CLINICAL STUDY PROTOCOL

An international, multicenter, randomized, double-blind, double-dummy, two-way, parallel group, controlled study to compare the efficacy and safety of intravenous and oral Nemonoxacin versus Tavanic® in adult patients with community-acquired pneumonia.

Test medicinal products	Nemonoxacin 500mg (250 ml), solution for infusion Nemonoxacin 250 mg, capsules
Indication	Treatment of community-acquired pneumonia
Protocol code	CJ01060044
Sponsor	R-Pharm Legal address: 19/1, Berzarina str., 123154, Moscow, Russia Mailing address: 111B, Leninskiy Prospekt, 119421, Moscow, Russia. Tel: +7 (495) 956-79-37 Fax: +7 (495) 956-79-38
Phase	III
Version	Final version 5.0
Date	26-Apr-2017
Amendments	Amendment No. 1 dated 17-Mar-2016 Amendment No. 3 dated 26-Dec-2016 Amendment No. 4 dated 26-Apr-2017

SPONSOR SIGNATURE PAGE

I have read the protocol and agree that it contains all necessary details for conducting this clinical study in strict accordance with the specifications outlined herein.

Sponsor Study Contact Person

Medical Director of R-Pharm JSC Mikhail Samsonov, MD, PhD Legal address: 19/1, Berzarina str., 123154, Moscow, Russia Mailing address: 111B, Leninskiy Prospekt, 119421, Moscow, Russia Tel: +7 (495) 956-79-37 Fax: +7 (495) 956-79-38	Date

Study medical expert, appointed by the Sponsor

Aleksandr Chernavin Head of Medical Affairs Group, R-Pharm JSC Legal address: 19/1, Berzarina str., 123154, Moscow, Russia. Mailing address: 111B, Leninskiy Prospekt, 119421, Moscow, Russia. Tel: +7 (495) 956-79-37 Fax: +7 (495) 956-79-38	Date

CONTRACT RESEARCH ORGANIZATION SIGNATURE PAGE

General Director of OCT Rus Ltd. Dmitry Sharov Legal address/ postal address: 5, Kovensky lane, letter “B”, 191014, Saint Petersburg, Russia Tel.: +7 (812) 449-86-34 Fax: +7 (812) 449-86-35	Date

INVESTIGATOR SIGNATURE PAGE

I have discussed the tasks of this study and contents of this protocol in detail with the Sponsor`s representative.

I understand, that information in the protocol or relating to the protocol is confidential and without a written consent of the Sponsor will not be disclosed, except for its transfer to the employees, that directly participate in this study and in checks of its compliance with ethical norms. However, this information may to be provided to patients to receive their consent for participation in the study.

I agree to conduct this study in accordance with the protocol, fulfill any requirements of the protocol and requirements of any provisions and directives related to ethics and safety, I also agree to conduct this research in accordance with the provisions of the Declaration of Helsinki, principles of GCP specified in Guidelines E6 of the International Conference of Harmonisation, and all applicable local regulatory requirements.

I agree to provide employees of the sponsoring company, its representatives and employees of regulating authorities with all documentation, related to the research in connection with my patients, with the aim to control the data I used to fill patients` individual electronic case report forms. I am aware of my duties as the principal investigator, reporter to me by the sponsor.

I understand, that the sponsor is entitled to suspend or discontinue the study any time and for any reason; I will be informed of such decision in writing. On the other hand, if I decide to discontinue the study, I will forthwith notify the Sponsor's representative thereof in writing.

Name of Investigator: _____

Affiliation: _____

Name and address of Study center: _____

_____

Signature of Investigator: _____

Date: _____

CONTACT INFORMATION

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Central Microbiological Laboratory:	Research Institute of Antimicrobial Therapy of Federal State Budget-funded Educational Establishment of Higher Education "Smolensk State Medical University of the Ministry of Health of the Russian Federation". Legal / mailing address: 46A, Kirova Str., Smolensk, 214019, Russia. Telephone: +7 (4812) 45-06-02
Central Pharmacokinetic Laboratory:	Bioanalytical Laboratory "Exacte Labs" Legal / mailing address: 20, Nauchnyi Proezd, Bldg. 2, Moscow, 117246, Russia. Telephone: +7 (499) 963-90-01

INVESTIGATIONAL SITES

List of Investigational Sites participating in this clinical study (name, address and telephone number of each site; name and title of the investigators) is provided in a separate List of Investigational Sites and Principal Investigators.

DESCRIPTION OF THE PROTOCOL CHANGES

The changes introduced into the Protocol by Amendment No. 4 dated 26 April 2017 are listed below:

Appendix 1 contains Intensive Care Unit admission criteria that have been corrected on the basis of the "Clinical guidelines for the diagnosis, treatment, and prevention of severe community-acquired pneumonia in adult patients of 2014" (referred to further in the protocol changes description as the "2014 Clinical Guidelines"). These criteria have been brought into agreement with the Infectious Diseases Society of America / American Thoracic Society criteria referenced by the 2014 Clinical Guidelines.

Section 11.5 now contains clarified requirements for the registration of pregnancies in the course of the study.

Sections 12.1 and 12.2 contain clarified requirements for the enrollment of subjects in the Clinically Evaluable (CE) population.

Section 13.3 now provides information on the financing and insurance of the study.

Minor formatting changes and correction of misprints in the protocol were performed as well.

The principal changes introduced into the Protocol by Amendment No. 3 dated 26 December 2016 are listed below.

The following changes were made in the inclusion criteria:

- Inclusion criterion No. 2 was modified: the maximum age of patients that can be enrolled in the study was increased to 70 years inclusive. This change was due to a significant proportion of such patients in the overall population of patients admitted to hospital with a diagnosis of "community-acquired pneumonia", and was aimed to enlarge the study population.
- Inclusion criterion No. 3 was clarified (the need to meet the requirements of Appendix 1 "Criteria for hospitalization" was again underlined).
- For Inclusion criterion No. 4, a clearer definition of required symptoms / signs was included: the terms "dyspnea" and "rigors" were excluded to avoid misunderstanding.

The following change was made in the exclusion criteria:

- For Exclusion criterion No. 4, a clearer definition of QT prolongation was included: *QTc(F) interval more than 450 ms.*

In the "Contact information" section, information on the Central Microbiological Laboratory and the Central Pharmacokinetic Laboratory was added.

Section 8.6 "Blinding" now contains a modified description of the package labeling, which will allow masking of blinding packages right at the investigational sites for more convenience of the investigational site personnel.

Section 8.7 “Prior and concomitant therapy” now contains a clarification that the eCRF documents information on previous drugs and treatments used from the onset of community-acquired pneumonia until the enrollment in the study (signing of the Informed Consent Form).

Section 9.1 “Schedule of study procedures” now includes, in the interests of study subjects, clarified requirements for the time frame of Visit 3, which should be conducted at least 24 hours after the last dose of the study drug.

The description of the screening procedures and Sections 10.3.4, 10.3.5, 10.3.6 now include information that *the Investigator may use laboratory test results obtained at the laboratory of the investigational site within 24 hours of study enrollment (Signing of the Informed Consent Form) if he / she considers that available data are sufficient to permit a decision on whether the subject meets the selection criteria. In this case, another blood sampling procedure has to be conducted in the period from the signing of the Informed Consent Form to the start of treatment in order to evaluate all other laboratory parameters that have to be determined on Day 1 in accordance with the study protocol.* This amendment was done in the interests of study subjects, in order to rule out more unnecessary material collection procedures, as well as to shorten the time to start of treatment.

The description of the screening procedures (9.2.1) now provides clarifying information that prior therapy should be evaluated *for the 30 days preceding the Visit* and treatment, *from the onset of community-acquired pneumonia.*

For all study visits including an ECG recording (Visit 1 “Screening procedures”, Visit 2 “Switch to oral therapy”, Visit 3, Visit 4), an opportunity was added, for more convenience of patients and investigators, to have an ECG recording not only before the blood sampling procedure, but also 30 minutes after it.

The description of the Visit 2 procedures (9.2.2) now provides clarifying information that, *in the event intravenous therapy is prolonged, the overall duration of treatment within this study will not exceed 14 days.*

Section 10.2.1 "Chest X-ray / Chest Computed Tomography” now includes clarifying information that *only one radiological method (X-ray imaging only or CT imaging only for all visits) should be used for a patient throughout the study* to ensure unified and improved quality of analysis.

Section 10.3.7 “Documentation of adverse events” now contains clarified requirements for the documentation of adverse events.

Section 11.1.1 “Adverse event (AE)” now provides clarifying information in order to improve the adverse event reporting procedure: *any worsening of symptoms of the primary disease (as compared with estimates made during the screening procedures) should also be registered as an AE;* there is now also information that *the Investigator will record all available information on each occurring SAE in the source documentation.*

The title of Section 11.4 “ Management of Non Serious Adverse Events (NSAEs) and/or laboratory abnormalities” was changed to 11.4 “Management of adverse events not classified as serious”. A requirement was also included to record information about adverse events in the source documentation.

Clarifying information was included in Appendix 1:

- Clearer criteria for preferred in-patient treatment and for hospitalization in an intensive care unit were included.
- One of the criteria for hospitalization in an intensive care unit was better defined: *Respiratory rate ≥ 30 movements per minute.*

Minor formatting changes and correction of misprints in the protocol were performed as well.

The changes introduced into the Protocol by Administrative Amendment No. 1 dated 17 March 2016:

The mailing address of the Study Sponsor was changed to *111B, Leninskiy Prospekt, 119421, Moscow, Russia.*

Section 8.9 "Treatment compliance" now mentions that the *volume (mL)* of the infusion (instead of the dose) will be recorded in the eCRF.

Information was added in Section 9.3 "Unscheduled visits" that, *if the Investigator makes a decision to withdraw a subject from the study during an unscheduled visit (a so-called "early termination visit"), the minimal number of completed procedures should correspond to that of the "End of treatment visit". For more information on discontinuation of therapy and early withdrawal of subjects from the study, see Section 7*

Section 10.3.2 "Vital signs" now contains clarifying information that both systolic and diastolic blood pressure should be measured.

The contact details for SAE reporting was changed in Section 11.3.1 "Reporting duties of the Investigator".

No changes were made in the study protocol following Amendment No. 2 dated 05 September 2016. Amendment No. 2 dated 05 September 2016 was abolished and was not used.

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1 ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event/experience
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase (alanine transaminase)
AST	Aspartate aminotransferase (aspartate transaminase)
BLNAR	β-lactamase negative ampicillin-resistant
CAP	Community-acquired pneumonia
CAPRIE	Community-Acquired Pneumonia Recovery in the Elderly
C. pneumoniae	Chlamydophila pneumoniae
CNS	Central nervous system
CRA	Clinical research associate
CRO	Contract research organization
CT	Computed tomography
DBP	Diastolic blood pressure
DNA	Deoxyribonucleic acid
DRSP	Drug-resistant S.pneumoniae
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
ESR	Erythrocyte sedimentation rate
GCP	Good Clinical Practice
GGTP	Gamma-glutamyl transpeptidase
GI	Gastrointestinal system
H. influenzae	Haemophilus influenzae
ICF	Informed consent form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
INN	International Non-proprietary Name
ISF	Investigator Site File
i.v.	Intravenous
IWRS	Interactive Web Response System
K. pneumoniae	Klebsiella pneumoniae
L. pneumophila	Legionella pneumophila
LRTI	Lower respiratory tract infection
MedDRA	Medical Dictionary for Regulatory Activities

MRSA	Methicillin-resistant Staphylococcus aureus
M. pneumoniae	Mycoplasma pneumoniae
NSAE	Non Serious Adverse Events
NFQ	Non-fluorinated quinolone
PISP	Penicillin-intermediate S. pneumonia
PRSP	Penicillin-resistant S. pneumonia
P. aeruginosa	Pseudomonas aeruginosa
pH	Hydrogen ion concentration
PQ	Cardiac PQ interval
QRS	Cardiac QRS interval
QT	Cardiac QT interval
QTc	Cardiac QT interval corrected for heart rate
SAE	Serious Adverse Event/experience
S. aureus	Staphylococcus aureus
SBP	Systolic blood pressure
SD	Standard deviation
SOPs	Standard Operating Procedures
S. pneumoniae	Streptococcus pneumoniae
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMP-SMX	Trimethoprim-sulfamethoxazole
ULN	Upper limit of normal
WBC	White blood cell
WHO	World Health Organization

