## PASS information

<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>Multicenter prospective open-label non-interventional uncontrolled Post-Authorisation Safety Study (PASS) to evaluate the safety profile of Polyoxidonium in daily practice</th>
</tr>
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<tbody>
<tr>
<td><strong>Version identifier of the final study report</strong></td>
<td>Final version 1.0</td>
</tr>
<tr>
<td><strong>Date of last version of the final study report</strong></td>
<td>8 May 2017</td>
</tr>
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</table>
| **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 |
| **Author** | Natalia V. Chirun, PhD, MD  
NPO PETROVAXPHARM |

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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 Pruzinec, Prof., MUDr. Csc

MONITOR PLUS, s.r.o.
## 2. List of abbreviations

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

Co-ordinating investigator/Consultant expert in immunology-allergology

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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).

<table>
<thead>
<tr>
<th>Name</th>
<th>Address</th>
<th>Responsibilities</th>
<th>Contact person (s)</th>
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<tr>
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<td>Krasnaya Presnya 22, Moscow, 123022, Russia</td>
<td>Sponsor</td>
<td>Natalia V. Chirun, PhD, MD Medical Director Tel.: +7(495) 730-75-45 ext. 125 e-mail:<a href="mailto:chirunnv@petrovax.ru">chirunnv@petrovax.ru</a></td>
</tr>
<tr>
<td>MEDIGROUP s.r.o.</td>
<td>Mlynské Nivy 54 821 05 Bratislava, Slovak Republic</td>
<td>Marketing Authorisation Holder</td>
<td>Peter Klembala, QPPV, Tel.: +421 917 273 156 e-mail: <a href="mailto:peter.klembala@klemtrade.sk">peter.klembala@klemtrade.sk</a></td>
</tr>
<tr>
<td>ZM Company, Inc.</td>
<td>ZM Company 96 Russell Street Georgetown, ON L7G 5Z1 Canada</td>
<td>Medical Monitor</td>
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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) occurred 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

<table>
<thead>
<tr>
<th>Study procedures</th>
<th>Day 1</th>
<th>Interim visits (3 to 8, depending on indication)</th>
<th>Day 7 to 23</th>
<th>Follow-up*</th>
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<tr>
<td>Inclusion/exclusion criteria</td>
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<td></td>
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<td>Informed consent</td>
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<td>Demographic data</td>
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<tr>
<td>Medical history</td>
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<tr>
<td>Physical examination**</td>
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<tr>
<td>Information about relevant infection, allergic condition, etc.</td>
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<tr>
<td>Vital signs (blood pressure, heart rate, body temperature)**</td>
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<td>Laboratory tests**</td>
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<td>ECG**</td>
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<td>Other diagnostic procedures</td>
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<td>Adverse events</td>
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<tr>
<td>Investigator’s and subject’s assessment of tolerability and improvement</td>
<td></td>
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</tbody>
</table>

*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 °C
- BMI ≤25, >25 to 30, and >30.0 kg/m²

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 was used 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 fell 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 resolved 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

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

*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

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

*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

<table>
<thead>
<tr>
<th>Previous and current prescriptions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previous Polyoxidonium prescriptions</strong></td>
</tr>
<tr>
<td>Subjects who previously received Polyoxidonium, n (%)</td>
</tr>
<tr>
<td>Number of previous treatment cycles</td>
</tr>
<tr>
<td>mean±SD</td>
</tr>
<tr>
<td>min</td>
</tr>
<tr>
<td>max</td>
</tr>
<tr>
<td><strong>Current Polyoxidonium prescription</strong></td>
</tr>
<tr>
<td>Number of injections</td>
</tr>
<tr>
<td>mean±SD</td>
</tr>
<tr>
<td>min</td>
</tr>
<tr>
<td>max</td>
</tr>
<tr>
<td>Subjects prescribed different number of injections, n (%)</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>Daily dose</td>
</tr>
<tr>
<td>mean±SD</td>
</tr>
<tr>
<td>min</td>
</tr>
<tr>
<td>max</td>
</tr>
<tr>
<td><strong>Polyoxidonium exposure</strong></td>
</tr>
<tr>
<td>Treatment duration, days</td>
</tr>
<tr>
<td>mean±SD</td>
</tr>
<tr>
<td>min</td>
</tr>
<tr>
<td>max</td>
</tr>
<tr>
<td>Number of doses taken</td>
</tr>
<tr>
<td>mean±SD</td>
</tr>
<tr>
<td>min</td>
</tr>
<tr>
<td>max</td>
</tr>
<tr>
<td>Total dose, mg</td>
</tr>
<tr>
<td>mean±SD</td>
</tr>
<tr>
<td>min</td>
</tr>
<tr>
<td>max</td>
</tr>
<tr>
<td>Subjects with dosage changes*, n (%)</td>
</tr>
<tr>
<td>not changed</td>
</tr>
<tr>
<td>reduced</td>
</tr>
<tr>
<td>increased</td>
</tr>
</tbody>
</table>

* 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**

<table>
<thead>
<tr>
<th>Adverse Drug Reaction (ADR)</th>
<th>n</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>1 (0.2%)</td>
<td>mild</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (0.2%)</td>
<td>moderate</td>
</tr>
<tr>
<td>Feeling hot</td>
<td>2 (0.4%)</td>
<td>mild</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (0.6%)</td>
<td>mild</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (0.2%)</td>
<td>mild</td>
</tr>
</tbody>
</table>

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 (%)**

<table>
<thead>
<tr>
<th>Investigators' assessment of tolerability</th>
<th>Study end visit</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>400 (79.7)</td>
<td>406 (80.9)</td>
</tr>
<tr>
<td>Good</td>
<td>97 (19.3)</td>
<td>87 (17.3)</td>
</tr>
<tr>
<td>Moderate</td>
<td>2 (0.4)</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Poor</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Missing data</td>
<td>2 (0.4)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>

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 (%)  

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

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).

