0.30	0.22
max	0.74	1.22	0.96						0.96		0.84	1.18
abnormal cs	0	0	0						0		0	0
Aspartate transaminase (AST), U/L												
n	24	7	2	0	0	0	0	0	2	0	14	9
mean±SD	0.44±0.20	0.40±0.12	0.45±0.13						0.45±0.13		0.41±0.16	0.45±0.19
min	0.21	0.22	0.35						0.35		0.27	0.23
max	1.07	0.57	0.54						0.54		0.72	0.79
abnormal cs	0	0	0						0		0	0
Sodium, mmol/L												
n	1	2	0	0	0	0	0	0	0	0	0	0
mean±SD	143	141.50±2.12										
min	143	140										
max	143	143										
abnormal cs	0	0										
Potasium, mmol/L												
n	1	1	0	0	0	0	0	0	0	0	0	0
mean±SD	5.20	5.20										
min	5.20	5.20										
max	5.20	5.20										
abnormal cs	0	0										

n, number of subjects with laboratory tests performed; cs, clinically significant

Table 8. *continued*

	Enrolment visit	Interim visits								Study end visit	Follow-up
		1	2	3	4	5	6	7	8	9		
	N=502	N=502	N=499	N=499	N=358	N=346	N=347	N=347	N=345	N=15	N=500	501
Total bilirubin, µmol/L												
n	1	2	0	0	0	0	0	0	0	0	0	0
mean±SD	13.20	15.30±4.10										
min	13.20	12.40										
max	13.20	18.20										
abnormal cs	0	0										
Albumin												
n	0	0	0	0	0	0	0	0	0	0	1	0
mean±SD											1.21	
min											1.21	
max											1.21	
abnormal cs											0	
Urinary parameters												
Subjects with tests performed, n (%)	12 (2.4)	0	4 (0.8)	0	0	0	0	0	3 (0.9)	0	9 (1.8)	8 (1.6)
pH												
n	4	0	0	0	0	0	0	0	0	0	0	0
mean±SD	6.50±0.58											
min	6.00											
max	7.00											
abnormal cs	0											
Specific gravidity, kg/m^3												
n	1	0	0	0	0	0	0	0	0	0	0	0
mean±SD	1004.00											
min	1004.00											
max	1004.00											
abnormal cs	0											
Protein, g/L												
n	7	0	0	0	0	0	0	0	0	0	7	4
mean±SD	0.14±0.38										0	0
min	0.00										0	0
max	1.00										0	0
abnormal cs	0										0	0

n, number of subjects with laboratory tests performed; cs, clinically significant

Table 8. *continued*

	Enrolment visit	Interim visits									Study end visit	Follow-up
		1	2	3	4	5	6	7	8	9		
	N=502	N=502	N=499	N=499	N=358	N=346	N=347	N=347	N=345	N=15	N=500	501
Glucose, mmol/L												
n	7	0	0	0	0	0	0	0	0	0	7	4
mean±SD	0										0	0
min	0										0	0
max	0										0	0
abnormal cs	0										0	0
Ketones, mmol/L												
n	7	0	0	0	0	0	0	0	0	0	7	4
mean±SD	0										0	0
min	0										0	0
max	0										0	0
abnormal cs	0										0	0
Bilirubin												
n	4	0	0	0	0	0	0	0	0	0	0	0
mean±SD	0											
min	0											
max	0											
abnormal cs	0											
Urobilinogen												
n	3	0	0	0	0	0	0	0	0	0	0	0
mean±SD	0											
min	0											
max	0											
abnormal cs	0											
Blood												
n	7	0	0	0	0	0	0	0	0	0	5	2
mean±SD	0.14±0.38										0	0
min	0										0	0
max	1.00										0	0
abnormal cs	0										0	0

n, number of subjects with laboratory tests performed; cs, clinically significant

Table 8. *continued*

	Enrolment visit	Interim visits									Study end visit	Follow-up
		1	2	3	4	5	6	7	8	9		
	N=502	N=502	N=499	N=499	N=358	N=346	N=347	N=347	N=345	N=15	N=500	501
WBC, /µl												
n	11	0	0	0	0	0	0	0	0	0	9	9
mean±SD	4.55±8.15										2.33±6.63	10.73±21.15
min	0										0	0
max	25.00										20.00	63.60
abnormal cs	0										0	1 (0.2)
RBC												
n	6	0	0	0	0	0	0	0	0	0	7	4
mean±SD	2.17±2.71										0.29±0.76	0.50±1.00
min	0										0	0
max	6.00										2.00	2.00
abnormal cs	0										0	0
Other laboratory tests												
Subjects with tests performed, n (%)	23 (4.6)	25 (5.0)	3 (0.6)	4 (0.8)	0	1 (0.3)	0	1 (0.3)	0	0	6 (1.2)	16 (3.2)
Other diagnostic procedures												
Subjects with tests performed, n (%)	5 (1.0)*	0	0	1 (0.2)**	2 (0.6)**	0	1 (0.3)**	0	0	0	2 (0.4)**	0

n, number of subjects with laboratory tests performed; cs, clinically significant
**spirometry (n=4), urine cultivation (n=1); **spirometry*

Table 9. *Prior and concomitant medications taken by study subjects, n (%)*

Therapeutic group (ATC level 2)	Prior medication*	Concomitant medication**
Alimentary tract and metabolism		
Drugs for acid related disorders (A02)	0	12 (2.4)
Drugs for functional gastrointestinal disorders (A03)	0	2 (0.4)
Bile and liver therapy (A05)	0	3 (0.6)
Antidiarrheals, intestinal antiinflammatory/antiinfective agents (A07)	0	12 (2.4)
Digestives, incl. enzymes (A09)	0	2 (0.4)
Drugs used in diabetes (A10)	0	11 (2.2)
Vitamins (A11)	0	21 (4.2)
Mineral supplements (A12)	0	13 (2.6)
Alimentary tract and metabolism (A16)	0	2 (0.4)
Blood and blood forming organs		
Antithrombotic agents (B01)	1 (0.2)	12 (2.4)
Antianemic preparations (B03)	0	8 (1.6)
Cardiovascular system		
Cardiac therapy (C01)	0	5 (1.0)
Antihypertensives (C02)	1 (0.2)	3 (0.6)
Diuretics (C03)	0	6 (1.2)
Vasoprotectives (C05)	0	5 (1.0)
Beta blocking agents (C07)	0	22 (4.4)
Calcium channel blockers (C08)	0	12 (2.4)
Agents acting on the renin-angiotensin system (C09)	1 (0.2)	23 (4.6)
Lipid modifying agents (C10)	0	19 (3.8)
Dermatologicals		
Antifungals for dermatological use (D01)	0	2 (0.4)
Emollients and protectives (D02)	0	3 (0.6)
Preparations for treatment of wounds and ulcers (D03)	0	2 (0.4)
Antipsoriatics (D05)	0	1 (0.2)
Antibiotics and chemotherapeutics for dermatological use (D06)	1 (0.2)	1 (0.2)
Corticosteroids, dermatological preparations (D07)	0	10 (2.0)