2 SYNOPSIS

Title of Study:	An international, multicenter, randomized, double-blind, double-dummy, two-way, parallel group, controlled study to compare the efficacy and safety of intravenous and oral Nemonoxacin versus Tavanic® in adult patients with community-acquired pneumonia.
Protocol code:	CJ01060044
Sponsor:	R-Pharm JSC
Medical condition or disease under investigation:	Community-acquired pneumonia (CAP)
Objectives:	**Primary objective** • To evaluate the clinical efficacy of treatment with Nemonoxacin compared with Tavanic® in patients with CAP. **Secondary objectives** • To evaluate the clinical efficacy of treatment with intravenous Nemonoxacin compared with intravenous Tavanic® in patients with CAP • To assess the safety of treatment with Nemonoxacin compared with Tavanic® in patients with CAP • To assess the pharmacokinetic parameters of intravenous Nemonoxacin in adult patients with CAP • To evaluate the microbiological efficacy of treatment with Nemonoxacin compared with Tavanic® in patients with CAP.
Study design:	This is an international, multicenter, randomized, double-blind, double-dummy, controlled, parallel group study of efficacy and safety. Treatment-naive patients with community-acquired pneumonia (non-nosocomial pneumonia) and patients with treatment failure will be screened and if eligible will be randomized to receive either treatment with Nemonoxacin or Tavanic® in a ratio of 1:1. Patients will stay at hospital (non-intensive care unit) and receive daily i.v. treatment with either invesigational product (Nemonoxacin 500 mg (250 ml), solution for infusion) with Placebo (100 ml), solution for infusion, or comparator (Tavanic® 500 mg (100 ml), solution for infusion) with Placebo (250 ml), solution for infusion, for at least 3 days. The i.v. treatment may be prolonged by decision of investigator until and including Day 7 of the study. Thus the investigator will switch a patient from i.v. to

	oral therapy at Day 4(8) of the study if the specific criteria of clinical stability are achieved. The treatment will be continued with appropriate oral therapy. If the patient receives i.v. therapy with Nemonoxacin he/she will continue oral therapy with Nemonoxacin 250 mg, 2 capsules per day. If the patient receives i.v. therapy with Tavanic® he/she will continue oral therapy with Tavanic® 250 mg, 2 over-encapsulated film coated tablets per day. The duration of oral therapy will be judged by investigator and oral therapy will last until and including Day 7(14) of the study. The study includes 5 visits: 1. Visit 1 (Screening /randomization/ intravenous therapy, Days 1-3(7) of the study) 2. Visit 2 (Switch to oral therapy /oral therapy, Days 4(8)-7(14) of the study) 3. Visit 3 (End of treatment visit, within 1-2 days after the last dose) 4. Visit 4 (Test of cure visit, within 7-9 days after the last dose) 5. Visit 5 (Long-term follow-up visit; within 21-23 days after the last dose).
Number of Subjects:	A total of 342 eligible patients (171 patients per test group) will be enrolled and randomized in the study. Presumably screening of 382 patients will allow randomization of 342 patients.
Inclusion Criteria:	1. Written informed consent obtained from the patient. 2. Female and male patients aged between 18 and 70 years inclusive. 3. Patients with moderate to severe community-acquired pneumonia who need inpatient treatment (correspodence to at least one of the criteria for hospitalization / preferred hospitalization described in the Appendix 1 of this protocol) but do not need ICU treatment (in case of correspondence to at least one «major» or three «minor» criteria for hospitalization in intensive care unit described in Appendix 1 of this protocol, patient should not be enrolled in the study). 4. The presence of at least 3 of the following symptoms/signs: • Cough • Purulent sputum production • Tachypnea (respiratory rate > 24 breaths/minute) • Chills • Fever (rectal/ tympanic temperature ≥ 38.5°C or axillary/ oral/ cutaneous temperature ≥ 38.0°C) • WBC count of ≥10.0 x 10^9/L or ≥15% immature

	neutrophils (bands; regardless of peripheral WBC count). 5. Radiological evidence of (a) new infiltrate(s) consistent with bacterial pneumonia at baseline. 6. Treatment-naive patients or patients who have received single dose of a short-acting antibacterial drug within 24 hours of enrollment or patients with treatment failure who have received antibiotics (with the exception of quinolones or fluoroquinolones) for less than 72 hours. 7. Consent to use contraception during participation in the study (for women of childbearing potential and men).
Exclusion Criteria:	1. Known hypersensitivity to quinolones, fluoroquinolones or any of the excipients. 2. Female patients who are pregnant or nursing. 3. History of tendon disease/disorder related to quinolone treatment. 4. Known congenital or documented-acquired QT/QTc(F) prolongation on ECG (QTc(F) interval more than 450 ms); concomitant use of drugs, reported to increase the QT interval; uncorrected hypokalaemia and uncorrected hypomagnesemia; clinically relevant bradycardia; clinically relevant heart failure with reduced left-ventricular ejection fraction; previous history of symptomatic arrhythmias. 5. History of bronchiectasis, cystic fibrosis, bronchial obstructions excluding chronic obstructive pulmonary disease. 6. History of epilepsy and/or history of psychotic disorder. 7. Patients with history of myasthenia gravis. 8. Patients with diabetes mellitus. 9. Known glucose-6-phosphate dehydrogenase deficiency. 10. Active hepatitis or decompensated cirrhosis. 11. Alanine transaminase or aspartate transaminase increase > 3 fold ULN. 12. Patients with creatinine ≥ 1.1 fold ULN. 13. Patients requiring concomitant systemic or inhaled antibiotics (e.g., tobramycin). 14. Known or suspected active tuberculosis or endemic fungal infection. 15. Concomitant immunosuppressive therapy including a long-term (more than 2 weeks) treatment with oral or intravenous glucocorticoids at doses of 20 mg and higher of prednisone daily or an equivalent dose of other glucocorticoids. 16. Patients known to have HIV-positive status or AIDS or known to have other disease that seriously affects the

	immune system such as active haematological or solid organ malignancy, or splenectomy. 17. History of drug or alcohol abuse. 18. Patients have received quinolones or fluoroquinolones within 14 days before enrollment. 19. Previous enrolment in this study or participation in another study within the previous 4 weeks. 20. Patients with any severe medical condition as determined by medical history that, in the opinion of the investigator, does not allow the patient to carry out all planned procedure of the protocol.
Investigational products, dosage and mode of administration:	• Investigational product 1: Nemonoxacin 500 mg (250 ml), solution for infusion. Dosage and mode of administration: 500 mg (250ml) daily administered as single intravenous infusion over 90-110 minutes. • Investigational product 2: Nemonoxacin 250 mg, capsules. Dosage and mode of administration: a dose of 500 mg (two 250 mg capsules) will be administered orally once a day.
Comparators, dosage and mode of administration:	• Comparator 1: Tavanic® 500 mg (100 ml), solution for infusion. Dosage and mode of administration: 500 mg (100 ml) daily administered as single intravenous infusion over a minimum duration of 60 minutes. • Comparator 2: Tavanic® 250 mg, film coated tablets. Each tablet is placed into a capsule shell (over-encapsulated) for blinding purposes. Dosage and mode of administration: a dose of 500 mg (two 250 mg over-encapsulated film coated tablets) will be administered orally once a day.
Placebo, dosage and mode of administration:	• Placebo (100 ml), solution for infusion. Dosage and mode of administration: 100 ml of solution will be administered daily as single intravenous infusion over a minimum duration of 60 minutes after the infusion of Nemonoxacin, solution for injection. • Placebo (250 ml), solution for infusion. Dosage and mode of administration: 250 ml of solution will be administered daily as single intravenous infusion over 90-110 minutes before the infusion of Tavanic®, solution for infusion.
Duration of treatment:	For each patient treatment duration will be approximately 7 – 14 days.

Endpoints:	**Efficacy endpoints:** Primary endpoint: • Proportion of patients with clinical success as judged by the investigator at the test of cure visit (Visit 4). Secondary endpoints: • Proportion of patients with clinical success as judged by the investigator at the Visit 2 (switch to oral therapy) and Visit 3 • Proportion of patients with infection relapse at Visit 5 • Time to switch therapy from i.v. to oral therapy • Need for other antibiotic treatment • Proportion of patients with microbiological responses at the Visit 2 (switch to oral treatment), Visit 3 and Visit 4. **Safety endpoints:** • Adverse events • Changes in vital signs • Clinical laboratory results • ECG results • Physical examination results. **PK parameters:** • C_{max} • $C_{22.5h}$ • $AUC_{0-22.5}$ • AUC_{0-inf} • CL • V_{ss} • $T_{1/2}$
Statistical methods:	**Samples size calculation** The primary efficacy objective is to show that Nemonoxacin is not inferior to Levofloxacin (Tavanic®) for the treatment of CAP, on the basis of the primary efficacy endpoint - clinical success at Visit 4 (Test of cure visit) in the mITT population. The sample size calculation for this endpoint is based on assuming a clinical success rate of 82% in the treatment and in the active control group, and an eligibility of 80% of the randomized patients for mITT population. Non-inferiority margin is chosen to be 15% (i.e., δ= -15%), a one-sided significance level α is set at 5%. Then, to achieve power of 80%, the sample size for equal allocation is estimated as 171 randomized patients in each group (342 patients totally) that provides about 137 patients in each group (274 patients totally) in the mITT population. Presumably screening of 382 patients will allow randomization of 342 patients.

	Statistical methods ***Primary efficacy analysis*** The percentage and the number of patients with different categories of clinical response ("clinical success", "clinical failure", "indeterminate") will be summarized by treatment group in mITT and CE populations for Visits 2 (switch to oral therapy), Visit 3 and Visit 4. The percentage of patients with clinical success (as judged by the investigator) at the test of cure Visit 4 is defined as primary endpoint variable. In regards to efficacy for CAP, non-inferiority of Nemonoxacin compared to Tavanic® will be evaluated for clinical response by using a one-sided 95% confidence interval for the difference in the primary efficacy endpoint (investigational product minus comparator). Non-inferiority of Nemonoxacin will be stated if the lower boundary of the estimated one-sided 95% confidence interval for the difference in the clinical success rate of Nemonoxacin and Tavanic® is above -15% the Farrington-Manning test. The primary analysis will be performed in the mITT population. If non-inferiority is shown, a test on superiority will be performed in addition using the two-sided 95% confidence interval. The test on superiority is significant, if the lower two-sided 95% confidence interval limit is above "0". ***Secondary efficacy analyses*** As a supportive analysis, the primary efficacy endpoint will be analyzed in the CE population using the same method as that used for the primary efficacy analysis. For secondary efficacy analyses, the clinical success rates of the patients in the mITT and CE populations at Visits 2 and 3 as well as the number (proportion) of patients who needed other antibiotic treatment (treatment failure) will be analyzed using a two-sided 95% confidence interval (equality test) calculated based on the same statistical test as for the primary analysis. Additionally, the results of statistical comparison of the clinical success rates using the logistic regression will also be provided. Microbiological efficacy endpoints will include microbiological success rates evaluated per each patient and by identified pathogens in b-mITT and BE. The percentage and the number of patients with microbiological success and failure will be summarized by visit and treatment group. Microbiological success is defined as the

	assessments of eradication and presumed eradication. Other results of assessments (excluding unevaluable) will be regarded as microbiological failure. The difference between microbiological success rates and its CI will be calculated using the same method as that used for the secondary efficacy endpoints. The percentage and number of the baseline-identified strains (sputum and blood culture) with microbiological success and failure will be summarized by visit and treatment group. The frequency of each category and sample source (sputum and blood culture) will be presented separately and by treatment group. Microbiological data by identified pathogens will be analyzed descriptively. Time to switch therapy from i.v. to oral therapy will be evaluated using the Kaplan – Meier survival analysis method and compared by log-rank test between treatment groups. The Kaplan-Meier curves will be presented graphically. ***Safety evaluation*** Safety evaluation will include assessment of AEs, vital signs, ECG and physical examination data and laboratory tests in the safety population. All safety statistical analyses will be performed descriptively. ***Pharmacokinetic parameters*** The non-compartment method will be used to analyze the Nemonoxacin concentration-time data after the first intravenous Nemonoxacin infusion in adult patients with CAP. The following pharmacokinetic parameters will be estimated from the measured concentrations: the peak drug concentration (C_{max}), 22.5-h drug concentrations ($C_{22.5h}$), areas under the concentration-time curve from 0 to 22.5 h, and 0 h to infinity ($AUC_{0-22.5}$, $AUC_{0-\infty}$), total systemic clearance (CL), volume of distribution at steady state (V_{ss}), and terminal elimination half-life ($T_{1/2}$).