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 (%)  

<table>
<thead>
<tr>
<th>Investigators’ assessment</th>
<th>Study end visit</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete resolution</td>
<td>131 (26.1)</td>
<td>145 (28.9)</td>
</tr>
<tr>
<td>Marked improvement</td>
<td>281 (56.0)</td>
<td>268 (53.4)</td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>73 (14.5)</td>
<td>68 (13.5)</td>
</tr>
<tr>
<td>Slight improvement</td>
<td>11 (2.2)</td>
<td>12 (2.4)</td>
</tr>
<tr>
<td>No appreciable improvement</td>
<td>4 (0.8)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Missing data</td>
<td>2 (0.4)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>
Table 10.8. Subjects’ assessment of global improvement at the end of study, n (%)  

<table>
<thead>
<tr>
<th>Subjects’ assessment</th>
<th>Study end visit</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greatly improved</td>
<td>180 (35.9)</td>
<td>191 (38.0)</td>
</tr>
<tr>
<td>Somewhat improved</td>
<td>304 (60.6)</td>
<td>272 (54.2)</td>
</tr>
<tr>
<td>Same</td>
<td>5 (1.0)</td>
<td>16 (3.2)</td>
</tr>
<tr>
<td>Somewhat worse</td>
<td>2 (0.4)</td>
<td>0</td>
</tr>
<tr>
<td>Much worse</td>
<td>1 (0.2)</td>
<td>0</td>
</tr>
<tr>
<td>Missing data</td>
<td>10 (2.0)</td>
<td>23 (4.6)</td>
</tr>
</tbody>
</table>

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

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

* number of fever episodes; **number of subjects with a given symptom
Table 10.10. continued

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

* 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)×10⁹/L (range, 4.60 to 14.03 × 10⁹/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), ×10⁹/L

<table>
<thead>
<tr>
<th>Laboratory parameter</th>
<th>First measurement</th>
<th>Last measurement</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total WBC (blood)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>23</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Mean±SD</td>
<td>7.05±2.67</td>
<td>6.43±1.33</td>
<td>0.194</td>
</tr>
<tr>
<td><strong>WBC differential</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils, x10⁹/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>10</td>
<td>10</td>
<td>0.575</td>
</tr>
<tr>
<td>mean±SD</td>
<td>4.57±1.26</td>
<td>4.39±0.80</td>
<td></td>
</tr>
<tr>
<td>Neutrophils, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>7</td>
<td>7</td>
<td>0.866</td>
</tr>
<tr>
<td>mean±SD</td>
<td>58.61±7.07</td>
<td>56.39±9.35</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes, x10⁹/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>9</td>
<td>9</td>
<td>0.678</td>
</tr>
<tr>
<td>mean±SD</td>
<td>1.95±0.91</td>
<td>2.00±0.73</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes, %</td>
<td></td>
<td></td>
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<tr>
<td>n</td>
<td>7</td>
<td>7</td>
<td>0.397</td>
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<tr>
<td>mean±SD</td>
<td>30.39±6.64</td>
<td>32.77±9.98</td>
<td></td>
</tr>
<tr>
<td>Monocytes, %</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>n</td>
<td>2</td>
<td>2</td>
<td>0.655</td>
</tr>
<tr>
<td>mean±SD</td>
<td>4.31±5.65</td>
<td>7.20±0.14</td>
<td></td>
</tr>
<tr>
<td>Eosinophils, x10⁹/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>2</td>
<td>2</td>
<td>0.180</td>
</tr>
<tr>
<td>mean±SD</td>
<td>0.18±0.09</td>
<td>0.26±0.13</td>
<td></td>
</tr>
<tr>
<td>Eosinophils, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>2</td>
<td>2</td>
<td>0.655</td>
</tr>
<tr>
<td>mean±SD</td>
<td>2.15±0.49</td>
<td>2.10±1.13</td>
<td></td>
</tr>
<tr>
<td>Basophils, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>2</td>
<td>2</td>
<td>0.655</td>
</tr>
<tr>
<td>mean±SD</td>
<td>0.21±0.28</td>
<td>0.35±0.07</td>
<td></td>
</tr>
<tr>
<td><strong>Urine WBC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>2</td>
<td>2</td>
<td>0.655</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>12.50±17.68</td>
<td>0.50±0.71</td>
<td></td>
</tr>
</tbody>
</table>

*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 (%)

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Chronic recurrent bacterial infection</th>
<th>Chronic recurrent viral infection</th>
<th>Acute bacterial infection</th>
<th>Acute viral infection</th>
<th>Allergic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with at least one AE</td>
<td>19 (3.8%)</td>
<td>5 (2.6)</td>
<td>13 (6.2)</td>
<td>0</td>
<td>1 (4.3)</td>
<td>0</td>
</tr>
<tr>
<td>Subjects with at least one AE related to Polyoxidonium</td>
<td>1 (0.2)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subjects with at least one adverse renal effect</td>
<td>1 (0.2)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subjects with at least one SAE</td>
<td>2 (0.4)</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subjects with at least one SAE related to Polyoxidonium</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 10.13. Summary of adverse events

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

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

<table>
<thead>
<tr>
<th>Actions taken with Polyoxodonium</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with Polyoxidonium withdrawn due to an AE</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Subjects with Polyoxidonium dose reduced due to an AE</td>
<td>0</td>
</tr>
<tr>
<td>Subjects with Polyoxidonium interrupted due to an AE</td>
<td>2 (0.4)</td>
</tr>
</tbody>
</table>

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*

<table>
<thead>
<tr>
<th>Study site No</th>
<th>Site name</th>
<th>Enrolled subjects n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>RAFMED s.r.o.</td>
<td>31 (6.2)</td>
</tr>
<tr>
<td>02</td>
<td>Analyticko-diagnostické laboratórium a ambulancie s.r.o.</td>
<td>31 (6.2)</td>
</tr>
<tr>
<td>03</td>
<td>IMUNOSPOL s.r.o</td>
<td>39 (7.8)</td>
</tr>
<tr>
<td>04</td>
<td>Spimal s.r.o</td>
<td>11 (2.2)</td>
</tr>
<tr>
<td>05</td>
<td>Alfa El, spol s.r.o</td>
<td>9 (1.8)</td>
</tr>
<tr>
<td>06</td>
<td>Stalerg s.r.o</td>
<td>27 (5.4)</td>
</tr>
<tr>
<td>07</td>
<td>Zoll-Med s.r.o</td>
<td>30 (6.0)</td>
</tr>
<tr>
<td>08</td>
<td>Milrea s.r.o</td>
<td>71 (14.1)</td>
</tr>
<tr>
<td>09</td>
<td>Alersa s.r.o</td>
<td>14 (2.8)</td>
</tr>
<tr>
<td>10</td>
<td>Pollex s.r.o</td>
<td>30 (6.0)</td>
</tr>
<tr>
<td>11</td>
<td>Imuno s.r.o</td>
<td>80 (15.9)</td>
</tr>
<tr>
<td>12</td>
<td>Imunoalergy s.r.o</td>
<td>11 (2.2)</td>
</tr>
<tr>
<td>13</td>
<td>IMUNO - ALERGO JB, s.r.o.</td>
<td>43 (8.6)</td>
</tr>
<tr>
<td>14</td>
<td>Albatros K+K s.r.o</td>
<td>33 (6.6)</td>
</tr>
<tr>
<td>15</td>
<td>Specialized St.Svorad Hospital Nitra Zobor, Nonprofit Org.</td>
<td>42 (8.4)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>502 (100.0)</td>
</tr>
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</table>
### Table 2. Listing of subjects who withdrew from the study