**any previous clinically relevant disease(s) which occurred within 5 years before enrolment; **current concomitant disease*

Table 9. *continued*

Therapeutic group (ATC level 2)	Prior medication*	Concomitant medication**
Antiseptics and disinfectants (D08)	1 (0.2)	2 (0.4)
Anti-acne preparations (D10)	0	3 (0.6)
Other dermatological preparations (D11)	0	1 (0.2)
Genito urinary system and sex hormones		
Sex hormones and modulators of the genital system (G03)	0	7 (1.4)
Urologicals (G04)	0	3 (0.6)
Systemic hormonal preparations, excl. sex hormones and insulins		
Corticosteroids for systemic use (H02)	0	4 (0.8)
Thyroid therapy (H03)	0	18 (3.6)
Antiinfectives for systemic use		
Antibacterials for systemic use (J01)	9 (1.8)	13 (2.6)
Antimycotics for systemic use (J02)	0	1 (0.2)
Antivirals for systemic use (J05)	4 (0.8)	7 (1.4)
Vaccines (J07)	4 (0.8)	5 (1.0)
Antineoplastic and immunomodulating agents		
Antineoplastic agents (L01)	0	1 (0.2)
Endocrine therapy (L02)	0	3 (0.6)
Immunostimulants (L03)	0	1 (0.2)
Musculo-skeletal system		
Antiinflammatory and antirheumatic products (M01)	2 (0.4)	6 (1.2)
Antigout preparations (M04)	0	2 (0.4)
Drugs for treatment of bone diseases (M05)	0	2 (0.4)
Other drugs for disorders of the musculo-skeletal system (M09)	0	1 (0.2)
Nervous system		
Anesthetics (N01)	0	1 (0.2)
Analgesics (N02)	3 (0.6)	11 (2.2)
Antiepileptics (N03)	0	3 (0.6)
Psycholeptics (N05)	0	9 (1.8)
Psychoanaleptics (N06)	0	9 (1.8)

**any previous clinically relevant disease(s) which occurred within 5 years before enrolment; **current concomitant disease*

Table 9. *continued*

Therapeutic group (ATC level 2)	Prior medication*	Concomitant medication**
Other nervous system drugs (N07)	0	2 (0.4)
Respiratory system		
Nasal preparations (R01)	1 (0.2)	65 (12.9)
Drugs for obstructive airway diseases (R03)	7 (1.4)	107 (21.3)
Cough and cold preparations (R05)	0	2 (0.4)
Antihistamines for systemic use (R06)	4 (0.8)	154 (30.7)
Sensory organs		
Ophthalmologicals (S01)	0	7 (1.4)
Various		
Allergens (V01)	0	1 (0.2)
All other therapeutic products (V03)	0	4 (0.8)
General nutrients (V06)	0	5 (1.0)
V90***	0	9 (1.8)

**any previous clinically relevant disease(s) which occurred within 5 years before enrolment; **current concomitant disease; ***under "V90" the following medicines assigned: silybum marianum (n=6), ginkgo biloba leaf extract (n=1) and unspecified herbal preparation (n=2)*

Table 10. *Prescribed regimens for Polyoxidonium use, n (%)*

Regimen	All subjects	Therapeutic indication				
		Chronic recurrent bacterial infection	Chronic recurrent viral infection	Acute bacterial infection	Acute viral infection	Allergic disease
	N=502	n=194	n=209	n=18	n=23	n=58
1 inj. every 2nd day	54 (10.8)	15 (7.7)	34 (16.3)	-	-	5 (8.6)
1 inj. every day for 5 days	3 (0.6)	-	1 (0.5)	1 (5.6)	1 (4.3)	-
1 inj. per day for 5 days (6 mg)	2 (0.4)	1 (0.5)	1 (0.5)	-	-	-
five 1 inj. every 2nd day	33 (6.6)	8 (4.1)	13 (6.2)	3 (16.7)	4 (17.4)	5 (8.6)
1 inj. per day	2 (0.4)	1 (0.5)	-	-	1 (4.3)	-
5 inj. every 2nd day	14 (2.8)	9 (4.6)	4 (1.9)	-	-	1 (1.7)
ten 1 inj. every 2nd day	73 (14.5)	6 (3.1)	59 (28.2)	1 (5.6)	1 (4.3)	6 (10.3)
1 inj.for 1 day, 2 days break, then 1 inj.per day for 4 days	1 (0.2)	1 (0.5)	-	-	-	-
1 inj.for 2 days, 2 days break, then 1 inj.every 2nd day	3 (0.6)	1 (0.5)	1 (0.5)	-	1 (4.3)	-
1 inj.for 2 days, then 1 inj.every 2nd day	11 (2.2)	3 (1.5)	-	2 (11.1)	1 (4.3)	5 (8.6)
1 inj.for 2 days, then 3 inj.for a week	1 (0.2)	1 (0.5)	-	-	-	-
1 inj. for 3 days, 1 day break, then 1 inj. for 2 days	1 (0.2)	1 (0.5)	-	-	-	-
1 inj. for 3 days, 2 days break, then 1 inj. for 2 days	1 (0.2)	1 (0.5)	-	-	-	-
1 inj. for 3 days, then 1 inj. every 2nd day	5 (1.0)	-	2 (1.0)	-	1 (4.3)	2 (3.4)
1 inj. for 3 days, then 2 inj. every 2nd day	9 (1.8)	6 (3.1)	-	3 (16.7)	-	-
1 inj. for 3 days, then 2 times a week	7 (1.4)	2 (1.0)	1 (0.5)	2 (11.1)	-	2 (3.4)