3 INTRODUCTION

3.1 Background information

The World Health Organization (WHO) estimates that lower respiratory tract infection (LRTI), including pneumonia, is the third most common cause of death worldwide. LRTI caused 3.1 million deaths in 2012 [23].

Pneumonia is an acute illness characterized by symptoms and signs of lower respiratory tract infection, with new radiographic shadowing for which there is no alternative explanation. Community-acquired pneumonia (CAP) is pneumonia acquired outside a hospital or long-term care facility and being diagnosed within 48 hours of hospital admission [14].

Evidence suggests CAP is most commonly caused by bacterial infection [14].

Streptococcus pneumoniae (the most common etiologic agent), nontypeable *Haemophilus influenzae*, and the atypical organisms (i.e., *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella pneumophila*) are the most frequently isolated pathogens from patients of any age who require hospitalization for CAP [17] [20].

Increasing resistance to a variety of antimicrobial agents has been documented in *S pneumoniae* and is common in *H influenzae* as well. In addition to penicillin resistance (penicillin-intermediate S. pneumonia - PISP, or penicillin-resistant S. pneumonia - PRSP), isolates of *S pneumoniae* have demonstrated increasing resistance to other classes of antimicrobials, including macrolides, tetracyclines, trimethoprim-sulfamethoxazole (TMP-SMX), and fluoroquinolones [8] [9]. Surveillance studies indicate that the prevalence of drug-resistant *S.pneumoniae* (DRSP) continues to increase worldwide [8].

The basic problem of resistance in *H. influenzae* species is defined by ampicillin as the resistance marker. The resistance of *H. influenzae* to ampicillin may occur due to production of β-lactamases (TEM-1, TEM-2, and with lower frequency ROB-1) or as a result of mutations in the *ftsI* gene that cause alterations in the amino acid sequences of penicillin-binding protein 3 (PBP3) in so called β-lactamase negative ampicillin-resistant (BLNAR) strains. Strains producing β-lactamases remain susceptible to amoxicillin/clavulanate; however, clavulanate is inactive against BLNAR strains, so such strains are resistant to amoxicillin/clavulanate. BLNAR strains are also resistant to ampicillin–sulbactam, cefaclor, and cefuroxime. Both mechanisms of resistance, i.e., β-lactamase production and mutations in the *ftsI* gene, are present in β-lactamase positive amoxicillin–clavulanic acid resistant (BLPACR) strains [2] [12].

The number of necrotizing or cavitary pneumonia may be caused by methicillin-resistant *Staphylococcus aureus* (MRSA) [19]. MRSA has been a major cause of nosocomial infections, and thus is alternatively called hospital-acquired MRSA (HA-MRSA). In addition, another class of MRSA has become a major concern worldwide as an emerging pathogen in the community. This new class of MRSA is called community-acquired MRSA (CA-MRSA) [22]. MRSA is resistant to b-lactam antibiotics, including penicillin and cephalosporins. Compared with nosocomial MRSA, CA-MRSA species are generally more susceptible to antibiotics, including trimethoprim–sulfamethoxazole, rifampin, quinolones, and clindamycin, though resistance to clindamycin may be selected [4]. Published data has suggested that CA-MRSA was not a frequent cause of community-acquired pneumonia (CAP), although with increasing incidence over the past few years the

frequency of CA-MRSA CAP can be estimated to be between one in 200 and one in 2000 cases of CAP [13].

Initial antimicrobial treatment for patients with CAP should provide appropriate coverage against the most common causative organisms, including resistant strains [17].

The European Respiratory Society (ERS) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) recommends that initial empirical treatment for hospitalized non-intensive care unit (non-ICU) patients with CAP should be provided with following antibiotics (with one of proposed regimens): aminopenicillin with or without macrolide; aminopenicillin/b-lactamase inhibitor ± macrolide; non-antipseudomonal cephalosporin; cefotaxime or ceftriaxone with or without macrolide; levofloxacin; moxifloxacin; penicillin G with or without macrolide [21].

The American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) consensus guidelines on the management of CAP in adults recommend that the standard empirical regimen should routinely cover the 3 most common pathogens that cause severe CAP, all of the atypical pathogens, and most of the relevant Enterobacteriaceae species. ATS/IDSA recommends treating CAP with a respiratory fluoroquinolone or a b-lactam plus a macrolide for hospitalized non-ICU adult patients [11].

According to Russian guidelines on the management of CAP in adults monotherapy with respiratory fluoroquinolones (levofloxacin; moxifloxacin) is an alternative to combination of b-lactam plus a macrolide [1].

In summary, fluoroquinolones are highly active and efficacious against respiratory pathogens [21] and in some cases should be used as first-line agents [18].

Although respiratory pathogens (e.g., Moraxella catarrhalis, Haemophilus influenzae, and Streptococcus pneumoniae) are generally susceptible to quinolones, resistance does occur, it has been reported in localized outbreaks [10], and is associated with clinical failure [6] [7]. Some CA-MRSA clones have become fluoroquionlone resistant [22].

The problem of fluoroquinolone resistance has brought great challenge into clinical practice. Therefore, the development of newer quinolone compounds with greater activity and less resistance is urgently required [15].

3.2 Investigational products

Nemonoxacin is a novel non-fluorinated quinolone (NFQ) and will be investigated as an investigational product in this clinical study. Nemonoxacin inhibits bacterial DNA gyrase, a key topoisomerase involved in the formation of bacterial DNA supercoils [28].

Nemonoxacin was first developed by Procter and Gamble Pharmaceuticals (Cincinnati, OH, USA) and completed the Phase IA single-dose escalation studies in 2004. Thereafter, it was authorized to TaiGen Biotechnology Co, Ltd (Taipei, Taiwan) for worldwide clinical trials and further development [15]. TaiGen Biotechnology Co., Ltd. licensed Russian pharmaceutical company R-Pharm JSC exclusive rights to develop and register Nemonoxacin in the Russian Federation, other members of the Commonwealth Independent States (CIS) countries and Turkey (http://r-pharm.com).

The drug is available in intravenous (i.v.) and capsules formulations. Nemonoxacin capsules has already been approved in Taiwan and China for treatment of CAP. Intravenous formulation has passed phase II of clinical studies and phase III clinical study is ongoing in China.

Tavanic® (levofloxacin) is an approved fluoroquinolone, which will be used as a comparator in this clinical study.

Levofloxacin is the optically active L-isomer of ofloxacin and acts on the DNA-DNA-gyrase complex and topoisomerase IV. Levofloxacin is indicated in adults for the treatment of community-acquired pneumonia, skin and soft tissue infections, uncomplicated and complicated urinary tract infections including acute pyelonephritis, chronic bacterial prostatitis, etc. The CAP indication is approved for both tablets and i.v. formulations of levofloxacin.

3.3 Preclinical and clinical studies of Nemonoxacin

Below there is brief information on the results of preclinical and clinical studies. Detailed information is presented in Investigational Brochure.

Nemonoxacin was investigated under the research number "TG-873870". The malate salt hemihydrate of TG-873870, "TG-875649", was determined to be conducted in the initial clinical studies; dosing was adjusted to reflect the clinical dosage of anhydrous free base, TG-873870.

3.3.1 Preclinical studies of Nemonoxacin

3.3.1.1 In vitro studies on antibacterial activity of nemonoxacin

Nemonoxacin had broad-antibacterial spectrum *in vitro*. It exhibited strong antibacterial activity against penicillin-sensitive or penicillin-intermediate, or penicillin-resistant *S. pneumoniae* (PSSP, PISP, PRSPA), some gram-negative bacteria (e.g., *M. catarrhalis*, *H. influenzae*, etc.), and atypical pathogens (such as *L. pneumophila*, *M. pneumoniae* and *C. pneumoniae*). In addition, this drug also showed good antibacterial activity against community-acquired methicillin-resistant *S. aureus* (CA-MRSA) and drug-resistant *S. pneumoniae* (DRSP) [28]. In case of respiratory pathogens nemonoxacin had the same or superior activity to marketed fluoroquinolones [5][28].

In accordance to the drug resistance tests on Nemonoxacin it was shown that mutation site of the drug in the quinolone resistance-determining regions (QRDRs) was different from other quinolones (mutation generally occurred in *gyrA* and *parC*) [28].

3.3.1.2 Efficacy of nemonoxacin in pulmonary model of infection

The *in vivo* antibacterial efficacy of nemonoxacin was evaluated in a mouse pulmonary model of infection by *Streptococcus pneumonia* and in a mouse pulmonary model of infection by penicillin-resistant *S. pneumoniae* and *K. pneumoniae*. During the first study nemonoxacin significantly reduced the amount of viable bacteria in lungs and blood samples at all dosage levels when compared to vehicle-treated controls and protected from death in 100% cases. Moreover nemonoxacin was more effective than moxifloxacin at the same dosage levels. In the second study nemonoxacin also significantly reduced the viable bacteria counts of penicillin-resistant *S. pneumoniae* in lungs when compared to vehicle-treated controls and had slightly higher efficacy than levofloxacin. Against the *K. pneumoniae* infections, oral administration of nemonoxacin showed a significantly reduction in bacteria counts when compared to vehicle-treated controls but the drug had lower efficacy than levofloxacin [28].

3.3.1.3 Animal pharmacokinetics and metabolism

Nemonoxacin absorption was nearly complete after single oral dosing in dogs and monkeys (bioavailability of 80% in monkeys and 100% in dogs), while bioavailability was lower (~30%) in rats. Food decreased the bioavailability by up to 77% in monkeys.

Protein binding to mouse, rat, rabbit, dog, monkey and human plasma was low (ranging from 12 to 48%) over the concentration range of 0.1 to 1000 µg/mL, indicating little potential for protein binding-based drug interactions.

After single-dose intravenous infusion (10 mg/kg) or oral gavage administration (30 mg/kg) of Nemonoxacin to rats, the drug was distributed to body immediately; the concentrations of Nemonoxacin in kidney, liver, submandibular gland, small intestine, lung and spleen were the higher, followed by heart, muscle, large intestine, pancreas and bladder. The concentrations of nemonoxacin in brain and fat were relatively lower. There was a significant difference between ovary gonads and testicles. For both administration routes, drug was distributed similar in body.

Monkey and human hepatocytes did not metabolize nemonoxacin. The rat hepatocytes produced one metabolite (a glucuronide conjugate) but the extent of metabolism was low (<5% of total drug) [28].

3.3.1.4 Toxicological studies

The in vitro genotoxicity (mutagenicity) was considered to be related to its mechanism on inhibition of DNA gyrase by the drug. In mice micronucleus tests and rat unscheduled DNA synthesis tests, animals administered with nemonoxacin at a dose up to 2000 mg/kg did not produce in vivo genotoxicity. The drug had no potential to cause hemolytic effect in *in vitro* hemolysis test with rabbit erythrocytes.

In repeated dose toxicity studies renal tubular effects were observed at ≥ 20 mg/kg following 7 days of dosing, but these effects were not observed at up to 1000 mg/kg (AUC ≈ 130 h*µg/mL) following 1 month of dosing in rats, or up to 500→300 mg/kg (AUC ≈ 680 h*µg/mL) in monkeys. This likely represents the large capacity of the kidney to adapt to the effect.

In the 1-month monkey study, watery stools were observed at a dose of 30 mg/kg (AUC = 60 h* µg/mL), emesis, sinus bradycardia, and increased urine protein at a dose of 100 mg/kg (AUC = 230 h* µg/mL), and QRS widening, decreased activity, ptosis, pale skin, dilated pupils, and thymic atrophy at a dose of 500 mg/kg (AUC = 690 h* µg/mL). There was a dose-dependent prolongation of mean QTc and a reduction of the mean heart rate (prolonged R-R interval) for the high dose group (500/300 mg/kg) at 3 hours post dose on Days 5 and 26. The mean QTc was mildly prolonged in the female monkeys and the mean heart rate reduced for the mid dose group (100 mg/kg). The mean QTc and heart rate recovered by the subsequent 24-hour timepoint for both groups. These changes were attributed to the administration of TG-875649 (nemonoxacin malic acid salt, hemihydrate).