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Primary reason for early withdrawal</th>
<th>Last visit before withdrawal</th>
</tr>
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<tbody>
<tr>
<td>0506</td>
<td>subject withdrew consent</td>
<td>interim visit 1</td>
</tr>
<tr>
<td>0807</td>
<td>adverse event</td>
<td>interim visit 4</td>
</tr>
<tr>
<td>1203</td>
<td>lost to follow-up</td>
<td>interim visit 1</td>
</tr>
<tr>
<td>1340</td>
<td>adverse event</td>
<td>interim visit 7</td>
</tr>
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</table>

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

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

*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*

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

<table>
<thead>
<tr>
<th>Clinical diagnosis</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gynaecological chlamydia infection</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>15 (3.0)</td>
</tr>
<tr>
<td>Herpes virus infection</td>
<td>10 (2.0)</td>
</tr>
<tr>
<td>Herpes virus infection &amp; Bacterial infection</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Herpes virus infection &amp; Bronchitis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Herpes virus infection &amp; Viral infection</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>11 (2.2)</td>
</tr>
<tr>
<td>Herpes zoster &amp; Rhinitis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>Impetigo</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Intestinal cyst</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Keratitis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Leukoplakia</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Lyme disease</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Ophthalmic herpes simplex</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Ophthalmic herpes zoster</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Oral herpes</td>
<td>12 (2.4)</td>
</tr>
<tr>
<td>Oral herpes &amp; Asthma</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Oral herpes &amp; Nasal herpes</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pemphigus</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>25 (5.0)</td>
</tr>
<tr>
<td>Pharyngotonsillitis</td>
<td>23 (4.6)</td>
</tr>
<tr>
<td>Pharyngotonsillitis &amp; Stomatitis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pilonidal cyst</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pneumonia &amp; Primary ciliary dyskinesia</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Clinical diagnosis</td>
<td>n (%)</td>
</tr>
<tr>
<td>--------------------------------------------------------</td>
<td>--------</td>
</tr>
<tr>
<td>Rash papulosquamous</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>22 (4.4)</td>
</tr>
<tr>
<td>Respiratory tract infection &amp; Urinary tract infection bacterial</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Respiratory tract infection bacterial</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Respiratory tract infection viral</td>
<td>49 (9.8)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Rhinitis allergic</td>
<td>11 (2.2)</td>
</tr>
<tr>
<td>Seasonal allergy</td>
<td>9 (1.8)</td>
</tr>
<tr>
<td>Seasonal allergy &amp; Urinary tract infection</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Seborrhoeic dermatitis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Secondary immunodeficiency &amp; Viral infection</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Sinobronchitis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>52 (10.4)</td>
</tr>
<tr>
<td>Skin bacterial infection</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Skin infection</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Skin papilloma</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>9 (1.8)</td>
</tr>
<tr>
<td>Subcutaneous abscess</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Tracheitis</td>
<td>3 (.6)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Urinary tract infection bacterial</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Urticaria chronic</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Vaginal infection</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Varicose vein</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Viral infection</td>
<td>28 (5.6)</td>
</tr>
<tr>
<td>Viral infection &amp; Aphthous ulcer</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Viral infection &amp; Candida infection</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Vulvovaginitis</td>
<td>1 (0.2)</td>
</tr>
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</table>
Table 5. *Prevalence of concomitant diseases among study subjects*

<table>
<thead>
<tr>
<th>Concomitant disease</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abscess drainage</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Acne</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Adenovirus infection</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Aphthous ulcer</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Arthroscopy</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Asthma</td>
<td>74 (14.7)</td>
</tr>
<tr>
<td>Atypical benign partial epilepsy</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Autoimmune thyroiditis</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>Back pain</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Balanoposthitis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Bone neoplasm</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Breast neoplasm</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Bronchial hyperreactivity</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Bronchitis chronic</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Cerebral palsy</td>
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<tr>
<td>Cervical polypectomy</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Cervicobrachial syndrome</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Chlamydial infection</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Chronic gastritis</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Cyst drainage</td>
<td>1 (0.2)</td>
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<td>Cyst removal</td>
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<tr>
<td>Cystitis</td>
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</tr>
<tr>
<td>Cytomegalovirus test positive</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Concomitant disease</td>
<td>n (%)</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Coeliac disease</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Conjunctivitis allergic</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Cow's milk intolerance</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Depression</td>
<td>9 (1.8)</td>
</tr>
<tr>
<td>Dermatitis atopic</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Dermatitis contact</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>diabetes mellitus</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Diverticulum</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Eczema</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Eye disorder</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Embolism</td>
<td>1 (0.2)</td>
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<tr>
<td>Eosinophilic oesophagitis</td>
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</tr>
<tr>
<td>Epilepsy</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Epstein-Barr virus infection</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Face oedema</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Food allergy</td>
<td>5 (1.0)</td>
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<tr>
<td>Foot deformity</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Gastric disorder</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Gastrooesophageal reflux disease</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Goitre</td>
<td>1 (0.2)</td>
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<tr>
<td>Granuloma annulare</td>
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</tr>
<tr>
<td>Haemorrhage</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Hepatic steatosis</td>
<td>2 (0.4)</td>
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</tbody>
</table>
Table 5. continued

<table>
<thead>
<tr>
<th>Concomitant disease</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes simplex</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Herpes simplex test positive</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Herpes virus infection</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Hiatus hernia</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Histamine intolerance</td>
<td>12 (2.4)</td>
</tr>
<tr>
<td>Hyperchlorhydria</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>10 (2.0)</td>
</tr>
<tr>
<td>Hypercoagulation</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>11 (2.2)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>44 (8.8)</td>
</tr>
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<td>Hypertriglyceridaemia</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Hypogammaglobulinaemia</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>14 (2.8)</td>
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<tr>
<td>Hysterectomy</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Immune system disorder</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>2</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Iron deficiency anaemia</td>
<td>3 (0.6)</td>
</tr>
<tr>
<td>Ischaemic heart disease prophylaxis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Ischaemic stroke</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Yersinia infection</td>
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ncs, not clinically significant; cs, clinically significant
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**n, number of subjects with assessments performed; ncs, not clinically significant; cs, clinically significant**
Table 7. continued

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

Subjects with tests performed, n (%)

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| n            | 35             | 6              | 2         | 0         | 0              | 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         | 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
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n, number of subjects with laboratory tests performed; cs, clinically significant
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n, number of subjects with laboratory tests performed; cs, clinically significant
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<td>max</td>
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</table>

**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)** |

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 (%)