Table 10. *continued*

Regimen	All subjects	Therapeutic indication				
		Chronic recurrent bacterial infection	Chronic recurrent viral infection	Acute bacterial infection	Acute viral infection	Allergic disease
	N=502	n=194	n=209	n=18	n=23	n=58
first 3 days 1 inj. per day, 1 inj. on the sixth day, 1 inj. on the eighth day	1 (0.2)	-	-	-	-	1 (1.7)
1 inj. for 4 days, 2 days break, then 1 inj. every day	1 (0.2)	1 (0.5)	-	-	-	-
2 inj. per day, then 3 1 inj. every 2nd day	1 (0.2)	1 (0.5)	-	-	-	-
3 inj. per day, then 2inj. every 2nd day	3 (0.6)	-	-	-	2 (8.7)	1 (1.7)
5 inj. every 2nd day, then 2 times a week	16 (3.2)	11 (5.7)	3 (1.4)	-	1 (4.3)	1 (1.7)
6 inj. every 2nd day, then 2 times a week	3 (0.6)	2 (1.0)	-	-	-	1 (1.7)
five 1 inj. every 2nd day , then twice a week	167 (33.3)	67 (34.5)	62 (29.7)	4 (22.2)	8 (34.8)	26 (44.8)
every 2nd day	17 (3.4)	15 (7.7)	-	1 (5.6)	-	1 (1.7)
every 3rd day	2 (0.4)	2 (1.0)	-	-	-	-
1 time a week	30 (6.0)	23 (11.9)	7 (3.3)	-	-	-
2 times a week	23 (4.6)	11 (5.7)	10 (4.8)	-	1 (4.3)	1 (1.7)
3 times a week, then 2 times a week	7 (1.4)	3 (1.5)	2 (1.0)	1 (5.6)	1 (4.3)	-
Not specified	11 (2.2)	2 (1.0)	9 (4.3)	-	-	-

Table 11. *Details on previous treatment with Polyoxidonium and Polyoxidonium exposure during the study in subjects with different therapeutic indications*

	Chronic recurrent bacterial infection	**Chronic recurrent viral infection**	**Acute bacterial infection**	**Acute viral infection**	**Allergic disease**
	n=194	n=209	n=18	n=23	n=58
Previous Polyoxidonium prescriptions					
Subjects who previously received Polyoxidonium, n (%)	38 (19.6)	40 (19.1)	3 (16.7)	2 (8.7)	3 (5.2)
Number of previous treatment cycles					
mean±SD	3.24±2.38	2.80±2.23	2.00±1.00	2.00±0.00	1.67±1.56
min	1	1	1	2	1
max	10	8	3	2	3
Current Polyoxidonium prescription					
Number of injections					
mean±SD	7.84±2.52	9.14±1.89	6.94±2.51	7.83±2.53	8.28±2.40
min	1	5	5	5	5
max	10	10	10	10	10
Subjects prescribed different number of injections, n (%)					
1 injection	1 (0.5)	0	0	0	0
5 injections	82 (42.3)	36 (17.2)	11 (61.1)	10 (43.5)	20 (34.5)
10 injections	111 (57.2)	173 (82.8)	7 (38.9)	13 (56.5)	38 (65.5)
Daily dose					
mean±SD	5.97±0.36	6.00±0.00	6.00±0.00	6.00±0.00	6.00±0.00
min	1	6	6	6	6
max	6	6	6	6	6
Polyoxidonium exposure					
Treatment duration					
mean±SD	22.11±8.91	22.38±6.57	18.50±12.50	20.35±10.49	20.17±8.73
min	4	4	4	4	6
max	57	43	43	31	30
Number of doses taken	7.88±2.57	9.14±1.90	7.50±2.57	8.26±2.44	8.38±2.38
mean±SD	1	4	5	5	5
min	11	10	10	10	11
max					

Table 11. *continued*

	Chronic recurrent bacterial infection	**Chronic recurrent viral infection**	**Acute bacterial infection**	**Acute viral infection**	**Allergic disease**
	n=194	n=209	n=18	n=23	n=58
Total dose, mg					
mean±SD	47.06±15.70	54.67±11.77	45.00±15.44	49.57±14.61	50.28±14.30
min	6	15	30	30	30
max	66	60	60	60	66
Subjects with dosage changes*, n (%)	176 (90.7)	205 (98.1)	16 (88.9)	21 (91.3)	52 (89.7)
not changed	4 (2.1)	2 (1.0)	0	0	0
reduced	14 (7.2)	2 (1.0)	2 (11.1)	2 (8.7)	6 (10.3)
increased					

** difference in number of doses (i.e., injections) prescribed and received*

Table 12. *Global tolerability assessment by investigators and subjects at the end of study in different therapeutic indication subgroups, n (%)*

	All subjects		**Chronic recurrent bacterial infection**		**Chronic recurrent viral infection**		**Acute bacterial infection**		**Acute viral infection**		**Allergic disease**	
	Study end	**Follow-up**	**Study end**	**Follow-up**	**Study end**	**Follow-up**	**Study end**	**Follow-up**	**Study end**	**Follow-up**	**Study end**	**Follow-up**
Investigators' assessment												
very good	400 (79.7)	406 (80.9)	154 (80.2)	161 (83.4)	186 (89.0)	185 (88.5)	11 (61.1)	11 (61.1)	16 (69.6)	15 (65.2)	33 (56.9)	34 (58.6)
good	97 (19.3)	87 (17.3)	38 (19.8)	27 (14.0)	20 (9.6)	21 (10.0)	7 (38.9)	7 (38.9)	7 (30.4)	8 (34.8)	25 (43.1)	24 (41.4)
moderate	2 (0.4)	7 (1.4)	0	5 (2.6)	2 (1.0)	2 (1.0)	0	0	0	0	0	0
poor	1 (0.2)	1 (0.2)	0	0	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Subjects' assessment												
very good	378 (75.3)	374 (74.5)	141 (77.5)	137 (78.7)	182 (88.3)	175 (89.8)	10 (55.6)	12 (66.7)	15 (65.2)	18 (78.3)	30 (52.6)	31 (56.4)
good	106 (21.1)	89 (17.7)	40 (22.0)	35 (20.1)	23 (11.2)	19 (9.7)	8 (44.4)	6 (33.3)	8 (34.8)	5 (21.7)	27 (47.4)	24 (43.6)
moderate	1 (0.2)	2 (0.4)	1 (0.5)	2 (1.1)	0	0	0	0	0	0	0	0
poor	1 (0.2)	1 (0.2)	0	0	1	1	0	0	0	0	0	0

Table 13. *Global improvement assessment by investigators and subjects at the end of study in different therapeutic indication subgroups, n (%)*