In a 28-day dog study, QTc prolongation was observed in dogs treated with second dose of 100 mg/kg at 1 hour post-dose, but this sign was not seen at 24 hour post-dose. No ECG change was noted after the last dose administration.

A battery of safety pharmacology studies was conducted to assess the effect of TG-873870 on the central nervous system (CNS), cardiovascular system, respiratory system, gastrointestinal (GI) system, and renal system. Based on the results of the studies it was demonstrated that TG-873870 had effects on the CNS, GI systems and on cardiac electrophysiology, which were

consistent with the known pharmacology of quinolones. The hERG and Purkinje findings suggest the possibility of QTc prolongation in man. Mild effects were also seen at the high dose (1000 mg/kg) in some CNS (decreased SMA) and GI (decreased gastric motility) studies.

Nemonoxacin did not elicit cutaneous phototoxicity when administered orally either once or repeatedly; did not produce systemic hypersensitive reactions during active systemic anaphylaxis test. In the bone/cartilage studies in juvenile dogs administered nemonoxacin at 10, 20, or 40 mg/kg/day for 4 weeks, the microscopic changes were noted in 2/3 males and 3/3 females of the 40 mg/kg/day dose group, the changes were graded minimal to moderate in severity and characterized by degeneration/necrosis with or without horizontal clefting and/or erosion of the articular cartilage. The nature and distribution (targeting the weight bearing area and middle zone of the proximal and distal femur) of these microscopic changes were compatible with quinolone-induced arthropathy/chondrotoxicity. No apparent changes were seen after 13 weeks recovery, suggesting a complete reversibility of the changes [28].

3.3.1.5 Interaction with cytochrome P450

Human primary hepatocytes were used to test the inducing potential of nemonoxacin. Nemonoxacin showed no significant induction or inhibition of CYP 1A2, 2B6, 2C8, 2C9, 2C19 and 3A4 at concentration up to 100 µg/mL [28].

3.3.2 Clinical studies of nemonoxacin

At this time thirteen clinical studies of nemonoxacin, oral capsules, with a total of more than 870 subjects have been completed in U.S., China, South Africa and Taiwan. Five clinical studies of nemonoxacin, solution for infusion, have been already conducted in more than 380 subjects.

3.3.2.1 Phase I clinical trials

During a randomized, double-blind, placebo-controlled, parallel-design, single ascending dose study (#2003107) carried out in the USA the safety, tolerability, and pharmacokinetics of orally administered nemonoxacin in healthy male and female volunteers were investigated. Fifty six subjects were enrolled in the study. Healthy volunteers were randomized to the nemonoxacin group and the control (placebo) group at a ratio of 3:1. Nine escalating dose cohorts, i.e. 25 mg, 50 mg, 125 mg, 250 mg, 500 mg, 1000 mg, 1500 mg, 2000 mg and 2500 mg, were planned. However, because of the AEs (pruritus and erythema), dose escalation was stopped after 1500 mg dose. Therefore, 1500 mg was defined as the maximum tolerated dose. There were no significant laboratory and ECG abnormalities and also no vital signs abnormalities. Nemonoxacin was rapidly absorbed after oral administration in the fasted state, with peak plasma concentrations attained within 1 to 2 hours post-dose. The mean terminal exponential half-life ($T_{1/2}$) was approximately 10 hours over the 25 mg to 250 mg dose range and increased to approximately 15 hours at higher doses. The mean renal clearance rate was approximately 0.09 L/h/kg; the mean oral clearance rate was approximately 0.22 L/h/kg; and the mean terminal volume of distribution was 3.8 L/kg. The mean urinary excretion was approximately 45% of the administered dose over the 25mg to 1500 mg dose range and 75% of the urinary excretion occurred within the first 24h after drug administration. In addition, the mean plasma protein binding of approximately 16% was observed over the concentration range of 141 ng/mL to 4270 ng/mL [28].

The safety, tolerability and pharmacokinetics of multiple orally administered doses of nemonoxacin were investigated during a randomized, double-blinded, placebo-controlled, escalating, multiple-dose study (#TG-873870-01) conducted in the USA in healthy volunteers. A total of 46 subjects were enrolled in the study. Each subject received an assigned dose of the study drug or the placebo once daily for ten days. Five dose groups, e.g. 75 mg, 250 mg, 500 mg, 750 mg and 1000 mg, were studied. Each of the 75 mg and 250 mg dose groups consisted of 8 subjects. The ratio of the investigational drug to placebo was 3:1 (6 active, 2 placebo). Each of the 500 mg, 750 mg and 1000 mg dose groups consisted of 10 subjects. The ratio of the investigational drug to placebo was 4:1 (8 active, 2 placebo). There were no apparent differences in laboratory test, ECG intervals, ECG morphology, vital signs measurement and physical examination findings during the study. With the exception of changes in serum amylase and serum lipase in one subject each, there were no clinical laboratory findings of potential clinical concern during the study. There was rapid absorption of nemonoxacin following oral administration in the fasted state, with peak plasma concentrations attained within 1 to 2 hours post-dose. Half-life ranged from approximately 7 to 8 hours after single dose administration of 75 mg - 1000 mg. The half-life appeared to increase after repeated administration for 10 days (ranged from approximately 18-23 hours). The presence of food led to decrease in both C_{max} and AUC (C_{max} and AUC_{0-24h} decreased by approximately 46% and 27% respectively in the fed state) and a 3-hour delay in median T_{max} [28].

A phase I clinical study of intravenous administration of Nemonoxacin malate sodium chloride injection was carried out in China and consisted of four parts (TG-873870-C-2: part A, B, C-1 and C-2). During the part A of study the tolerability of intravenous Nemonoxacin malate injection was investigated. To explore the safe dose by evaluating the safety and tolerability of eight dose levels of nemonoxacin (25, 50, 125, 250, 500, 750, 1000 and 1250 mg) the drug was given as single intravenous dose in Chinese healthy subjects. A total of 92 subjects were assigned into 12 groups with equal numbers of male and female. The tolerated-dose study of the nemonoxacin indicated that the tolerated-dose ranged from 25 mg to 1250 mg and the maximum dose was 1250 mg. The most common drug-related AE was local reaction at administration sites (27/68) and skin rash with or without pruritus (13/68) All AEs were mild and transient, and recovered spontaneously during the administration or shortly after administration. No important or serious AEs that led to study discontinuation and clinical significant change in ECG was observed. As for the laboratory tests, no drug related hyperglycemia or hypoglycemia occurred. The infusion rate of the drug ranged from 0.42 mg/min to 8.33mg/min. The occurrence of skin rash was more common with infusion rate of 8.33 mg/min (3 subjects each in 500 mg and 750 mg group), and all other infusion rates (0.42 mg/min to 5.56 mg/min) were tolerated well.

Part B of the trial evaluated the pharmacokinetic profiles of single-dose nemonoxacin malate sodium chloride injection at 250, 500, and 750mg in healthy Chinese volunteers (see Brochure for details).

During the part C-1 (500 mg and 750 mg doses were investigated) and C-2 (500 mg, 650 mg and 750 mg doses were investigated) of study the tolerability and pharmacokinetics of the multi-dose continuous intravenous infusion of nemonoxacin malate was investigated. During these studies there were no serious AEs and clinical significant change in ECG. In the C-1 study after the multiple intravenous infusions of nemonoxacin C_{max} on day 10 (steady state) in the 500mg and 750mg group was 9.600±1.838 µg/mL and 11.039±2.177 µg/mL respectively. AUC_{0-t} (for 500 mg group: 22.5h; for 750 mg group: 21.75h) was 44.03±8.62 µg.h/mL and 65.82±10.78 µg.h/mL respectively. Statistical analysis revealed no cumulative effect in both groups after administration for consecutive 10 days [28].

3.3.2.2 Phase II clinical trials

A randomized, double-blind, comparative, multi-center study (#TG-873870-02) of the safety and efficacy of oral nemonoxacin versus oral levofloxacin in adult patients with CAP was carried out in 19 study centers in South Africa and Taiwan. A total of 265 subjects were enrolled and randomized in the study: 86 patients in the nemonoxacin 750 mg group, 89 in the nemonoxacin 500 mg group and 90 in the levofloxacin 500 mg group. Patients received therapy once daily for 7 days. The study revealed that 750 and 500 mg nemonoxacin had similar clinical efficacy when compared with 500 mg levofloxacin once daily for 7 days. The safety profile of nemonoxacin was also similar to that of levofloxacin and it was consistent with the favorable safety results of nemonoxacin in previous phase I studies [28].

Efficacy and safety of Nemonoxacin malate sodium chloride injection versus Moxifloxacin hydrochloride sodium chloride injection in the treatment of moderate to severe adult CAP were evaluated during a multi-center, randomized, double-blind, parallel, controlled, phase II study. Patients received either 500 mg nemonoxacin, 650 mg nemonoxacin, or comparator drug moxifloxacin 400 mg once a day for 7 to 14 days. A total of 207 subjects were randomly enrolled in 30 research centers: 69 subjects were in the nemonoxacin 500mg group, 68 subjects were in the nemonoxacin 650 mg group and 70 subjects were in the control group (moxifloxacin 400mg). Nemonoxacin had shown similar clinical efficacy, microbiological efficacy, and overall efficacy when compared with moxifloxacin hydrochloride sodium chloride injection once a day for 7 to 14 days. The AEs reported during the study were mostly mild, transient, and tolerated by most patients. The main drug-related AEs in patients who received nemonoxacin were local reactions at the infusion site. The main drug-related laboratory abnormalities were elevated liver transaminases without bilirubin elevation [24].

3.3.2.3 Phase III clinical trials

During a multicenter, randomized, double-blind, double-dummy, parallel, comparative, phase III study the efficacy and safety of oral administration with Nemonoxacin versus Levofloxacin in treating adult patients with CAP were evaluated (TG-873870-C-4). The study was conducted in 53 study centers in China and Taiwan. A total of 532 patients were randomized into the study at a ratio of 2:1 into two groups: the investigational group (nemonoxacin 500 mg) and the control group (levofloxacin 500 mg), respectively. There were 357 patients in the investigational group (nemonoxacin) and 175 patients in the control group (levofloxacin). Duration of therapy was 7 – 10 days. The results of the study indicate that oral administration of 500 mg nemonoxacin malate capsules for 7 to 10 consecutive days achieved excellent clinical and microbiological efficacies in treating adult CAP patients. Nemonoxacin had similar clinical and microbiological efficacies as compared with levofloxacin. Statistical analysis demonstrated that nemonoxacin was non-inferior to in clinical and microbiological efficacies. The AEs reported in the study were mostly mild in intensity, well-tolerated, and did not affect the course of the treatment. No deaths were reported during this study [25].

3.4 Assessment of Potential risks and benefits for participants

Comparator Tavanic® (Levofloxacin) is effective antibiotic approved for treatment of a wide variety of infectious diseases, including CAP. The drug may be administered for empiric antimicrobial therapy in patients with CAP.

Investigational product Nemonoxacin, capsules, has already been approved in Taiwan and China for treatment of CAP and the phase III clinical study of efficacy and safety of Nemonoxacin intravenous formulation is ongoing. At this time more than 1000 subjects were participated in various clinical studies of nemonoxacin, capsules or solution for infusion.

Nemonoxacin has shown similar clinical and microbiological efficacies as compared with levofloxacin during clinical studies in patients with CAP (see Sections 3.3.2.2 and 3.3.2.3). Nemonoxacin was well tolerated and had acceptable safety profile either when administered by intravenous and oral routs. The majority of AEs reported during the studies were mild and transient.

The risk to patients in this clinical study will be minimized by compliance with selection criteria. Taking into account available safety data for investigational medicinal products, both Levofloxacin and Nemonoxacin (e.g., possibility of QT prolongation, hypoglycemia, tendinitis and tendon rupture, etc.), these medicinal products will be avoided in patients with renal impairment, diabetes mellitus, QT prolongation, uncorrected hypokalemia, receiving class Ia or III antiarrhythmic agents, receiving corticosteroids, etc.