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

*any previous clinically relevant disease(s) which occurred within 5 years before enrolment; **current concomitant disease
<table>
<thead>
<tr>
<th>Therapeutic group (ATC level 2)</th>
<th>Prior medication*</th>
<th>Concomitant medication**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiseptics and disinfectants (D08)</td>
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<td>2 (0.4)</td>
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<tr>
<td>Other dermatological preparations (D11)</td>
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<tr>
<td><strong>Genito urinary system and sex hormones</strong></td>
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<td></td>
</tr>
<tr>
<td>Sex hormones and modulators of the genital system (G03)</td>
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<td>7 (1.4)</td>
</tr>
<tr>
<td>Urologicals (G04)</td>
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<td>3 (0.6)</td>
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<tr>
<td><strong>Systemic hormonal preparations, excl. sex hormones and insulins</strong></td>
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<td>Corticosteroids for systemic use (H02)</td>
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<td>4 (0.8)</td>
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<td>Thyroid therapy (H03)</td>
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<tr>
<td><strong>Antiinfectives for systemic use</strong></td>
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<tr>
<td>Antibacterials for systemic use (J01)</td>
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<td>13 (2.6)</td>
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<tr>
<td>Antimycotics for systemic use (J02)</td>
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<td>Antivirals for systemic use (J05)</td>
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<td>7 (1.4)</td>
</tr>
<tr>
<td>Vaccines (J07)</td>
<td>4 (0.8)</td>
<td>5 (1.0)</td>
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<td><strong>Antineoplastic and immunomodulating agents</strong></td>
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<tr>
<td>Endocrine therapy (L02)</td>
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<tr>
<td>Immunostimulants (L03)</td>
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<td>1 (0.2)</td>
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<td><strong>Musculo-skeletal system</strong></td>
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<tr>
<td>Antiinflammatory and antirheumatic products (M01)</td>
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<td>6 (1.2)</td>
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<td>Antigout preparations (M04)</td>
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<tr>
<td>Drugs for treatment of bone diseases (M05)</td>
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<td>2 (0.4)</td>
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<tr>
<td>Other drugs for disorders of the musculo-skeletal system (M09)</td>
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<tr>
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<td>Psychoanaleptics (N06)</td>
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*any previous clinically relevant disease(s) which occurred within 5 years before enrolment; **current concomitant disease
### Table 9. continued

<table>
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<tr>
<th>Therapeutic group (ATC level 2)</th>
<th>Prior medication*</th>
<th>Concomitant medication**</th>
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<tr>
<td>Other nervous system drugs (N07)</td>
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<td><strong>Respiratory system</strong></td>
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<tr>
<td>Allergens (V01)</td>
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<td>1 (0.2)</td>
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<tr>
<td>All other therapeutic products (V03)</td>
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<tr>
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<tr>
<td>V90***</td>
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<td>9 (1.8)</td>
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</table>

*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 (%)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>All subjects</th>
<th>Chronic recurrent bacterial infection</th>
<th>Chronic recurrent viral infection</th>
<th>Acute bacterial infection</th>
<th>Acute viral infection</th>
<th>Allergic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=502</td>
<td>n=194</td>
<td>n=209</td>
<td>n=18</td>
<td>n=23</td>
<td>n=58</td>
</tr>
<tr>
<td>1 inj. every 2nd day</td>
<td>54 (10.8)</td>
<td>15 (7.7)</td>
<td>34 (16.3)</td>
<td>-</td>
<td>-</td>
<td>5 (8.6)</td>
</tr>
<tr>
<td>1 inj. every day for 5 days</td>
<td>3 (0.6)</td>
<td>-</td>
<td>1 (0.5)</td>
<td>1 (5.6)</td>
<td>1 (4.3)</td>
<td>-</td>
</tr>
<tr>
<td>1 inj. per day for 5 days (6 mg)</td>
<td>2 (0.4)</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>five 1 inj. every 2nd day</td>
<td>33 (6.6)</td>
<td>8 (4.1)</td>
<td>13 (6.2)</td>
<td>3 (16.7)</td>
<td>4 (17.4)</td>
<td>5 (8.6)</td>
</tr>
<tr>
<td>1 inj. per day</td>
<td>2 (0.4)</td>
<td>1 (0.5)</td>
<td>-</td>
<td>-</td>
<td>1 (4.3)</td>
<td>-</td>
</tr>
<tr>
<td>5 inj. every 2nd day</td>
<td>14 (2.8)</td>
<td>9 (4.6)</td>
<td>4 (1.9)</td>
<td>-</td>
<td>-</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>ten 1 inj. every 2nd day</td>
<td>73 (14.5)</td>
<td>6 (3.1)</td>
<td>59 (28.2)</td>
<td>1 (5.6)</td>
<td>1 (4.3)</td>
<td>6 (10.3)</td>
</tr>
<tr>
<td>1 inj. for 1 day, 2 days break, then 1 inj. per day for 4 days</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1 inj. for 2 days, 2 days break, then 1 inj. every 2nd day</td>
<td>3 (0.6)</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
<td>-</td>
<td>1 (4.3)</td>
<td>-</td>
</tr>
<tr>
<td>1 inj. for 2 days, then 1 inj. every 2nd day</td>
<td>11 (2.2)</td>
<td>3 (1.5)</td>
<td>-</td>
<td>2 (11.1)</td>
<td>1 (4.3)</td>
<td>5 (8.6)</td>
</tr>
<tr>
<td>1 inj. for 2 days, then 3 inj. for a week</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1 inj. for 3 days, 1 day break, then 1 inj. for 2 days</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1 inj. for 3 days, 2 days break, then 1 inj. for 2 days</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1 inj. for 3 days, then 1 inj. every 2nd day</td>
<td>5 (1.0)</td>
<td>-</td>
<td>2 (1.0)</td>
<td>-</td>
<td>1 (4.3)</td>
<td>2 (3.4)</td>
</tr>
<tr>
<td>1 inj. for 3 days, then 2 inj. every 2nd day</td>
<td>9 (1.8)</td>
<td>6 (3.1)</td>
<td>-</td>
<td>3 (16.7)</td>
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<td>-</td>
</tr>
<tr>
<td>1 inj. for 3 days, then 2 times a week</td>
<td>7 (1.4)</td>
<td>2 (1.0)</td>
<td>1 (0.5)</td>
<td>2 (11.1)</td>
<td>-</td>
<td>2 (3.4)</td>
</tr>
</tbody>
</table>
### Table 10. continued