	All subjects		Chronic recurrent bacterial infection		Chronic recurrent viral infection		Acute bacterial infection		Acute viral infection		Allergic disease	
	Study end	Follow-up	Study end	Follow-up	Study end	Follow-up	Study end	Follow-up	Study end	Follow-up	Study end	Follow-up
Investigators' assessment												
complete resolution	131 (26.1)	145 (28.9)	52 (27.1)	59 (30.6)	68 (32.5)	68 (32.5)	2 (11.1)	3 (16.7)	1 (4.3)	5 (21.7)	8 (13.8)	10 (17.2)
marked improvement	281 (56.0)	268 (53.4)	91 (47.4)	85 (44.0)	119 (56.9)	116 (55.5)	13 (72.2)	14 (77.8)	20 (87.0)	16 (69.6)	38 (65.5)	37 (63.8)
moderate improvement	73 (14.5)	68 (13.5)	44 (22.9)	39 (20.2)	16 (7.7)	19 (9.1)	3 (16.7)	1 (5.6)	1 (4.3)	1 (4.3)	9 (15.5)	8 (13.8)
slight improvement	11 (2.2)	12 (2.4)	4 (2.1)	5 (2.6)	3 (1.4)	3 (1.4)	0	0	1 (4.3)	1 (4.3)	3 (5.2)	3 (5.2)
no appreciable improvement	4 (0.8)	8 (1.6)	1 (0.5)	5 (2.6)	3 (1.4)	3 (1.4)	0	0	0	0	0	0
Subjects' assessment												
greatly improved	180 (35.9)	191 (38.0)	71 (37.4)	69 (37.7)	83 (40.5)	87 (43.3)	7 (38.9)	8 (44.4)	6 (27.3)	12 (54.5)	13 (22.8)	15 (27.3)
somewhat improved	304 (60.6)	272 (54.2)	115 (60.5)	105 (57.4)	118 (57.6)	108 (53.7)	11 (61.1)	10 (55.6)	16 (72.7)	10 (45.5)	44 (77.2)	39 (70.9)
same	5 (1.0)	16 (3.2)	4 (2.1)	9 (4.9)	1 (0.5)	6 (3.0)	0	0	0	0	0	1 (1.8)
somewhat worse	2 (0.4)	0	0		2 (1.0)		0		0		0	
much worse	1 (0.2)	0	0		1 (0.5)		0		0		0	

Table 14. *Mean duration of primary treatment of disease of interest (days)*

Pharmaco-terapeutic group (ATC level 2)	All subjects	Chronic recurrent bacterial infection	Chronic recurrent viral infection	Acute bacterial infection	Acute viral infection	Allergic disease
Antidiarrheals, intestinal antiinflammatory/ antiinfective agents (A07)						
n	7	6	0	0	1	0
mean±SD	10.29±5.28	11.33±4.93			4	
min	4	6			4	
max	17	17			4	
Vitamins (A11)						
n	7	4	1	0	2	0
mean±SD	7.86±2.04	8.25±2.63	8		7.00±1.41	
min	6	6	8		6	
max	11	11	8		8	
Antifungals for dermatological use (D01)						
n	1	0	0	0	1	0
mean±SD	4				4	
min	4				4	
max	4				4	
Emollients and protectives (D02)						
n	1	0	0	1	0	0
mean±SD	8			8		
min	8			8		
max	8			8		
Preparations for treatment of wounds and ulcers (D03)						
n	2	0	1	0	1	0
mean±SD	38.50±33.23		15		62	
min	15		15		62	
max	62		15		62	
Antipsoriatics (D05)						
n	1	1	0	0	0	0
mean±SD	24	24				
min	24	24				
max	24	24				
Antibiotics and chemotherapeutics for dermatological use (D06)						
n	2	0	1	0	0	1
mean±SD	15.00±11.31		23			7
min	7		23			7
max	23		23			7
Corticosteroids, dermatological preparations (D07)						
n	5	3	0	0	0	2
mean±SD	36.00±40.82	41.33±16.00				28.00±29.70
min	6	6				7
max	102	102				49
Antiseptics and disinfectants (D08)						
n	3	1	0	2	0	0
mean±SD	17.00±2.65	15		18.00±2.83		
min	15	15		16		
max	20	15		20		

n, number of subjects taking medication

Table 14. *continued*

Pharmaco-terapeutic group (ATC level 2)	All subjects	Chronic recurrent bacterial infection	Chronic recurrent viral infection	Acute bacterial infection	Acute viral infection	Allergic disease
Corticosteroids for systemic use (H02)						
n	1	0	0	0	0	1
mean±SD	568					568
min	568					568
max	568					568
Antibacterials for systemic use (J01)						
n	17	9	0	6	1	1
mean±SD	10.53±8.97	12.33±11.82		6.67±2.34	14	14
min	3	4		3	14	14
max	33	33		10	14	14
Antivirals for systemic use (J05)						
n	10	0	7	0	3	0
mean±SD	27.40±31.14		35.43±24.00		8.67±3.79	
min	6		7		6	
max	87		87		13	
*Vaccines (J07)**						
n	5	4	1	0	0	0
mean±SD	23.20±16.39	27.25±15.78	7			
min	6	6	7			
max	44	44	7			
Antiinflammatory and antirheumatic products (M01)						
n	2	0	0	0	2	0
mean±SD	4.50±2.12				4.50±2.12	
min	3				3	
max	6				6	
Other drugs for disorders of the musculo-skeletal system (M09)						
n	1	0	0	0	1	0
mean±SD	77				77	
min	77				77	
max	77				77	
Analgesics (N02)						
n	3	0	0	2	1	0
mean±SD	3.00±0.00			3.00±0.00	3	
min	3			3	3	
max	3			3	3	
Nasal preparations (R01)						
n	14	7	1	0	0	6
mean±SD	288.36±911.81	512.57±1293.32	7			73.67±113.47
min	3	7				3
max	3445	3445				294
Drugs for obstructive airway diseases (R03)						
n	11	3	1	3	1	3
mean±SD	601.82±941.31	1815.67±1129.15	513	2.00±3.46	266	129.33±108.00
min	0	1026	513	0	266	40
max	3109	3109	513	6	266	240