Levofloxacin was shown to have photosensitization activity. Therefore, in order to prevent photosensitization in patients the Patient Information Leaflet provides precautions for study participants not to expose themselves unnecessarily to strong sunlight or to artificial ultra-violet rays. Although Nemonoxacin did not elicit cutaneous phototoxicity in preclinical studies and by now there is no clinical data suggested phototoxicity of the drug the aforementioned precautions will be taken by all participants (i.e., regardless of treatment group) because of double-blind design of the study and because of absence of certainty the drug has not such activity.

In consideration of the foregoing assumptions the risk-benefit ratio for the participants is acceptable.

This clinical study will be conducted in compliance with the Protocol, ICH GCP and all other applicable local regulatory requirements.

3.5 Dose, route, regimen and treatment period rationale

Nemonoxacin, solution for infusion, and Nemonoxacin, capsules, will be administered at daily dose of 500 mg. The choice of the dose is based on the results of previous clinical trials (please, refer to Section 3.3.2).

Tavanic® (levofloxacin), solution for infusion, is available in one dosage strength of 500 mg (100 ml). Tavanic® (levofloxacin), film coated tablets, is available in two dosage strengths of 250 and 500 mg. The usual dose of Levofloxacin (either solution for infusion and tablets) for treatment of community-acquired pneumonia is 500 mg administered once or twice a day for 7-14 days, as indicated in product label [26][27]. In this clinical study the daily dose of Tavanic® (levofloxacin) was chosen to be 500 mg because this daily dose was approved for the treatment of CAP in the countries where this clinical study will be carried out.

Therapy of the patients will start with intravenous infusions and after 3-7 days patients will be switched to oral treatment. In accordance with Russian recommendations for management of

CAP taking into consideration that hospitalized patients usually tend to have more severe course of CAP it is reasonable to start treatment with parenteral antibiotics and to switch to oral treatment after the normalization of temperature and abatement of the symptoms [1]. Switch from intravenous to oral antibiotics is generally considered appropriate and safe in clinical practice when criteria indicative of clinical stability of disease are met. In the CAPRIE study the majority of patients were switched to oral therapy on day 3-4 after the start of treatment with levofloxacin [3]. In another study the median time to actual switch to oral therapy was 5 days (range from 2 to 7 days) for levofloxacin-treated patients and the total duration of study therapy was 7 to 14 days at the investigator's discretion [16]. In general, as many as two-thirds of all patients with CAP have clinical improvement and meet criteria for a therapy switch in the first 3 days, and most non-intensive care unit patients meet these criteria by day 7 [11]. Therefore, the switch to oral treatment was chosen to be Day 4-8 of the study, after 3-7 days of intravenous therapy.

4 STUDY OBJECTIVES

4.1 Primary Objective

To evaluate the clinical efficacy of treatment with Nemonoxacin compared with Tavanic® in patients with CAP.

4.2 Secondary Objectives

- To evaluate the clinical efficacy of treatment with intravenous Nemonoxacin compared with intravenous Tavanic® in patients with CAP
- To assess the safety of treatment with Nemonoxacin compared with Tavanic® in patients with CAP
- To assess the pharmacokinetic parameters of intravenous Nemonoxacin in adult patients with CAP
- To evaluate the microbiological efficacy of treatment with Nemonoxacin compared with Tavanic® in patients with CAP.

5 CLINICAL STUDY ENDPOINTS

5.1 Efficacy endpoints

5.1.1 Primary efficacy endpoint

The primary efficacy endpoint is the proportion of patients with clinical success as judged by the investigator at the test of cure visit (Visit 4).

5.1.2 Secondary efficacy endpoints

The secondary efficacy endpoints are the following:

- Proportion of patients with clinical success as judged by the investigator at the Visit 2 (switch to oral therapy) and Visit 3
- Proportion of patients with infection relapse at Visit 5
- Time to switch therapy from i.v. to oral therapy
- Need for other antibiotic treatment
- Proportion of patients with microbiological responses at the Visit 2 (switch to oral therapy), Visit 3 and Visit 4.

5.2 Safety endpoints

The following safety endpoints will be evaluated:

- Adverse events
- Changes in vital signs
- Clinical laboratory results
- ECG results
- Physical examination results.

5.3 Pharmacokinetic parameters

The following pharmacokinetic parameters will be evaluated:

- C_{max}
- $C_{22.5h}$
- $AUC_{0\text{-}22.5}$
- $AUC_{0\text{-}inf}$
- CL
- V_{ss}
- $T_{1/2}$

6 STUDY DESIGN

6.1 Design Summary

This is an international, multicenter, randomized, parallel group, double-blind, double-dummy, controlled study of efficacy and safety.

Treatment-naive patients with community-acquired pneumonia (non-nosocomial pneumonia) and patients with treatment failure will be screened and if eligible will be randomized in a ratio of 1:1 to receive either treatment with investigational product (Nemonoxacin) or comparator (Tavanic®). After randomization patients will start to receive intravenous therapy with investigational product or comparator and then upon a decision of investigator patients will be switched to oral therapy with the same product. To maintain double-blinding during the intravenous treatment the patients will receive placebo solution (100 ml or 250 ml) along with intravenous

antibiotic (Nemonoxacin or Tavanic®) solution. To maintain double-blinding during oral antibiotic therapy each Tavanic® tablet was placed into a capsule shell (over-encapsulated), that is identical in appearance to a Nemonoxacin-containing capsules; therefore, the patients will receive daily treatment with 2 capsules either containing nemonoxacin or levofloxacin (tablet of Tavanic®) (see Table 6-1).

Table 6-1 Summary of treatment groups

Group	Number of patients	Intravenous therapy (once a day)		Oral therapy (once a day)
		First infusion	Second infusion	
Investigational drug (Nemonoxacin)	171	Nemonoxacin 500 mg (250 ml), solution for infusion, will be given over 90-110 minutes	Placebo (100 ml), solution for infusion, will be given over a minimum of 60 minutes	Nemonoxacin 250 mg x 2 capsules
Comparator (Tavanic®)	171	Placebo (250 ml), solution for infusion, will be given over 90-110 minutes	Tavanic® 500 mg (100 ml), solution for infusion, will be given over a minimum of 60 minutes	Tavanic® 250 mg x 2 over-encapsulated film coated tablets
Total number of patients	342			

Intravenous therapy will be administered once a day and will include two consequence infusions (antibiotic solution and placebo solution). Solution with volume of 250 ml will always be infused over 90-110 minutes and before the infusion of solution with volume of 100 ml that will be infused over at least 60 minutes. Intravenous therapy should be given for at least 3 days and may be prolonged by a decision of investigator up to 7 days. Then investigator will switch a patient from intravenous to oral therapy on Day 4(8) of the study if the specific criteria of clinical stability are achieved (please, refer to Appendix 2). However if the treatment with intravenous IMP should be prolonged after the 7 days of treatment are completed (according to the investigator's opinion) the investigator should contact the study Medical Adviser (please, refer to Contact information) for the approval of intravenous treatment prolongation.

In general since Day 4(8) of the study treatment will be continued with the same antibiotic administered orally. Patients will daily receive treatment either with 2 capsules of investigational drug (Nemonoxacin, 250 mg) or 2 over-encapsulated film coated tablets of Comparator (Tavanic® 250 mg).

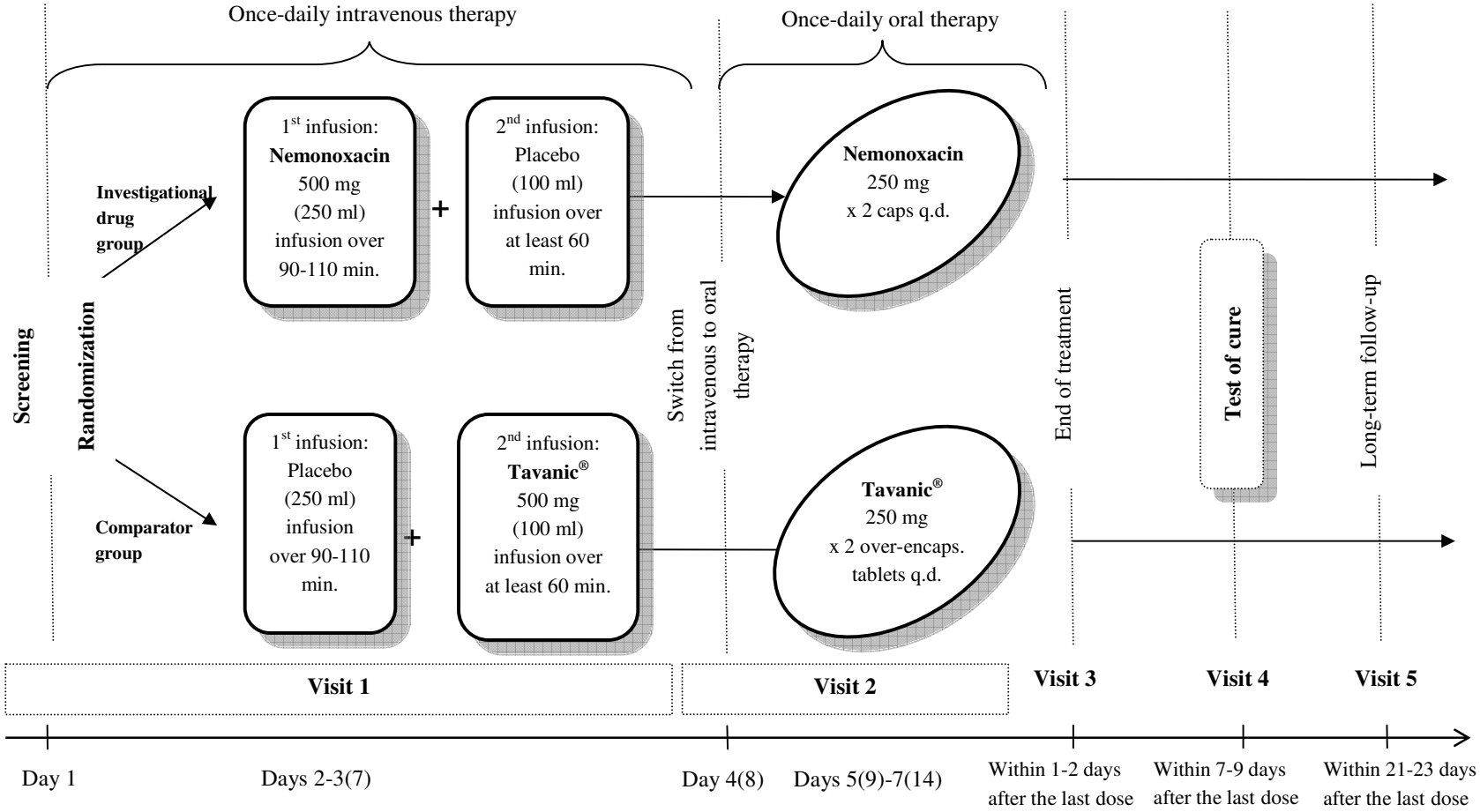
The average duration of treatment (including intravenous and oral therapy) for each patient will be 7(14) days and during this period patients should stay at hospital.

After completion of the treatment patients can be discharged from the hospital and should return for examinations at End of treatment visit (Visit 3) within 1-2 days after the last dose. Then the patients should attend the investigational site within 7-9 days after the last dose (test of cure visit). Then the investigator will contact the patients by phone within 21-23 days after the last dose (long-term follow-up visit).

The study includes 5 visits. The detailed description of visits is presented in Section 9.2.

A schematic diagram of the study design is presented in Figure 6-1.

Figure 6-1: Study design



7 SELECTION OF STUDY POPULATION

7.1 Inclusion Criteria

Patients will be eligible for inclusion in the study only if all of the following inclusion criteria are applied:

1. Written informed consent obtained from the patient.
2. Female and male patients aged between 18 and 70 years inclusive.
3. Patients with moderate to severe community-acquired pneumonia who need inpatient treatment (correspondence to at least one of the criteria for hospitalization / preferred hospitalization described in the Appendix 1 of this protocol) but do not need ICU treatment (in case of correspondence to at least one «major» or three «minor» criteria for hospitalization in intensive care unit described in Appendix 1 of this protocol, patient should not be enrolled in the study).
4. The presence of at least 3 of the following symptoms/signs:
   - Cough
   - Purulent sputum production
   - Tachypnea (respiratory rate > 24 breaths/minute)
   - Chills
   - Fever (rectal/ tympanic temperature ≥ 38.5°C or axillary/ oral/ cutaneous temperature ≥ 38.0°C)
   - WBC count of ≥10.0 x 10^9/L or ≥15% immature neutrophils (bands; regardless of peripheral WBC count).
5. Radiological evidence of (a) new infiltrate(s) consistent with bacterial pneumonia at baseline.
6. Treatment-naive patients or patients who have received single dose of a short-acting antibacterial drug within 24 hours of enrollment or patients with treatment failure who have received antibiotics (with the exception of quinolones or fluoroquinolones) for less than 72 hours.
7. Consent to use contraception during participation in the study (for women childbearing potential and men).