<table>
<thead>
<tr>
<th>Regimen</th>
<th>All subjects</th>
<th>Chronic recurrent bacterial infection</th>
<th>Chronic recurrent viral infection</th>
<th>Acute bacterial infection</th>
<th>Acute viral infection</th>
<th>Allergic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=502</td>
<td>n=194</td>
<td>n=209</td>
<td>n=18</td>
<td>n=23</td>
<td>n=58</td>
</tr>
<tr>
<td>first 3 days 1 inj. per day, 1 inj. on the sixth day, 1 inj. on the eighth day</td>
<td>1 (0.2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>1 inj. for 4 days, 2 days break, then 1 inj. every day</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2 inj. per day, then 3 inj. every 2nd day</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3 inj. per day, then 2 inj. every 2nd day</td>
<td>3 (0.6)</td>
<td>-</td>
<td>-</td>
<td>2 (8.7)</td>
<td>1 (1.7)</td>
<td></td>
</tr>
<tr>
<td>5 inj. every 2nd day, then 2 times a week</td>
<td>16 (3.2)</td>
<td>11 (5.7)</td>
<td>3 (1.4)</td>
<td>-</td>
<td>1 (4.3)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>6 inj. every 2nd day, then 2 times a week</td>
<td>3 (0.6)</td>
<td>2 (1.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>five 1 inj. every 2nd day, then twice a week</td>
<td>167 (33.3)</td>
<td>67 (34.5)</td>
<td>62 (29.7)</td>
<td>4 (22.2)</td>
<td>8 (34.8)</td>
<td>26 (44.8)</td>
</tr>
<tr>
<td>every 2nd day</td>
<td>17 (3.4)</td>
<td>15 (7.7)</td>
<td>-</td>
<td>1 (5.6)</td>
<td>-</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>every 3rd day</td>
<td>2 (0.4)</td>
<td>2 (1.0)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>1 time a week</td>
<td>30 (6.0)</td>
<td>23 (11.9)</td>
<td>7 (3.3)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2 times a week</td>
<td>23 (4.6)</td>
<td>11 (5.7)</td>
<td>10 (4.8)</td>
<td>-</td>
<td>1 (4.3)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>3 times a week, then 2 times a week</td>
<td>7 (1.4)</td>
<td>3 (1.5)</td>
<td>2 (1.0)</td>
<td>1 (5.6)</td>
<td>1 (4.3)</td>
<td>-</td>
</tr>
<tr>
<td>Not specified</td>
<td>11 (2.2)</td>
<td>2 (1.0)</td>
<td>9 (4.3)</td>
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</tr>
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</table>
Table 11. Details on previous treatment with Polyoxidonium and Polyoxidonium exposure during the study in subjects with different therapeutic indications

<table>
<thead>
<tr>
<th></th>
<th>Chronic recurrent bacterial infection</th>
<th>Chronic recurrent viral infection</th>
<th>Acute bacterial infection</th>
<th>Acute viral infection</th>
<th>Allergic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>194 (9.9)</td>
<td>209 (10.2)</td>
<td>18 (9.1)</td>
<td>23 (11.7)</td>
<td>58 (29.5)</td>
</tr>
</tbody>
</table>

**Previous Polyoxidonium prescriptions**

| Subjects who previously received Polyoxidonium, n (%) | 38 (19.6) | 40 (19.1) | 3 (16.7) | 2 (8.7) | 3 (5.2) |

<table>
<thead>
<tr>
<th>Number of previous treatment cycles</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3.24±2.38</td>
<td>1</td>
<td>10</td>
<td>2.80±2.23</td>
<td>1</td>
<td>8</td>
<td>2.00±1.00</td>
<td>1</td>
<td>3</td>
<td>2.00±0.00</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1.67±1.56</td>
<td>1</td>
<td>3</td>
<td>2.80±2.23</td>
<td>1</td>
<td>8</td>
<td>2.00±1.00</td>
<td>1</td>
<td>3</td>
<td>2.00±0.00</td>
<td>2</td>
<td>1</td>
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</tbody>
</table>

**Current Polyoxidonium prescription**

<table>
<thead>
<tr>
<th>Number of injections</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 injection</td>
<td>7.84±2.52</td>
<td>1</td>
<td>10</td>
<td>9.14±1.89</td>
<td>5</td>
<td>10</td>
<td>6.94±2.51</td>
<td>5</td>
<td>10</td>
<td>7.83±2.53</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>5 injections</td>
<td>8.28±2.40</td>
<td>5</td>
<td>10</td>
<td>8.28±2.40</td>
<td>5</td>
<td>10</td>
<td>8.28±2.40</td>
<td>5</td>
<td>10</td>
<td>8.28±2.40</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>10 injections</td>
<td>111 (57.2)</td>
<td>173 (82.8)</td>
<td>7 (38.9)</td>
<td>13 (56.5)</td>
<td>38 (65.5)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subjects prescribed different number of injections, n (%)</th>
<th>1 injection</th>
<th>5 injections</th>
<th>10 injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 injection</td>
<td>1 (0.5)</td>
<td>82 (42.3)</td>
<td>111 (57.2)</td>
</tr>
<tr>
<td>5 injections</td>
<td>0</td>
<td>36 (17.2)</td>
<td>173 (82.8)</td>
</tr>
<tr>
<td>10 injections</td>
<td>0</td>
<td>11 (61.1)</td>
<td>7 (38.9)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Daily dose</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 injection</td>
<td>5.97±0.36</td>
<td>1</td>
<td>6</td>
<td>6.00±0.00</td>
<td>6</td>
<td>6</td>
<td>6.00±0.00</td>
<td>6</td>
<td>6</td>
<td>6.00±0.00</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>5 injections</td>
<td>9.00±0.00</td>
<td>6</td>
<td>6</td>
<td>9.00±0.00</td>
<td>6</td>
<td>6</td>
<td>9.00±0.00</td>
<td>6</td>
<td>6</td>
<td>9.00±0.00</td>
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<td>6</td>
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</table>

**Polyoxidonium exposure**

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>22.11±8.91</td>
<td>4</td>
<td>57</td>
<td>22.38±6.57</td>
<td>4</td>
<td>43</td>
<td>18.50±12.50</td>
<td>4</td>
<td>43</td>
<td>20.35±10.49</td>
<td>4</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>20.17±8.73</td>
<td>6</td>
<td>30</td>
<td>20.35±10.49</td>
<td>6</td>
<td>30</td>
<td>20.17±8.73</td>
<td>6</td>
<td>30</td>
<td>20.17±8.73</td>
<td>6</td>
<td>30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of doses taken</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
<th>mean±SD</th>
<th>min</th>
<th>max</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.88±2.57</td>
<td>1</td>
<td>11</td>
<td>9.14±1.90</td>
<td>4</td>
<td>10</td>
<td>7.50±2.57</td>
<td>5</td>
<td>10</td>
<td>8.26±2.44</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>8.38±2.38</td>
<td>5</td>
<td>11</td>
<td>8.38±2.38</td>
<td>5</td>
<td>11</td>
<td>8.38±2.38</td>
<td>5</td>
<td>11</td>
<td>8.38±2.38</td>
<td>5</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Chronic recurrent bacterial infection</td>
<td>Chronic recurrent viral infection</td>
<td>Acute bacterial infection</td>
<td>Acute viral infection</td>
<td>Allergic disease</td>
<td></td>
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<td></td>
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<tr>
<td>-------------------------</td>
<td>----------------------------------------</td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>194</td>
<td>209</td>
<td>18</td>
<td>23</td>
<td>58</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Total dose, mg</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>mean±SD</strong></td>
<td>47.06±15.70</td>
<td>54.67±11.77</td>
<td>45.00±15.44</td>
<td>49.57±14.61</td>
<td>50.28±14.30</td>
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</tr>
<tr>
<td><strong>min</strong></td>
<td>6</td>
<td>15</td>
<td>30</td>
<td>30</td>
<td>30</td>
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<td></td>
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<td></td>
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</tr>
<tr>
<td><strong>max</strong></td>
<td>66</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>66</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subjects with dosage changes</strong>, n (%)</td>
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<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>not changed</td>
<td>176 (90.7)</td>
<td>205 (98.1)</td>
<td>16 (88.9)</td>
<td>21 (91.3)</td>
<td>52 (89.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>reduced</td>
<td>4 (2.1)</td>
<td>2 (1.0)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>increased</td>
<td>14 (7.2)</td>
<td>2 (1.0)</td>
<td>2 (11.1)</td>
<td>2 (8.7)</td>
<td>6 (10.3)</td>
<td></td>
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</tbody>
</table>