*n, number of subjects taking medication; *ribomunyl, bacterial lysate*

Table 14. *continued*

Pharmaco-terapeutic group (ATC level 2)	All subjects	Chronic recurrent bacterial infection	Chronic recurrent viral infection	Acute bacterial infection	Acute viral infection	Allergic disease
Cough and cold preparations (R05)						
n	2	0	0	1	1	0
mean±SD	10.00±5.66			6	14	
min	6			6	14	
max	14			6	14	
Antihistamines for systemic use (R06)						
n	23	8	0	0	1	14
mean±SD	151.35±244.53	210.75±321.70			4	127.93±202.56
min	1	1			4	6
max	786	786			4	604
Ophthalmologicals (S01)						
n	4	1	1	0	2	0
mean±SD	62.25±38.38	109	15		62.50±0.71	
min	15	109	15		62	
max	109	109	15		63	
All other therapeutic products (V03)						
n	1	0	0	0	0	1
mean±SD	79					79
min	79					79
max	79					79
General nutrients (V06)						
n	1	0	0	0	0	1
mean±SD	49					49
min	49					49
max	49					49

n, number of subjects taking medication

Table 15. *Symptoms of disease of interest at baseline, n (%)*

Disease symptoms	All subjects	Chronic recurrent bacterial infection	Chronic recurrent viral infection	Acute bacterial infection	Acute viral infection	Allergic disease
	N=502	n=194	n=209	n=18	n=23	n=58
Abdominal pain	1 (0.2)	-	-	-	-	1 (1.7)
Abscess	1 (0.2)	1 (0.5)	-	-	-	-
Angular cheilitis	1 (0.2)	1 (0.5)	-	-	-	-
Anogenital warts	1 (0.2)	-	1 (0.5)	-	-	-
Aphonia	1 (0.2)	-	-	-	1 (4.3)	-
Arthralgia	3 (0.6)	1 (0.5)	-	1 (5.6)	1 (4.3)	-
Asthenia	4 (0.8)	-	3 (1.4)	-	1 (4.3)	-
Blister	1 (0.2)	1 (0.5)	-	-	-	-
Bronchial irritation	1 (0.2)	-	1 (0.5)	-	-	-
Chest pain	2 (0.4)	-	-	1 (5.6)	1 (4.3)	-
Chills	4 (0.8)	-	-	-	4 (17.4)	-
Cough	27 (5.4)	9 (4.6)	14 (6.7)	3 (16.7)	1 (4.3)	-
Dermatitis	1 (0.2)	-	-	-	-	1 (1.7)
Diarrhea	1 (0.2)	-	-	-	-	1 (1.7)
Dyslalia	1 (0.2)	-	-	-	1 (4.3)	-
Dysphonia	3 (0.6)	1 (0.5)	2 (1.0)	-	1 (4.3)	-
Dyspnea	1 (0.2)	1 (0.5)	-	-	-	-
Dysuria	4 (0.8)	4 (2.1)	-	-	-	-
Dry skin	3 (0.6)	-	1 (0.5)	-	-	2 (3.4)
Ear pain	1 (0.2)	-	-	-	1 (4.3)	-
Eczema	2 (0.4)	-	-	-	-	2 (3.4)
Eye abscess	1 (0.2)	1 (0.5)	-	-	-	-
Eye discharge	1 (0.2)	1 (0.5)	-	-	-	-
Eye oedema	1 (0.2)	-	-	-	1 (4.3)	-
Eye pruritus	1 (0.2)	1 (0.5)	-	-	-	-
Eyelid oedema	1 (0.2)	-	1 (0.5)	-	-	-
Erythema	6 (1.2)	2 (1.0)	-	-	-	4 (6.9)
Facial pain	1 (0.2)	1 (0.5)	-	-	-	-
Fatigue	13 (2.6)	3 (1.5)	8 (3.8)	-	-	2 (3.4)
Granuloma annulare	1 (0.2)	1 (0.5)	-	-	-	-

Table 15. *continued*

Disease symptoms	All subjects	Chronic recurrent bacterial infection	Chronic recurrent viral infection	Acute bacterial infection	Acute viral infection	Allergic disease
	N=502	n=194	n=209	n=18	n=23	n=58
Headache	7 (1.4)	1 (0.5)	1 (0.5)	-	2 (8.7)	3 (5.2)
Herpes virus infection	6 (1.2)	1 (0.5)	5 (2.4)	-	-	-
Hyperkeratosis	1 (0.2)	-	-	1 (5.6)	-	-
Hyposmia	1 (0.2)	1 (0.5)	-	-	-	-
Impaired healing	1 (0.2)	1 (0.5)	-	-	-	-
Infection	1 (0.2)	-	-	1 (5.6)	-	-
Joint stiffness	1 (0.2)	-	1 (0.5)	-	-	-
Lacrimation increased	1 (0.2)	-	1 (0.5)	-	-	-
Lip blister	2 (0.4)	-	2 (1.0)	-	-	-
Lip oedema	1 (0.2)	-	-	-	1 (4.3)	-
Lip pain	3 (0.6)	-	2 (1.0)	-	1 (4.3)	-
Lymph node pain	1 (0.2)	-	-	-	1 (4.3)	-
Lymphadenopathy	1 (0.2)	-	-	-	1 (4.3)	-
Myalgia	3 (0.6)	-	-	1 (5.6)	-	-
Muscle twitching	1 (0.2)	1 (0.5)	-	-	2 (8.7)	-
Nasal congestion	8 (1.6)	3 (1.5)	3 (1.4)	-	-	2 (3.4)
Neuralgia	1 (0.2)	-	1 (0.5)	-	-	-
Night sweats	1 (0.2)	-	1 (0.5)	-	-	-
Ocular hyperaemia	1 (0.2)	1 (0.5)	-	-	-	-
Oral disorder	1 (0.2)	-	1 (0.5)	-	-	-
Oral herpes	2 (0.4)	1 (0.5)	-	-	1 (4.3)	-
Oropharyngeal pain	11 (2.2)	4 (2.1)	5 (2.4)	2 (11.1)	-	-
Pain	3 (0.6)	1 (0.5)	1 (0.5)	1 (5.6)	-	-
Pain in extremity	1 (0.2)	-	-	-	1 (4.3)	-
Pain of skin	2 (0.4)	-	2 (1.0)	-	-	-
Pallor	1 (0.2)	-	1 (0.5)	-	-	-
Pelvic pain	5 (1.0)	5 (2.6)	-	-	-	-
Penile erythema	1 (0.2)	1 (0.5)	-	-	-	-