7.2 Exclusion Criteria

Patients won't be eligible for inclusion in the study if any of the following exclusion criteria is applied:

1. Known hypersensitivity to quinolones, fluoroquinolones or any of the excipients.
2. Female patients who are pregnant or nursing.
3. History of tendon disease/disorder related to quinolone treatment.
4. Known congenital or documented-acquired QT/QTc(F) prolongation on ECG (QTc(F) interval more than 450 ms); concomitant use of drugs, reported to increase the QT interval; uncorrected hypokalaemia and uncorrected hypomagnesemia; clinically relevant bradycardia; clinically relevant heart failure

with reduced left-ventricular ejection fraction; previous history of symptomatic arrhythmias.

5. History of bronchiectasis, cystic fibrosis, bronchial obstructions excluding chronic obstructive pulmonary disease.
6. History of epilepsy and/or history of psychotic disorder.
7. Patients with history of myasthenia gravis
8. Patients with diabetes mellitus
9. Known glucose-6-phosphate dehydrogenase deficiency.
10. Active hepatitis or decompensated cirrhosis.
11. Alanine transaminase or aspartate transaminase increase > 3 fold ULN.
12. Patients with creatinine ≥ 1.1 fold ULN.
13. Patients requiring concomitant systemic or inhaled antibiotics (e.g., tobramycin).
14. Known or suspected active tuberculosis or endemic fungal infection.
15. Concomitant immunosuppressive therapy including a long-term (more than 2 weeks) treatment with oral or intravenous glucocorticoids at doses of 20 mg and higher of prednisone daily or an equivalent dose of other glucocorticoids.
16. Patients known to have HIV-positive status or AIDS or known to have other disease that seriously affects the immune system such as active haematological or solid organ malignancy, or splenectomy.
17. History of drug or alcohol abuse.
18. Patients have received quinolones or fluoroquinolones within 14 days before enrollment.
19. Previous enrolment in this study or participation in another study within the previous 4 weeks.
20. Patients with any severe medical condition as determined by medical history that, in the opinion of the investigator, does not allow the patient to carry out all planned procedure of the protocol.

7.3 Discontinuation of Therapy and Withdrawal of the Patients from the Study

Study therapy should be discontinued and the patient should be withdrawn from the study due to any of the following reasons:

- Informed consent withdrawal (the patient has made the decision to stop the participation in study for any reason)
- The patients require other antibiotic treatment
- Development of any adverse event, including serious adverse event, clinical significant deviation in the laboratory results, or concomitant disease, which at the investigator's opinion indicates, that continuation of the study medication administration is not at the patient's best interest
- Pregnancy
- Termination of the study by the Sponsor (e.g. in case of poor safety results)
- Termination of the study by the Regulatory Authority (e.g. in case of poor safety results).

In all cases the reason of termination of participation in study must be recorded in eCRF. When the patient is withdrawn from the study, all efforts should be made to perform all procedures scheduled for the "early termination visit":

- if the "early termination visit" coincides in time with scheduled visit the procedures of that visit should be done (Section 9.2);
- if the "early termination visit" coincides in time with unscheduled visit the minimum number of procedures should comply with the "End of treatment visit" (Section 9.2.3).

All the patients withdrawn from the study will receive treatment in accordance with the standards adopted in the hospital.

Withdrawn patients will not be replaced.

8 TREATMENT

8.1 Treatments Administered

Two investigation products, two comparators and 2 placebos will be used during the study. All the investigational medicinal products will be blinded (please refer to Section 8.6).

In this trial the investigational products are Nemonoxacin 500 mg (250 ml), solution for infusion, and Nemonoxacin 250 mg, capsules.

Nemonoxacin 500 mg (250 ml), solution for infusion, will be administered daily as single intravenous infusion over 90-110 minutes followed by infusion of Placebo (100 ml), solution for infusion, over a minimum duration of 60 minutes to maintain the blinding. Daily dose of Nemonoxacin will be 500 mg (250 ml). Intravenous therapy will be given for at least 3 days and may be prolonged by a decision of investigator up to 7 days. The possibility of further prolongation of intravenous treatment (for more than 7 days) has to be discussed with the study Medical Adviser. The decision about switching to oral therapy should be based on assessment of patient's condition using the criteria of clinical stability.

After the switch to oral therapy on Day 4(8) of the study the patients who receive intravenous therapy with Nemonoxacin, solution for infusion, will receive therapy with Nemonoxacin, capsules. Please note that the first dose of oral drug will be administered on the same day when the "switch" is performed (e.g. the patient will receive the first dose of oral drug on Day 4 if the "switch" is performed at Day 4, etc.).

Nemonoxacin 250 mg, capsules, will be administered at a dose of 500 mg once daily (two 250 mg capsules). The duration of oral therapy will be judged by investigator and oral therapy will last until and including Day 7(14) of the study.

Tavanic® 500 mg (100 ml), solution for infusion, and Tavanic® 250 mg, over-encapsulated for the blinding purpose film coated tablets, will be used as the comparators in this study.

Tavanic® 500 mg (100 ml), solution for infusion, will be administered daily as single intravenous infusion over a minimum duration of 60 minutes. Daily dose will be 500 mg (100 ml). To maintain double-blinding before the infusion patients in this group will receive Placebo (250 ml), solution for infusion, over 90-110 minutes. Intravenous

therapy will be given for at least 3 days and may be prolonged by a decision of investigator up to 7 days. Further prolongation of intravenous treatment (for more than 7 days) has to be discussed with the study Medical Adviser. The decision about switching to oral therapy should be based on assessment of patient's condition using the criteria of clinical stability.

After the switch to oral therapy on Day 4(8) of the study the patients who receive intravenous therapy with Tavanic®, solution for infusion, will receive therapy with Tavanic®, over-encapsulated film coated tablets. Please note that the first dose of oral drug will be administered on the same day when the "switch" is performed (e.g. the patient will receive the first dose of oral drug on Day 4 if the "switch" is performed at Day 4, etc.).

Tavanic® 250 mg, over-encapsulated film coated tablets, will be administered at a dose of 500 mg once daily (two capsules each containing 250 mg film coated tablet). The duration of oral therapy will be judged by investigator and oral therapy will last until and including Day 7(14) of the study.

8.2 Investigational Medicinal Products (IMPs)

Table 8-1 Investigational Medicinal Products (IMPs)

Investigational product 1:	**Nemonoxacin**
INN:	Nemonoxacin
Chemical name:	7-[(3S,5S)-3-Amino-5-methyl-peperidin-1-yl]-1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
Pharmaceutical form:	Solution for infusion
Strength:	500 mg (250 ml)
Rout of administration:	Intravenous
Supplier:	R-Pharm JSC (Russia)
Manufacturer:	Zhejiang Medicine Co. (China)
Investigational product 2:	**Nemonoxacin**
INN:	Nemonoxacin
Chemical name:	7-[(3S,5S)-3-Amino-5-methyl-peperidin-1-yl]-1-cyclopropyl-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid
Pharmaceutical form:	Capsules
Strength:	250 mg
Rout of administration:	Orally
Supplier:	R-Pharm JSC (Russia)
Manufacturer:	Lotus Pharmaceutical Co., Ltd. (Taiwan)
Comparator 1:	**Tavanic®**
INN:	Levofloxacin
Chemical name:	(-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate
Pharmaceutical form:	Solution for infusion

Strength:	500 mg (100 ml)
Rout of administration:	Intravenous
Supplier:	R-Pharm JSC (Russia)
Manufacturer:	Sanofi-Aventis Deutschland GmbH, Germany (Germany)
Comparator 2:	**Tavanic®**
INN:	Levofloxacin
Chemical name:	(-)-(S)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methyl-1-piperazinyl)-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzoxazine-6-carboxylic acid hemihydrate
Pharmaceutical form:	Film coated tablets (each tablet is placed into a capsule shell (over-encapsulated) for blinding purposes)
Strength:	250 mg
Route of administration:	Orally
Supplier:	R-Pharm JSC (Russia)
Manufacturer:	Tablets manufactured by Sanofi Winthrop Industrie, France (France), are over-encapsulated into capsule shells by Lotus Pharmaceutical Co. Ltd. (Taiwan)

There will be two placebo formulations used during the study:

- Placebo (250 ml) - 0.9% NaCl (250 ml), solution for infusion
- Placebo (100 ml) - 0.9% NaCl (100 ml), solution for infusion

All placebo formulations will be supplied by the Sponsor. Placebo (250 ml), solution for infusion, is manufactured by Zhejiang Medicine Co. (China). Placebo (100 ml), solution for infusion, is manufactured by Dalchempharm OJSC (Russia).

8.3 Non-Investigational Medicinal Products

There will be no Non-Investigational Medicinal Products (NIMP) in this study.

8.4 Packaging, labeling and storage of IMPs

Nemonoxacin 500 mg (250 ml), solution for infusion, and Placebo (250 ml), solution for infusion, will be supplied in the flexible bags. Tavanic® 500 mg (100 ml) solution for infusion, and Placebo (100 ml), solution for infusion, will be supplied in the glass bottles.

Nemonoxacin 250 mg capsules and Tavanic® 250 mg over-encapsulated film coated tablets will be supplied in the plastic bottles.

Each unit of container will be appropriately labeled in accordance with local regulations. The label will clearly indicate “only for clinical study”. The label will be affixed to the primary container (bottles/flexible bags).

All IMPs will be stored at room temperature (less than or equal to 25°C) under secure conditions and protected from light. The temperature in the storage room should be controlled on a regular basis and should be documented in the Temperature Log.

At the site the IMPs should be stored in a locked room. Only unblinded staff appointed by Principal Investigator (PI) will have an access to the room. Unblinded staff will be instructed on the proper storage conditions of IMPs, return of drug and package.

All containers of the IMPs, both used and unused, must be saved for a monitoring by unblinded CRA and possible audit by an assigned Sponsor's designee.

8.5 Method of Assigning Patients to Treatment Groups

At Visit 1 (Day 1) to minimize or avoid bias randomization will be done. The study will utilize IWRS for randomization of the eligible patients. In accordance with randomization number each patient will be assigned to one of two treatment groups at the ratio of 1:1 (see Table 6-1):

- Investigational drug (Nemonoxacin) group
- Comparator (Tavanic®) group.

8.6 Blinding

This study has a double-blind and double-dummy design with 2 placebo formulations (see Section 8.2) needed for maintaining the blinding of intravenous treatment.

Intravenous drug dispensing procedure

Only the unblinded staff appointed by PI at each investigational site and an unblinded CRA will be aware of the intravenous treatment received by the patient. Neither the patients nor any of the principal investigators (PI)/ co-investigators/ other clinical staff (blinded staff), involved in the treatment of the patients, Sponsor and CRO (except an aforementioned unblinded CRA) will be aware of the intravenous treatment received by the patient.

The unblinded staff will include person, appointed by PI from study site staff (e.g. a doctor, a nurse, a pharmacist) at each investigational site. These unblinded person will be responsible for the supply of the drugs intravenous treatment for the certain patient.

After enrollment and obtainment of the subject study number using the interactive web response system (IWRS) each eligible patient will be randomized. The PI or one of the unblinded persons appointed by PI will access the IWRS at Visit 1 and IWRS will randomize the patient and provide the medication identification number of the investigational drug to be dispensed. For details refer to the IWRS manual, please.

Once the unblinded person receives the number, he/she will prepare the supply.

Unblinded person will take the appropriate solutions according to the medication identification number.

Nemonoxacin 500 mg (250 ml)/Placebo (250 ml), solutions

The flexible bag with Nemonoxacin/Placebo (250 ml) solution will be packed in an opaque bag that will be sealed by a sticker to prevent breaking the code. Then, the opaque bag with flexible bag inside will be put into the special designed empty packing box with number "1" on the label. The label with randomization number will be stuck to the box. After that the unblinded person will insert a spike of infusion set into the administration port of the flexible bag with Nemonoxacin /Placebo (250 ml) solution and will prime the infusion set.