* 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 (%)  

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Chronic recurrent bacterial infection</th>
<th>Chronic recurrent viral infection</th>
<th>Acute bacterial infection</th>
<th>Acute viral infection</th>
<th>Allergic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study end</td>
<td>Follow-up</td>
<td>Study end</td>
<td>Follow-up</td>
<td>Study end</td>
<td>Follow-up</td>
</tr>
<tr>
<td><strong>Investigators’ assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>very good</td>
<td>400 (79.7)</td>
<td>406 (80.9)</td>
<td>154 (80.2)</td>
<td>161 (83.4)</td>
<td>186 (89.0)</td>
<td>185 (88.5)</td>
</tr>
<tr>
<td>good</td>
<td>97 (19.3)</td>
<td>87 (17.3)</td>
<td>38 (19.8)</td>
<td>27 (14.0)</td>
<td>20 (9.6)</td>
<td>21 (10.0)</td>
</tr>
<tr>
<td>moderate</td>
<td>2 (0.4)</td>
<td>7 (1.4)</td>
<td>0</td>
<td>5 (2.6)</td>
<td>2 (1.0)</td>
<td>2 (1.0)</td>
</tr>
<tr>
<td>poor</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>0</td>
<td>0</td>
<td>1 (0.5)</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td><strong>Subjects’ assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>very good</td>
<td>378 (75.3)</td>
<td>374 (74.5)</td>
<td>141 (77.5)</td>
<td>137 (78.7)</td>
<td>182 (88.3)</td>
<td>175 (89.8)</td>
</tr>
<tr>
<td>good</td>
<td>106 (21.1)</td>
<td>89 (17.7)</td>
<td>40 (22.0)</td>
<td>35 (20.1)</td>
<td>23 (11.2)</td>
<td>19 (9.7)</td>
</tr>
<tr>
<td>moderate</td>
<td>1 (0.2)</td>
<td>2 (0.4)</td>
<td>1 (0.5)</td>
<td>2 (1.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>poor</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 13. Global improvement assessment by investigators and subjects at the end of study in different therapeutic indication subgroups, n (%)  

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Chronic recurrent bacterial infection</th>
<th>Chronic recurrent viral infection</th>
<th>Acute bacterial infection</th>
<th>Acute viral infection</th>
<th>Allergic disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study end</td>
<td>Follow-up</td>
<td>Study end</td>
<td>Follow-up</td>
<td>Study end</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Investigators’ assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>complete resolution</td>
<td>131 (26.1)</td>
<td>145 (28.9)</td>
<td>52 (27.1)</td>
<td>59 (30.6)</td>
<td>68 (32.5)</td>
<td>68 (32.5)</td>
</tr>
<tr>
<td>marked improvement</td>
<td>281 (56.0)</td>
<td>268 (53.4)</td>
<td>91 (47.4)</td>
<td>85 (44.0)</td>
<td>119 (56.9)</td>
<td>116 (55.5)</td>
</tr>
<tr>
<td>moderate improvement</td>
<td>73 (14.5)</td>
<td>68 (13.5)</td>
<td>44 (22.9)</td>
<td>39 (20.2)</td>
<td>16 (7.7)</td>
<td>19 (9.1)</td>
</tr>
<tr>
<td>slight improvement</td>
<td>11 (2.2)</td>
<td>12 (2.4)</td>
<td>4 (2.1)</td>
<td>5 (2.6)</td>
<td>3 (1.4)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>no appreciable improvement</td>
<td>4 (0.8)</td>
<td>8 (1.6)</td>
<td>1 (0.5)</td>
<td>5 (2.6)</td>
<td>3 (1.4)</td>
<td>3 (1.4)</td>
</tr>
<tr>
<td>Subjects’ assessment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>greatly improved</td>
<td>180 (35.9)</td>
<td>191 (38.0)</td>
<td>71 (37.4)</td>
<td>69 (37.7)</td>
<td>83 (40.5)</td>
<td>87 (43.3)</td>
</tr>
<tr>
<td>somewhat improved</td>
<td>304 (60.6)</td>
<td>272 (54.2)</td>
<td>115 (60.5)</td>
<td>105 (57.4)</td>
<td>118 (57.6)</td>
<td>108 (53.7)</td>
</tr>
<tr>
<td>same</td>
<td>5 (1.0)</td>
<td>16 (3.2)</td>
<td>4 (2.1)</td>
<td>9 (4.9)</td>
<td>1 (0.5)</td>
<td>6 (3.0)</td>
</tr>
<tr>
<td>somewhat worse</td>
<td>2 (0.4)</td>
<td>0</td>
<td>0</td>
<td>2 (1.0)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>much worse</td>
<td>1 (0.2)</td>
<td>0</td>
<td>0</td>
<td>1 (0.5)</td>
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</table>
### Table 14. Mean duration of primary treatment of disease of interest (days)

<table>
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<tr>
<th>Pharmaco-terapeutic group (ATC level 2)</th>
<th>All subjects</th>
<th>Chronic recurrent bacterial infection</th>
<th>Chronic recurrent viral infection</th>
<th>Acute bacterial infection</th>
<th>Acute viral infection</th>
<th>Allergic disease</th>
</tr>
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n, number of subjects taking medication
### Table 15. Symptoms of disease of interest at baseline, n (%)  