Table 15. *continued*

Disease symptoms	All subjects	Chronic recurrent bacterial infection	Chronic recurrent viral infection	Acute bacterial infection	Acute viral infection	Allergic disease
	N=502	n=194	n=209	n=18	n=23	n=58
Peripheral swelling	1 (0.2)	-	-	1 (5.6)	-	-
Pharyngeal erythema	2 (0.4)	1 (0.5)	1 (0.5)	-	-	-
Pilonidal cyst	1 (0.2)	1 (0.5)	-	-	-	-
Pollakiuria	1 (0.2)	1 (0.5)	-	-	-	-
Postoperative wound complication	1 (0.2)	1 (0.5)	-	-	-	-
Proctalgia	1 (0.2)	-	-	1 (5.6)	-	-
Productive cough	2 (0.4)	2 (1.0)	-	-	-	-
Pruritus	9 (1.8)	3 (1.5)	-	1 (5.6)	1 (4.3)	4 (6.9)
Psychomotor retardation	1 (0.2)	-	1 (0.5)	-	-	-
Purulent discharge	6 (1.2)	3 (1.5)	-	3 (16.7)	-	-
Rash	4 (0.8)	-	-	1 (5.6)	-	3 (5.2)
Rash papular	2 (0.4)	-	-	-	2 (8.7)	1 (1.7)
Rash pustular	1 (0.2)	-	-	-	-	-
Rhinitis	4 (0.8)	1 (0.5)	1 (0.5)	-	-	2 (3.4)
Rhinorrhea	5 (1.0)	3 (1.5)	-	-	-	2 (3.4)
Secretion discharge	8 (1.6)	1 (0.5)	7 (3.3)	-	-	-
Sinus headache	1 (0.2)	-	-	-	1 (4.3)	-
Sinusitis	3 (0.6)	1 (0.5)	1 (0.5)	1 (5.6)	-	-
Skin burning sensation	1 (0.2)	-	-	-	1 (4.3)	-
Skin disorder	1 (0.2)	-	-	-	-	1 (1.7)
Skin erosion	1 (0.2)	-	-	-	-	1 (1.7)
Skin exfoliation	2 (0.4)	1 (0.5)	-	-	-	1 (1.7)
Skin fissures	1 (0.2)	-	-	-	-	1 (1.7)
Skin lesion	1 (0.2)	1 (0.5)	-	-	-	-
Skin necrosis	1 (0.2)	-	-	1 (5.6)	-	-
Skin papilloma	3 (0.6)	-	3 (1.4)	-	-	-
Sneezing	1 (0.2)	-	-	-	-	1 (1.7)

Table 15. *continued*

Disease symptoms	All subjects	Chronic recurrent bacterial infection	Chronic recurrent viral infection	Acute bacterial infection	Acute viral infection	Allergic disease
	N=502	n=194	n=209	n=18	n=23	n=58
Speech disorder	9 (1.8)	6 (3.1)	-	1 (5.6)	-	2 (3.4)
Sputum abnormal	3 (0.6)	2 (1.0)	-	1 (5.6)	-	-
Subcutaneous abscess	1 (0.2)	1 (0.5)	-	-	-	-
Swelling	1 (0.2)	-	-	-	-	-
Throat irritation	2 (0.4)	1 (0.5)	-	-	-	1 (1.7)
Upper-airway cough syndrome	9 (1.8)	3 (1.5)	1 (0.5)	2 (11.1)	2 (8.7)	1 (1.7)
Vaginal discharge	1 (0.2)	1 (0.5)	-	-	-	-
Vomiting	1 (0.2)	-	-	-	1 (4.3)	-
Wheezing	4 (0.8)	3 (1.5)	-	-	1 (4.3)	-
Not specified	381 (75.9)	145 (74.5)	172 (82.3)	8 (44.4)	14 (60.9)	42 (72.4)

Table 16. *New symptoms of diseases of interest observed during the study, n (%)*

Disease symptoms	**All subjects**
Bronchitis	2 (0.4)
Fatigue	1 (0.2)
Furuncle	2 (0.4)
Genital herpes	1 (0.2)
Oropharyngeal pain & Cough	1 (0.2)
Pain in extremity	1 (0.2)
Pharyngitis	1 (0.2)
Skin hyperpigmentation	1 (0.2)

Table 17. *Adverse events listing*

Subject ID	Reported term	PT English term	SOC	Start date	Worsening date	End date	Severity	Serious	Seriousness category	Relation to Polyoxidonium	Action with Polyoxidonium	Outcome	Caused study discontinuation	Time from injection to AE (days)	AE related to effect on renal system
0608	Acute bronchitis	Bronchitis	Infections and Infestations	10-OCT-2016		15-OCT-2016	mild	no		not related	interrupted	resolved	no	6	no
0706	lym diseas worsening	Lyme disease - Condition aggravated	Infections and Infestations General disorders and administration site condition	30-SEP-2016			mild	no		not related	none	not resolved	no	2	no
0706	Pain in extremities	Pain in extremity	Musculoskeletal and connective tissue disorders	30-SEP-2016			mild	no		not related	none	resolving	no	2	no
0706	Fatigue	Fatigue	General disorders and administration site conditions	30-SEP-2016			mild	no		not related	none	resolving	no	2	no
0807	hepatric test parameters elevation	Liver function test increased	Investigations	27-JUL-2016		02-AUG-2016	mild	yes	Hospitalization	not related	withdrawn	resolved with sequelae	yes	7	no
1202	herpes genital	Genital herpes	Infections and Infestations	19-SEP-2016		30-SEP-2016	mild	no		not related	none	resolved	no	5	no
1303	Diarrhea	Diarrhoea	Gastrointesti-nal disorders	19-SEP-2016		19-SEP-2016	mild	no		not related	none	resolved	no	5	no

Table 17. *continued*

Sub-ject ID	Reported term	PT English term	SOC	Start date	Worsen-ing date	End date	Seve-rity	Seriu os	Serious-ness category	Relation to Polyoxi-donium	Action with Polyoxi-donium	Outcome	Caused study discon-ti-nuation	Time from injection to AE (days)	AE related to effect on renal system
1304	Sickness	Mailaise	General disorders and administra-tion site conditions	29-AUG-2016		29-AUG-2016	mild	no		not related	none	resolved	no	3	no
1308	Slight edema at the injection site	Injection site oedema	General disorders and administra-tion site conditions	09-SEP-2016		09-SEP-2016	mild	no		not related	none	resolved	no	2	no
1311	Difficult breath through the nose	Dyspnoea	Respiratory, thoracic and mediastinal disorders	10-SEP-2016		19-SEP-2016	mild	no		not related	none	resolved	no	1	no
1313	Sore throat	Oropharynge al pain	Respiratory, thoracic and mediastinal disorders	03-OCT-2016		04-OCT-2016	mild	no		not related	none	resolved	no	4	no
1314	Fatigue, malaise, subfebrile, spill	Fatigue	General disorders and administratio n site conditions	23-SEP-2016		26-SEP-2016	mode rate	no		related	none	resolved	no	4	no
1314	Restless	Restlessness	Psychiatric disorders	07-SEP-2016		08-SEP-2016	mild	no		related	none	resolved	no	0	no
1314	Feeling of warmth	Feeling hot	General disorders and administra-tion site conditions	09-SEP-2016		10-SEP-2016	mild	no		related	none	resolved	no	2	no