Tavanic® 500 mg (100 ml)/Placebo (100 ml), solutions

The unblinded person will peel off the outer aluminum band from the top of the glass bottle with Tavanic®/Placebo (100 ml) solution. The bottle will be packed in a carton with a hole on the bottom for the administration port of the bottle. The carton will be sealed by a sticker to avoid breaking the code. Then, the carton with glass bottle inside will be put into the special designed empty packing box with number "2" on the label. The label with randomization number will be stuck to the box. After that the unblinded person will insert a spike of infusion set into the administration port of the bottle with Tavanic®/Placebo (100 ml) solution and will prime the infusion set.

Then, a person from blinded staff will take the supply, dose the patient, and return the supply after the dosing to the unblinded staff.

Oral drug dispensing procedure

Neither the patients nor any of the principal investigators (PI)/ co-investigators/ other clinical staff (blinded staff), involved in the treatment of the patients, Sponsor and CRO will be aware of the oral treatment received by the patient.

Since Day 4(8) of the study (switch from i.v. to oral therapy) the patients will receive the blinded capsules of oral drugs according to the medication identification number. Each patient will receive daily treatment with 2 capsules containing either Nemonoxacin (Nemonoxacin 250 mg capsules) or Levofloxacin (Tavanic® 250 mg, film coated tablets).

The randomization number will only be broken for an individual patient in an emergency such as an SAE that requires knowledge of which IMP was taken so that the SAE can be treated appropriately. In the event of SAE, if possible, the investigator should contact the medical adviser before the investigational drug blind will be broken to discuss the need for unblinding. If the randomization number for a patient is broken, the investigator must withdraw the patient from the study.

8.7 Prior and Concomitant therapy

For patients with treatment failure who have received antibiotics for less than 72 hours the information on therapy should be obtained and recorded in the eCRF (i.e., the trade name, INN/name of active ingredients, dosage, date of start, termination date).

The information on prior/concomitant drugs (the trade name, INN/name of active ingredients, dosage or change of dosage, indication, frequency of intake, prescription method, date of start, termination date) which the patient took before and takes during the study, should be registered in the corresponding section of the eCRF. All subsequent changes of concomitant therapy during the study should also be reflected in the eCRF. It will document information on previous drugs and treatments used from the onset of community-acquired pneumonia until the enrollment in the study (signing of the Informed Consent Form).

If there are any questions regarding concomitant therapy, the study Medical Adviser (see CONTACT information) should be contacted.

8.7.1 Permitted concomitant therapy

Females enrolled in study who use oral contraceptives can continue to take these drugs during whole study.

Patients are prohibited from using other drugs, except for necessary medical requirements, including:

- Treatment of concomitant pathology if it is not an exclusion criterion. In that case usual treatment regimen shouldn't contain prohibited drugs (see Section 8.7.2)
- Symptomatic treatment of the CAP (e.g., drugs such as antipyretics, analgesics, antihistamines, or cough suppressants) within the first 2 days of the treatment if necessary required by the opinion of the investigator. Since Day 3 (including) of the therapy these drugs are prohibited (see Section 8.7.2).

Information about all the concomitant drugs should be documented in the electronic Case Report Form (eCRF) in details (see Section 8.7).

8.7.2 Prohibited and limited in use therapy

During treatment period (from Visit 1 to Visit 3) the following medications should be prohibited:

1. Antacids, multivitamins containing calcium, magnesium, iron, zinc, or aluminum, and sucralfate should be prohibited within 3 hours before and after oral administration of the investigational drug. Intravenous therapy should not be co-administered with any solution containing multivalent cations, e.g., magnesium, through the same intravenous line.
2. Probenecid.

During study period (from Visit 1 to Visit 5) the following medications should be prohibited:

1. Drugs that may prolong the QT interval with known risk or possible risk of Torsades de Pointes (TdP). The list of these drugs is presented in Appendix 3.
2. Chemotherapeutic agents or antitumor drugs.
3. Other systemic antibacterial drugs (except for treatment failure).
4. Systemic immunosuppressive drugs, including inhaled steroids.
5. Drugs that may act to alter the signs and symptoms of infections (e.g., antipyretics, analgesics, antihistamines, or cough suppressants) – since day 3 (including) of the treatment.
6. Investigational products other than studied in this trial and other than the patient has been randomized.

8.8 Contraception

From the signing of informed consent on Visit 1 and throughout the duration of the study (until the last procedure at Visit 5) women of childbearing potential and men must use highly effective birth control methods.

A woman of childbearing potential is defined as a premenopausal female or a female who is less than 12 months post-menopausal and who has not undergone a

hysterectomy or surgical sterilization, e.g. bilateral tubal ligation, bilateral ovariectomy (oophorectomy).

In this study the patients can use the following birth control methods:

1. Barrier methods:
    - Male condom + spermicide
    - Cervical cap + spermicide
    - Diaphragm + spermicide
2. Intrauterine device (IUD)
3. Intrauterine hormone-releasing system (IUS)
4. Hormonal contraceptives:
    - Hormonal implants
    - Hormonal injections
    - Combined Oral Contraceptive Pill
    - Mini pill
    - Birth Control Patch
5. Sexual abstinence.

Patients will be provided with information on acceptable methods of contraception as part of the informed consent process obtainment.

8.9 Treatment compliance

Intravenous treatment will be administered under the supervision of investigational site personnel and date, start and stop time, volume (mL) of each infusion will be documented in the eCRF. Oral dosing will be also performed under the supervision of investigational site personnel. The total amount of oral dosing completed (capsules count) as well as dose administered, date and time of dosing will be recorded in the eCRF.

Patients should be informed that compliance with taking all oral medication as instructed is imperative.

9 STUDY VISITS AND PROCEDURES

9.1 Schedule of study procedures

The time points at which each procedure and assessment will be performed are presented in study schedule of procedures/assessments (see Table 9-1).

Table 9-1 Schedule of procedures/assessments

Study procedures/assessments	Visit 1[1]			Visit 2[1]		Visit 3[1]	Visit 4[1]	Visit 5[1]
	Day 1[2]		Days 2-3(7)	Day 4(8)	Days 5(9)-7(14)	Within 1-2 days after the last dose[3]	Within 7-9 days after the last dose[4]	Within 21-23 days after the last dose
	Screening procedures	Randomization and initiation of therapy	Continuation of intravenous therapy	Switch to oral therapy	Continuation of oral therapy	End of treatment visit	Test of cure visit	Long-term follow up visit
Initiation procedures								
Written informed consent (before all other procedures)	X							
Demographic data and other baseline characteristics	X							
Medical history	X							
Pregnancy test (for women of childbearing potential only)	X							
Check of inclusion/exclusion criteria	X							
Randomization (before starting of intravenous therapy)		X						
Safety assessments								
Physical examination	X		XXX[5]	X[5]	XXX[5]	X	X	
Vital signs	X	X[6]	XXX[6]	X[6]	XXX[6]	X	X	
ECG (before or 30 minutes after blood samples collection)	X			X[5]		X	X	
Haematology test	X[7]			X[5]		X	X	
Biochemical assay	X[7]			X[5]		X	X	

Study procedures/assessments	Visit 1[1]			Visit 2[1]		Visit 3[1]	Visit 4[1]	Visit 5[1]
	Day 1[2]		Days 2-3(7)	Day 4(8)	Days 5(9)-7(14)	Within 1-2 days after the last dose[3]	Within 7-9 days after the last dose[4]	Within 21-23 days after the last dose
	Screening procedures	Randomization and initiation of therapy	Continuation of intravenous therapy	Switch to oral therapy	Continuation of oral therapy	End of treatment visit	Test of cure visit	Long-term follow up visit
Urinalysis	X[7]			X[5]		X	X	
Documentation of AEs/SAEs	X[8]	X[8]	XXX	X	XXX	X	X	X
Efficacy assessments								
Chest x-ray/ CT	X[9]						X	
Pulse oximetry	X			X[5]		X	X	
Sputum sample collection for culture (if the patient has sputum)	X			X[5]		X	X	
Blood sample collection for culture	X			X[5, 10]		X[10]	X[10]	
Clinical response assessment				X		X	X	
Infection relapse assessment								X
Pharmacokinetic parameters								
Blood sample collection for PK via venous catheter		X[11]						
IMP administration								
Start of intravenous therapy		X						
Daily intravenous therapy (at least 3 days and up to 7 days)			XXX					
Switch to oral therapy (first oral dose)				X[12]				
Daily oral therapy (until					XXX			

Study procedures/assessments	Visit 1[1]			Visit 2[1]		Visit 3[1]	Visit 4[1]	Visit 5[1]
	Day 1[2]		Days 2-3(7)	Day 4(8)	Days 5(9)-7(14)	Within 1-2 days after the last dose[3]	Within 7-9 days after the last dose[4]	Within 21-23 days after the last dose
	Screening procedures	Randomization and initiation of therapy	Continuation of intravenous therapy	Switch to oral therapy	Continuation of oral therapy	End of treatment visit	Test of cure visit	Long-term follow up visit
Day 7-14 of the study)								
Compliance check		X	XXX	X	XXX			
Other								
Prior/concomitant medication and therapies	X	X	XXX	X	XXX	X	X	X

X – All procedures should be performed during one day.

XXX – All procedures should be performed every day during mentioned period of time.

[1] – All procedures of Visit 1 and Visit 2 will be performed during patient's hospital stay. All procedures of Visit 3 and Visit 4 can be performed at outpatient department. Visit 5 will be conducted as a telephone contact.

[2] – The maximum duration is 24 hours after the signing of informed consent.

[3] – The Visit should be conducted at least 24 hours after the last dose of the study drug.

[4] – All the efforts should be made to conduct this visit (Visit 4) 7 days after the end of treatment.

[5] – The procedure should be done before dosing.

[6] – On Day 1 of Visit 1 the procedure should be done 2 hours ±30 minutes after the infusion of second solution is finished. On Days 2-3(7) of Visit 1 the procedure should be done before dosing and 2 hours ±30 minutes after the infusion of second solution is finished. At Visit 2 the procedure should be done before dosing and 2 hours ±30 minutes after capsules intake.

[7] – At screening, during the study selection criteria assessment, the Investigator may use laboratory test results obtained at the laboratory of the investigational site within 24 hours of study enrollment (signing of the Informed Consent Form) if he / she considers that available data are sufficient to permit a decision on whether the subject meets the selection criteria. In this case, another blood sampling procedure has to be conducted in the period from the signing of the Informed Consent Form to the start of treatment in order to evaluate all other laboratory parameters that have to be determined on Day 1 in accordance with the study protocol.

[8] – The investigator will record in eCRF all AEs occurred after the first IMP administration and until the last procedure at Visit 5 and all SAEs occurred after the obtainment of the informed consent (after the signing of ICF) and until the last procedure at Visit 5.

[9] – Chest x-ray/ computed tomography (CT) may not to be done if the patient has the results of chest x-ray/ computed tomography that was performed within 72 hours before enrollment.

[10] – Blood sampling should not be conducted if no bacterial growth (negative culture) has been detected by blood cultures of samples withdrawn at Visit 1.

[11] – Blood for drug concentration measurements will be withdrawn only in first 40 patients **in the investigational sites defined by the Sponsor**. The schedule for blood sample collection for the PK is as follows: pre-dose, 0 h, 0.5 h (±3min), 2.5h (±5min), 4h (±5min), 6h (±10min), 12h (±15min), 16h (±15min) and 22.5h (±15min) after the end of first infusion on Day 1. The last blood sampling for PK (22,5h after the end of the first infusion) should be conducted just prior to the IMP infusion on Day 2 of the study.

[12] – The investigator will switch the patient to oral treatment if the patent meets criteria of clinical stability. If the treatment with intravenous IMP should be prolonged after the 7 days of treatment are completed (according to the investigator's opinion) the investigator should contact the study Medical Adviser for the approval of intravenous treatment prolongation. Please note that the first dose of oral drug will be administered on the day when the switch is performed (e.g. the patient will receive the first dose of oral drug on Day 4 if the switch is performed at Day 4, etc.).