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<td>n=18</td>
<td>n=23</td>
<td>n=58</td>
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<tr>
<td>Speech disorder</td>
<td>9 (1.8)</td>
<td>6 (3.1)</td>
<td>-</td>
<td>1 (5.6)</td>
<td>-</td>
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</tr>
<tr>
<td>Sputum abnormal</td>
<td>3 (0.6)</td>
<td>2 (1.0)</td>
<td>-</td>
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<tr>
<td>Subcutaneous abscess</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>Swelling</td>
<td>1 (0.2)</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>Throat irritation</td>
<td>2 (0.4)</td>
<td>1 (0.5)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Upper-airway cough syndrome</td>
<td>9 (1.8)</td>
<td>3 (1.5)</td>
<td>1 (0.5)</td>
<td>2 (11.1)</td>
<td>2 (8.7)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Vaginal discharge</td>
<td>1 (0.2)</td>
<td>1 (0.5)</td>
<td>-</td>
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<tr>
<td>Vomiting</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (4.3)</td>
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<tr>
<td>Wheezing</td>
<td>4 (0.8)</td>
<td>3 (1.5)</td>
<td>-</td>
<td>-</td>
<td>1 (4.3)</td>
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<tr>
<td>Not specified</td>
<td>381 (75.9)</td>
<td>145 (74.5)</td>
<td>172 (82.3)</td>
<td>8 (44.4)</td>
<td>14 (60.9)</td>
<td>42 (72.4)</td>
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Table 16. New symptoms of diseases of interest observed during the study, n (%)

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<tr>
<th>Disease symptoms</th>
<th>All subjects</th>
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<tr>
<td>Bronchitis</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Furuncle</td>
<td>2 (0.4)</td>
</tr>
<tr>
<td>Genital herpes</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Oropharyngeal pain &amp; Cough</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Skin hyperpigmentation</td>
<td>1 (0.2)</td>
</tr>
<tr>
<td>Subject ID</td>
<td>Reported term</td>
</tr>
<tr>
<td>------------</td>
<td>----------------</td>
</tr>
<tr>
<td>0608</td>
<td>Acute bronchitis</td>
</tr>
<tr>
<td>0706</td>
<td>Lyme disease worsening</td>
</tr>
<tr>
<td>0706</td>
<td>Pain in extremities</td>
</tr>
<tr>
<td>0706</td>
<td>Fatigue</td>
</tr>
<tr>
<td>0807</td>
<td>Hepatic test parameter s elevation</td>
</tr>
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<td>1202</td>
<td>Genital herpes</td>
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<tr>
<td>1303</td>
<td>Diarrhea</td>
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Table 17. continued

<table>
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<th>Subject ID</th>
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<th>PT English term</th>
<th>SOC</th>
<th>Start date</th>
<th>Worsening date</th>
<th>End date</th>
<th>Severity</th>
<th>Seriousness category</th>
<th>Relation to Polyoxidonium</th>
<th>Action with Polyoxidonium</th>
<th>Outcome</th>
<th>Caused study discontinuation</th>
<th>Time from injection to AE (days)</th>
<th>AE related to effect on renal system</th>
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<td>Mailaise</td>
<td>General disorders and administration site conditions</td>
<td>29-AUG-2016</td>
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<td>no</td>
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<td>none</td>
<td>resolved</td>
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<td>3</td>
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<td>Injection site oedema</td>
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<td>not related</td>
<td>none</td>
<td>resolved</td>
<td>no</td>
<td>2</td>
<td>no</td>
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<tr>
<td>1311</td>
<td>Difficult breath through the nose</td>
<td>Dyspnœa</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>10-SEP-2016</td>
<td></td>
<td>19-SEP-2016</td>
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<td>no</td>
<td>not related</td>
<td>none</td>
<td>resolved</td>
<td>no</td>
<td>1</td>
<td>no</td>
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<td>1313</td>
<td>Sore throat</td>
<td>Oropharyngeal pain</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>03-OCT-2016</td>
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<td>no</td>
<td>not related</td>
<td>none</td>
<td>resolved</td>
<td>no</td>
<td>4</td>
<td>no</td>
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<tr>
<td>1314</td>
<td>Fatigue, malaise, subfebrile, spill</td>
<td>Fatigue</td>
<td>General disorders and administration site conditions</td>
<td>23-SEP-2016</td>
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<td>26-SEP-2016</td>
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<td>Restless</td>
<td>Restlessness</td>
<td>Psychiatric disorders</td>
<td>07-SEP-2016</td>
<td></td>
<td>08-SEP-2016</td>
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<td>no</td>
<td>related</td>
<td>none</td>
<td>resolved</td>
<td>no</td>
<td>0</td>
<td>no</td>
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<tr>
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<td>Feeling of warmth</td>
<td>Feeling hot</td>
<td>General disorders and administration site conditions</td>
<td>09-SEP-2016</td>
<td></td>
<td>10-SEP-2016</td>
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<td>related</td>
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<td>resolved</td>
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<td>no</td>
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<td>SOC</td>
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<td>Worsening date</td>
<td>End date</td>
<td>Severity</td>
<td>Seriousness category</td>
<td>Relation to Polyoxidonium</td>
<td>Action with Polyoxidonium</td>
<td>Outcome</td>
<td>Caused study discontinuation</td>
<td>Time from injection to AE (days)</td>
<td>AE related to effect on renal system</td>
</tr>
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<td>---------------------------------</td>
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<tr>
<td>1314</td>
<td>Pocit vnútorného tepla a slabostí, ľahko zvýšená teplota</td>
<td>Feeling hot</td>
<td>General disorders and administration site conditions</td>
<td>12-SEP-2016</td>
<td>13-SEP-2016</td>
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<td>no</td>
<td>related</td>
<td>none</td>
<td>resolved</td>
<td>no</td>
<td>3</td>
<td>no</td>
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<tr>
<td>1314</td>
<td>A feeling of inner warmth and weakness, light fever</td>
<td>Pyrexia</td>
<td>General disorders and administration site conditions</td>
<td>14-SEP-2016</td>
<td>15-SEP-2016</td>
<td>mild</td>
<td>no</td>
<td>related</td>
<td>none</td>
<td>resolved</td>
<td>no</td>
<td>2</td>
<td>no</td>
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<td>A feeling of inner warmth and weakness, burning and itching of the upper extremities a slightly elevated temperature</td>
<td>Asthenia</td>
<td>General disorders and administration site conditions</td>
<td>19-SEP-2016</td>
<td>22-SEP-2016</td>
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<td>resolved</td>
<td>no</td>
<td>5</td>
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<td>1314</td>
<td>Weakness, subfebrile</td>
<td>Pyrexia</td>
<td>General disorders and administration site conditions</td>
<td>06-OCT-2016</td>
<td>07-OCT-2016</td>
<td>mild</td>
<td>no</td>
<td>related</td>
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<td>resolved</td>
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<td>13</td>
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<td>End date</td>
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<td>Seriousness category</td>
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<td>Action with Polyoxodonium</td>
<td>Outcome</td>
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<td>AE related to effect on renal system</td>
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<td>1314</td>
<td>Weakness, subfebrile, headache, feeling virus infections, herpes nose, difficulty swallowing</td>
<td>Pyrexia</td>
<td>General disorders and administration site conditions</td>
<td>11-OCT-2016</td>
<td>17-OCT-2016</td>
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<td>no</td>
<td>related</td>
<td>none</td>
<td>resolved</td>
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<td>no</td>
<td>not related</td>
<td>none</td>
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<td>not related</td>
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<tr>
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<td>Bronchial asthma – Impairment</td>
<td>Asthma</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>01-OCT-2016</td>
<td>16-OCT-2016</td>
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<td>none</td>
<td>resolved</td>
<td>no</td>
<td>1</td>
<td>no</td>
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<tr>
<td>1329</td>
<td>Bronchial asthma – Impairment</td>
<td>Asthma</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>19-OCT-2016</td>
<td>20-OCT-2016</td>
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<td>no</td>
<td>not related</td>
<td>none</td>
<td>resolved</td>
<td>no</td>
<td>2</td>
<td>no</td>
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<td>Dyspnoea</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>11-OCT-2016</td>
<td>13-OCT-2016</td>
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<td>no</td>
<td>not related</td>
<td>none</td>
<td>resolved</td>
<td>no</td>
<td>1</td>
<td>no</td>
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<tr>
<td>1331</td>
<td>Dyspnoea</td>
<td>Dyspnoea</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>19-OCT-2016</td>
<td>mild</td>
<td>no</td>
<td>not related</td>
<td>none</td>
<td>resolving</td>
<td>no</td>
<td>2</td>
<td>no</td>
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Table 17. continued