Table 17. *continued*

Sub-ject ID	Reported term	PT English term	SOC	Start date	Worsen-ing date	End date	Seve-rity	Seriu os	Serious-ness category	Relation to Polyoxi-donium	Action with Polyoxi-donium	Outcome	Caused study discon-ti-nuation	Time from injection to AE (days)	AE related to effect on renal system
1314	Pocit vnútorného tepla a slabosť, ľahko zvýšená teplota	Feeling hot	General disorders and administration site conditions	12-SEP-2016		13-SEP-2016	mild	no		related	none	resolved	no	3	no
1314	A feeling of inner warmth and weakness, light fever	Pyrexia	General disorders and administra-tion site conditions	14-SEP-2016		15-SEP-2016	mild	no		related	none	resolved	no	2	no
1314	A feeling of inner warmth and weakness, burning and itching of the upper extremities a slightly elevated tempera-ture	Asthenia	General disorders and administra-tion site conditions	19-SEP-2016		22-SEP-2016	mild	no		related	none	resolved	no	5	no
1314	Weakness, subfebrile	Pyrexia	General disorders and administra-tion site conditions	06-OCT-2016		07-OCT-2016	mild	no		related	none	resolved	no	13	no

Table 17. *continued*

Sub-ject ID	Reported term	PT English term	SOC	Start date	Worsen-ing date	End date	Seve-rity	Seriu os	Serious-ness category	Relation to Polyoxi-donium	Action with Polyoxi-donium	Outcome	Caused study discon-ti-nuation	Time from injection to AE (days)	AE related to effect on renal system
1314	Weakness, subfebrile, headache, feeling virus infections, herpes nose, difficulty swallowing	Pyrexia	General disorders and administra-tion site conditions	11-OCT-2016		17-OCT-2016	mild	no		related	none	resolved	no	5	no
1319	Epistaxis	Epistaxis	Respiratory, thoracic and mediastinal disorders	23-SEP-2016		23-SEP-2016	mild	no		not related	none	resolved	no	2	no
1327	Small hematoma at the injection site	Injection site haematoma	General disorders and administra-tion site conditions	23-SEP-2016		25-SEP-2016	mild	no		not related	none	resolved	no	0	no
1329	Bronchial asthma – Impair-ment	Asthma	Respiratory, thoracic and mediastinal disorders	01-OCT-2016		16-OCT-2016	mode rate	no		not related	none	resolved	no	1	no
1329	Bronchial asthma – Impair-ment	Asthma	Respiratory, thoracic and mediastinal disorders	19-OCT-2016		20-OCT-2016	mild	no		not related	none	resolved	no	2	no
1331	Difficulty breathing	Dyspnoea	Respiratory, thoracic and mediastinal disorders	11-OCT-2016		13-OCT-2016	mild	no		not related	none	resolved	no	1	no
1331	Dyspnoea	Dyspnoea	Respiratory, thoracic and mediastinal disorders	19-OCT-2016			mild	no		not related	none	resolving	no	2	no

Table 17. *continued*

Subject ID	Reported term	PT English term	SOC	Start date	Worsening date	End date	Severity	Serious	Seriousness category	Relation to Polyoxidonium	Action with Polyoxidonium	Outcome	Caused study discontinuation	Time from injection to AE (days)	AE related to effect on renal system
1331	Dyspnoea	Dyspnoea	Respiratory, thoracic and mediastinal disorders	19-OCT-2016	24-OCT-2016		mild	no		not related	none	resolving	no	2	no
1340	Herpes lips	Oral herpes	Infections and Infestations	25-OCT-2016		27-OCT-2016	mild	no		not related	none	resolved	no	1	no
1340	Herpes lips	Oral herpes	Infections and Infestations	02-NOV-2016		03-NOV-2016	mild	no		not related	none	resolved	no	6	no
1340	Vertigo	Vertigo	Ear and labyrinth disorders	14-NOV-2016			moderate	no		not related	withdrawn	not resolved	yes	3	no
1340	Vertigo – Hospitalization in the department of neurology	Vertigo	Ear and labyrinth disorders	16-NOV-2016		19-NOV-2016	moderate	yes	Hospitalization	not related	interrupted	not resolved	no	5	no
1343	Herpes lips	Oral herpes	Infections and Infestations	01-DEC-2016		05-DEC-2016	mild	no		not related	none	resolved	no	3	no
1501	D16+56+ decreased	Natural killer cell count decreased	Investigations	25-JUL-2016			mild	no		not related	none	resolving	no	3	no
1531	hyperpigmentation	Skin hyperpigmentation	Skin and subcutaneous tissue disorders	12-OCT-2016			mild	no		not related	none	resolved	no	2	no
1537	renal insufficiency	Renal failure	Renal and urinary disorders	08-NOV-2016			mild	no		not related	none	resolving	no	0	yes

Table 18. *Adverse events: number observed, rate of occurence and subject identifications*

SOC level	Mild		Moderate		Severe		Total		Total
	Related	NR*	Related	NR	Related	NR	Related	NR	R**+NR
Infections and Infestations									
Bronchitis	0	1 (0.2%) 608***	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Genital herpes	0	1 (0.2%) 1202	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Oral herpes	0	3 (0.6%) 1340 1340 1343	0	0	0	0	0	3 (0.6%)	3 (0.6%)
Infections and Infestations **General disorders and administration site condition**									
Lyme disease - Condition aggravated	0	1 (0.2%) 706	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Psychiatric disorders									
Restlessness	1 (0.2%) 1314	0	0	0	0	0	1 (0.2%)	0	1 (0.2%)
Ear and labyrinth disorders									
Vertigo	0	0	0	2 (0.4%) 1340	0	0	0	2 (0.4%)	2 (0.4%)
Respiratory, thoracic and mediastinal disorders									
Dyspnoea	0	4 (0.8) 1311 1331 1331 1331	0	0	0	0	0	4 (0.8)	4 (0.8)

**NR, not related; **R, related, ***Subject ID*

Table 18. *continued*

SOC level	Mild		Moderate		Severe		Total		Total
	Related	NR*	Related	NR	Related	NR	Related	NR	R**+NR
Oropharyngeal pain	0	1 (0.2%) 1313	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Epistaxis	0	1 (0.2%) 1319	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Asthma	0	1 (0.2%) 1329	0	1 (0.2%) 1329	0	0	0	2 (0.4%)	2 (0.4%)
Gastrointestinal disorders									
Diarrhoea	0	1 (0.2%) 1303	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Skin and subcutaneous tissue disorders									
Skin hyperpigmentation	0	1 (0.2%) 1531	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Musculoskeletal and connective tissue disorders									
Pain in extremity	0	1 (0.2%) 706	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Renal and urinary disorders									
Renal failure	0	1 (0.2%) 1537	0	0	0	0	0	1 (0.2%)	1 (0.2%)
General disorders and administration site conditions									
Fatigue	0	1 (0.2%) 706	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Malaise	0	1 (0.2%) 1304	0	0	0	0	0	1 (0.2%)	1 (0.2%)

**NR, not related; **R, related*

Table 18. *continued*

SOC level	Mild		Moderate		Severe		Total		Total
	Related	NR*	Related	NR	Related	NR	Related	NR	R**+NR
Injection site oedema	0	1 (0.2%) 1308	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Fatigue	0	0	1 (0.2%) 1314	0	0	0	1 (0.2%)	0	1 (0.2%)
Feeling hot	2 (0.4%) 1314	0	0	0	0	0	2 (0.4%)	0	2 (0.4%)
Pyrexia	3 (0.6%) 1314	0	0	0	0	0	3 (0.6%)	0	3 (0.6%)
Asthenia	1 (0.2%) 1314	0	0	0	0	0	1 (0.2%)	0	1 (0.2%)
Injection site haematoma	0	1 (0.2%) 1327	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Investigations									
Liver function test increased	0	1 (0.2%) 807	0	0	0	0	0	1 (0.2%)	1 (0.2%)
Natural killer cell count decreased	0	1 (0.2%) 1501	0	0	0	0	0	1 (0.2%)	1 (0.2%)
TOTAL	**7**	**23**	**1**	**3**	**0**	**0**	**8**	**26**	**34**

**NR, not related; **R, related*

Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1	Final version 2.0	5 April 2016	Study protocol
2	Version 1.0	31 May 2016	Annotated Case Report Form*
3	Version 1.1	05 Apr 2016	List of investigators and study sites*
4	Final version 1.1	30 Jan 2017	Statistical analysis plan*
5	NA		Coordinating Investigator's Signature
6	NA		Sponsor's Responsible Person's Signature
7	NA		Manufacturing Authorization Holder Signatue
8	NA		Medical Monitor Signature
9	NA		Clinical Research Organization Signature

* *available on request*

COORDINATING INVESTIGATOR SIGNATURE

STUDY TITLE:

MULTICENTER PROSPECTIVE OPEN-LABEL NON-INTERVENTIONAL UNCONTROLLED POST-AUTHORISATION SAFETY STUDY (PASS) TO EVALUATE THE SAFETY PROFILE OF POLYOXIDONIUM IN DAILY PRACTICE

STUDY NUMBER:
PETRO/2015-01

REPORT VERSION:
Final version 1.0, 8 May 2017

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

COORDINATING INVESTIGATOR: **Peter Pružinec, Prof., MUDr. Csc**

AFFILIATON: **MONITOR PLUS, s.r.o.**

SIGNATURE: 

DATE: 16. 05 2017

SPONSOR'S RESPONSIBLE PERSON'S SIGNATURE

STUDY TITLE:

MULTICENTER PROSPECTIVE OPEN-LABEL NON-INTERVENTIONAL UNCONTROLLED POST-AUTHORISATION SAFETY STUDY (PASS) TO EVALUATE THE SAFETY PROFILE OF POLYOXIDONIUM IN DAILY PRACTICE

STUDY NUMBER:
PETRO/2015-01

REPORT VERSION:
Final version 1.0, 8 May 2017

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

SPONSOR'S RESPONSIBLE PERSON: **Natalia V. Chirun, PhD, MD**

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DATE: 11.05.2017.

MARKETING AUTHORIZATION HOLDER SIGNATURE

STUDY TITLE:

MULTICENTER PROSPECTIVE OPEN-LABEL NON-INTERVENTIONAL UNCONTROLLED POST-AUTHORISATION SAFETY STUDY (PASS) TO EVALUATE THE SAFETY PROFILE OF POLYOXIDONIUM IN DAILY PRACTICE

STUDY NUMBER:
PETRO/2015-01

REPORT VERSION:
Final version 1.0, 8 May 2017

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

QPPV of the MARKETING AUTHORIZATION HOLDER:	**Mgr. Peter Klembala**
AFFILIATON:	**Medigroup s.r.o.**
SIGNATURE:	
DATE:	12-May-2017

MEDICAL MONITOR SIGNATURE

STUDY TITLE:

MULTICENTER PROSPECTIVE OPEN-LABEL NON-INTERVENTIONAL UNCONTROLLED POST-AUTHORISATION SAFETY STUDY (PASS) TO EVALUATE THE SAFETY PROFILE OF POLYOXIDONIUM IN DAILY PRACTICE

STUDY NUMBER:
PETRO/2015-01

REPORT VERSION:
Final version 1.0, 8 May 2017

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

MEDICAL MONITOR: **Yuri Zaresky, MD**

AFFILIATON: **ZM Company**

SIGNATURE: Yuri Zaretsky, M.D.

DATE:

Digitally signed by Yuri Zaretsky, M.D.
DN: cn=Yuri Zaretsky, M.D., o=ZMCompany, Inc., ou=Director, Medical Affairs, email=yurizaretsky@zmcompany.ca, c=CA
Date: 2017.05.15 13:46:33 +05'00'

CLINCAL RESEARCH ORGANIZATION SIGNATURE

STUDY TITLE:

MULTICENTER PROSPECTIVE OPEN-LABEL NON-INTERVENTIONAL UNCONTROLLED POST-AUTHORISATION SAFETY STUDY (PASS) TO EVALUATE THE SAFETY PROFILE OF POLYOXIDONIUM IN DAILY PRACTICE

STUDY NUMBER:
PETRO/2015-01

REPORT VERSION:
Final version 1.0, 8 May 2017

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study

CLINICAL RESEARCH ORGANIZATION : **Nerijus Luksys**

AFFILIATON: **CRO Biomapas**

SIGNATURE: 

DATE: 12 MAY 2017