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<th>Subject ID</th>
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<th>PT English term</th>
<th>SOC</th>
<th>Start date</th>
<th>Worsening date</th>
<th>End date</th>
<th>Severity</th>
<th>Serious category</th>
<th>Relation to Polyoxidonium</th>
<th>Action with Polyoxidonium</th>
<th>Outcome</th>
<th>Caused study discontinuation</th>
<th>Time from injection to AE (days)</th>
<th>AE related to effect on renal system</th>
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<tbody>
<tr>
<td>1331</td>
<td>Dyspnoea</td>
<td>Dyspnoea</td>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>19-OCT-2016</td>
<td>24-OCT-2016</td>
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<td>no</td>
<td>not related</td>
<td>none</td>
<td>resolving</td>
<td>no</td>
<td>2</td>
<td>no</td>
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<tr>
<td>1340</td>
<td>Herpes lips</td>
<td>Oral herpes</td>
<td>Infections and Infestations</td>
<td>25-OCT-2016</td>
<td>27-OCT-2016</td>
<td>mild</td>
<td>no</td>
<td>not related</td>
<td>none</td>
<td>resolved</td>
<td>no</td>
<td>1</td>
<td>no</td>
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<td>Oral herpes</td>
<td>Infections and Infestations</td>
<td>02-NOV-2016</td>
<td>03-NOV-2016</td>
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<td>no</td>
<td>not related</td>
<td>none</td>
<td>resolved</td>
<td>no</td>
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<td>1340</td>
<td>Vertigo</td>
<td>Vertigo</td>
<td>Ear and labyrinth disorders</td>
<td>14-NOV-2016</td>
<td>mode rate</td>
<td>no</td>
<td>not related</td>
<td>withdrawn</td>
<td>not resolved</td>
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<td>3</td>
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<td>Ear and labyrinth disorders</td>
<td>16-NOV-2016</td>
<td>19-NOV-2016</td>
<td>mode rate</td>
<td>yes</td>
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<td>not related</td>
<td>interrupted</td>
<td>not resolved</td>
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<td>Oral herpes</td>
<td>Infections and Infestations</td>
<td>01-DEC-2016</td>
<td>05-DEC-2016</td>
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<td>no</td>
<td>not related</td>
<td>none</td>
<td>resolved</td>
<td>no</td>
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<td>1501</td>
<td>D16+56+ decreased</td>
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<td>Investigations</td>
<td>25-JUL-2016</td>
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<td>no</td>
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<td>none</td>
<td>resolving</td>
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<td>3</td>
<td>no</td>
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<td>hyper-pigmentation</td>
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<td>Skin and subcutaneous tissue disorders</td>
<td>12-OCT-2016</td>
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<td>resolved</td>
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<td>2</td>
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<td>1537</td>
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<td>Renal failure</td>
<td>Renal and urinary disorders</td>
<td>08-NOV-2016</td>
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<td>none</td>
<td>resolving</td>
<td>no</td>
<td>0</td>
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Table 18. Adverse events: number observed, rate of occurrence and subject identifications

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<tr>
<th>SOC level</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
<th>Total</th>
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<td>Related</td>
<td>NR*</td>
<td>Related</td>
<td>NR</td>
<td>Related</td>
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<td>Infections and Infestations</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bronchitis</td>
<td>0</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Genital herpes</td>
<td>0</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>Oral herpes</td>
<td>0</td>
<td>3 (0.6%)</td>
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<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infections and Infestations</td>
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<td></td>
</tr>
<tr>
<td>General disorders and administration site condition</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Lyme disease - Condition aggravated</td>
<td>0</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>0</td>
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<td>Psychiatric disorders</td>
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</tr>
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<td>Restlessness</td>
<td>1 (0.2%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>Ear and labyrinth disorders</td>
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<td>0</td>
<td>0</td>
<td>2 (0.4%)</td>
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<td>4 (0.8)</td>
<td>0</td>
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*NR, not related; **R, related; ***Subject ID
Table 18. continued

<table>
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<tr>
<th>SOC level</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
<th>Total</th>
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<td>Skin and subcutaneous tissue disorders</td>
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<tr>
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<td>General disorders and administration site conditions</td>
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<tr>
<td>Fatigue</td>
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<td>0</td>
<td>0</td>
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<td></td>
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<td></td>
<td>1304</td>
<td></td>
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*NR, not related; **R, related
### Table 18. continued

<table>
<thead>
<tr>
<th>SOC level</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Total</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
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<td>NR</td>
<td>Related</td>
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<td>Injection site oedema</td>
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<td>1 (0.2%)</td>
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<td>Feeling hot</td>
<td>2 (0.4%)</td>
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<td>Asthenia</td>
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<td><strong>Investigations</strong></td>
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<td>Liver function test increased</td>
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<td>Natural killer cell count decreased</td>
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<td><strong>TOTAL</strong></td>
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*NR, not related; **R, related
### Annex 1. List of stand-alone documents

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<td>9</td>
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<td>Clinical Research Organization Signature</td>
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*available on request*
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

AFFILIATION: 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

AFFILIATION: NPO PETROVAXPHARM

SIGNATURE: 

DATE: 11.05.2017
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

AFFILIATION: Medigroup s.r.o.

SIGNATURE:

DATE: 12-May-2017
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

AFFILIATION: ZM Company

SIGNATURE: Yuri Zaresky, M.D.

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

AFFILIATION: CRO Biomapas

SIGNATURE: [Signature]

DATE: 12 May 2017