9.2 Description of visits

9.2.1 Visit 1 (screening /randomization and intravenous therapy, Days 1-3(7) of the study)

The Visit 1 is scheduled on Days 1-3(7) of the study and will be performed at hospital. On Day 1 (no more than 24 hours) all screening procedures should be performed and eligible patients should be randomized and after randomization will receive the first intravenous dose of IMP. On Days 2-3(7) patients will receive intravenous therapy.

Therefore during the Visit 1 the following procedures will be performed:

Screening procedures (Day 1)

To evaluate the selection criteria of the study, the Investigator may use laboratory test results obtained at the laboratory of the investigational site within 24 hours of study enrollment (Signing of the Informed Consent Form) if he / she considers that available data are sufficient to permit a decision on whether the subject meets the selection criteria. In this case, another blood sampling procedure has to be conducted in the period from the signing of the Informed Consent Form to the start of treatment in order to evaluate all other laboratory parameters that have to be determined on Day 1 in accordance with the study protocol

- Obtainment of written informed consent (before all other procedures)
- Demographic and other baseline characteristic data collection
- Medical history taking
- Pregnancy test (for women of childbearing potential only)
- Physical examination
- Assessment of vital signs
- ECG (before or 30 minutes after blood samples collection)
- Haematology test
- Biochemical assay
- Urinalysis
- Documentation of SAEs occurred after the obtainment of the informed consent (after the signing of ICF)
- Chest x-ray (two-dimensional roentgenogram) or computed tomography. The results of chest x-ray (computed tomography) performed within 72 hours before enrollment are acceptable
- Pulse oximetry
- Collection of sputum sample for culture (if the patient has sputum)
- Collection of blood sample for culture
- Assessment of prior medication taken within 30 days before the Visit and therapies (beginning from the onset of community-acquired pneumonia)
- Check of inclusion/exclusion criteria

Randomization and initiation of therapy (Day 1)

- Before starting the therapy patients eligible for inclusion will be randomized
- Start of intravenous therapy with IMP
- Assessment of vital signs 2 hours ± 30 minutes after the second infusion (Tavanic®/Placebo) is finished
- Documentation of AEs/SAEs occurred after the first IMP administration
- Compliance check
- Assessment of concomitant medication and therapies
- Blood sample collection for PK (via venous catheter): pre-dose, 0 h, 0.5 h (±3min), 2.5h (±5min), 4h (±5min), 6h (±10min), 12h (±15min), 16h (±15min) and 22.5h (±15min) after the end of first infusion (**only for investigational sites defined by the Sponsor**). The last blood sampling for PK (22.5h after the end of the first infusion) should be conducted prior to the IMP infusion on Day 2.

Continuation of intravenous therapy (Days 2-3(7))

All of the following procedures should be performed on each day of Days 2-3(7) of the study:

- Physical examination before dosing
- Assessment of vital signs before dosing
- Intravenous therapy with IMP
- Assessment of vital signs 2 hours ± 30 minutes after the second infusion is finished
- Documentation of AEs/SAEs
- Compliance check
- Assessment of concomitant medication and therapies

9.2.2 Visit 2 (switch to oral therapy/oral therapy, Days 4(8)-7(14) of the study)

Visit 2 is scheduled on Days 4(8)-7(14) of the study and will be performed at hospital.

On Day 4(8) of the study the investigator will assess patient's medical condition and if the patent meets specified criteria he/she (see APPENDIX 2: ASSESSMENT OF CLINICAL STABILITY (POSSIBILITY OF SWITCH TO ORAL TREATMENT)) could be switched to oral treatment. However if the treatment with intravenous IMP should be prolonged after the 7 days of treatment are completed, according to the investigator's opinion, the investigator should contact the study Medical Adviser (see Contact information) for the approval of intravenous treatment prolongation. Despite prolonged intravenous therapy, the overall duration of treatment within this study will not exceed 14 days.

Note that the first dose of oral drug will be administered on the day when the switch is performed (e.g. the patient will receive the first dose of oral drug on Day 4 if the switch is performed at Day 4, etc.). Therefore, oral treatment will be started since Day 4(8) of Visit 2 and will last until and including Day 7(14) of Visit 2.

Switch to oral therapy (Day 4(8))

All the procedures scheduled on Day 4(8) of Visit 2 should be performed within one day. The following measures will be performed during Day 4(8) of the Visit 2 in accordance with the study schedule of assessments:

- Physical examination (before dosing)
- Assessment of vital signs (before dosing)
- ECG (before dosing; before or 30 minutes after blood samples collection)
- Haematology test (before dosing)
- Biochemical assay (before dosing)
- Urinalysis (before dosing)
- Pulse oximetry (before dosing)
- Collection of a sputum sample for culture (before dosing and if the patient has sputum)
- Collection of a blood sample for culture (before dosing, sampling should not be conducted in case of negative culture at Visit 1)
- Clinical response assessment
- Switch to oral therapy, the first dose of oral IMP
- Assessment of vital signs - 2 hours ± 30 minutes after oral dose administration
- Documentation of AEs/SAEs
- Compliance check
- Assessment of concomitant medication and therapies.

Continuation of oral therapy (Days 5(9)-7(14))

All of the following procedures should be performed on each day of Days 5(9)-7(14) of the study:

- Physical examination before dosing
- Assessment of vital signs before dosing
- Oral therapy with IMP
- Assessment of vital signs - 2 hours ± 30 minutes after oral dose administration
- Documentation of adverse events
- Compliance check
- Assessment of concomitant medication and therapies.

9.2.3 Visit 3 (end of treatment visit, within 1-2 days after the last dose)

Visit 3 will be performed within 1-2 days after the last dose, but not less than 24 hours after the last dose of the study drug. The Visit can be performed at outpatient department. The following measures will be performed during the Visit 3 in accordance with the study schedule of assessments:

- Physical examination
- Assessment of vital signs
- ECG (before or 30 minutes after blood samples collection)
- Haematology test

- Biochemical assay
- Urinalysis
- Pulse oximetry
- Collection of a sputum sample for culture (if the patient has sputum)
- Collection of a blood sample for culture (sampling should not be conducted in case of negative culture at Visit 1)
- Clinical response assessment
- Documentation of AEs/SAEs
- Assessment of concomitant medication and therapies

All the procedures should be performed within one day.

9.2.4 Visit 4 (test of cure visit, within 7-9 days after the last dose)

Visit 4 will be performed within 7-9 days after the last dose. The Visit can be performed at outpatient department. The following measures will be performed during the visit in accordance with the study schedule of assessments:

- Physical examination
- Assessment of vital signs
- ECG (before or 30 minutes after blood samples collection)
- Haematology test
- Biochemical assay
- Urinalysis
- Chest X ray (two-dimensional roentgenogram) or chest computed tomography
- Pulse oximetry
- Collection of a sputum sample for culture (if the patient has sputum)
- Collection of a blood sample for culture (sampling should not be conducted in case of negative culture at Visit 1)
- Clinical response assessment
- Documentation of AEs/SAEs occurred since the last visit
- Assessment of concomitant medication and therapies (since the last visit)

All the procedures should be performed within one day.

9.2.5 Visit 5 (long-term follow-up visit, within 21-23 days after the last dose)

Visit 5 will be performed within 21-23 days after the last dose as a telephone contact. The date of Visit 5 is the date of per protocol study termination for the patient.

The following measures will be performed during the visit in accordance with the study schedule of assessments:

- Documentation of AEs/SAEs occurred since the last visit
- Assessment of concomitant medication and therapies (since the last visit)
- Infection relapse assessment.

All the procedures should be performed within one day.

9.3 Unscheduled Visits

Patients may visit the investigational site for an unscheduled visit at any time if they have adverse events or in case if they need medical intervention.

An investigator should record the data in the source medical documents and in the eCRF. It is obligatory for an investigator to write down the following information: date of the visit, reason, the results of examinations and additional measures which were carried out during the visit.

The next visit after the unscheduled visit is carried out according to the earlier scheduled visit date in conformity with the protocol.

If the Investigator makes a decision to withdraw a subject from the study during an unscheduled visit (a so-called "early termination visit"), the minimal number of completed procedures should correspond to that of the "End of treatment visit". For more information on discontinuation of therapy and early withdrawal of subjects from the study, see Section **Ошибка! Источник ссылки не найден.**.

10 ASSESSMENTS

10.1 Initial assessments

10.1.1 Demographic data and other baseline characteristics

Demographic information such as date of birth, sex and race will be collected before treatment initiation on Day 1 of the study (at Visit 1, screening procedures) and then will be recorded in the eCRF.

Height and weight will be measured and alcohol use status and smoking status will be obtained and recorded in the eCRF on Day 1 of the study (at Visit 1, screening procedures) before treatment as well. Height will be used for calculation of body mass index (BMI).

10.1.2 Medical history

A medical history about all current medical conditions, any significant past conditions, operations, and therapeutic or diagnostic procedures will be obtained by the investigator or sub-investigator and recorded before treatment initiation on Day 1 of the study (at Visit 1, screening procedures).

10.1.3 Pregnancy test

Pregnancy test (urine dip-strip pregnancy test) will be performed before treatment initiation on Day 1 of the study (at Visit 1, screening procedures) only in women of childbearing potential (see definition in Section 8.8).

10.1.4 Pulse oximetry

Pulse oximetry will be done to evaluate blood oxygen saturation (SaO_2) before treatment initiation on Day 1 of the study (at Visit 1, screening procedures), before dosing on Day 4(8) of the study (at Visit 2), within 1-2 days (Visit 3) and 7-9 days (Visit 4) after the last dose.

10.2 Assessment of efficacy

10.2.1 Chest X-ray / Chest Computed Tomography

X-ray examination or computed tomography (CT) will be performed before treatment initiation on Day 1 (at Visit 1, screening procedures). However, the results of X-ray examination or CT performed within 72 hours before enrollment are acceptable.

Then X-ray examination or CT will be performed within 7-9 days after the last dose (at Visit 4).

Only one radiological method (X-ray imaging only or CT imaging only for all visits) should be used for a patient throughout the study.

Chest x-ray images/CT scans will be evaluated by radiologist. Radiologist's conclusion will be fixed in the source documentation.

At Visit 4 the investigator will categorize the results to one of the following categories and will document it in the eCRF:

1. Cured – if there is not any manifestation of pneumonia according to the chest x-ray images /chest CT scans.
2. Improved – if the chest x-ray /chest CT results are less serious relative to the baseline results (at Visit 1 or within 72 hours before enrollment).
3. Unchanged – if there is no change in the chest x-ray /chest CT results relative to the Visit 1 (Day 1).
4. Worsening – if the chest x-ray /chest CT results are worsening (more serious) relative to the baseline results (at Visit 1 or within 72 hours before enrollment).

10.2.2 Clinical response assessment

The investigator will evaluate clinical response to treatment on Day 4(8) of the study (at Visit 2, switch from intravenous to oral therapy), within 1-2 days (Visit 3, end of treatment) and within 7-9 days (Visit 4, test of cure) after the last dose. Criteria for evaluation of clinical response to the therapy are presented in Table 10-1.

Table 10-1 Criteria for evaluation of clinical response

Category	Criteria
Clinical success	• All signs and symptoms of pneumonia presented at Visit 1 (Day 1) are resolved (i.e., resolution of fever, absence of intoxication, purulent sputum, and respiratory insufficiency) or improved with no worsening or appearance of new signs and symptoms of pneumonia. • There is no requirement for additional antibiotic therapy. • Chest roentgenograms (CT scans) are cured or improved (only for TOC visit).
Clinical failure	• Persistence or worsening in signs and symptoms of the acute process with either failure to show improvement in the clinical findings, initial improvement in signs and symptoms followed by clinically significant worsening before the assessment. • Additional antimicrobial therapy required.

	• Progression (worsening) of chest roentgenogram (CT scans) abnormalities or unchanged chest roentgenogram features (only for TOC visit). • Death because of pneumonia.
Indeterminate	• No evaluation possible: the patient was lost to follow-up, or died because of noninfectious-related reasons or infection other than pneumonia (as judged by the investigator).

10.2.3 Bacteriological study

Sputum sample for the culture (bacteriological) study for isolation of pathogens will be collected before the initiation of therapy on Day 1 of the study (at Visit 1, during screening procedures) and before the first oral dose of IMP on Day 4(8) of the study (Visit 2, switch to oral therapy), within 1-2 days (Visit 3) and within 7-9 days (Visit 4) after the last dose. This procedure will be performed only if it will be necessary and possible (according to the judgment of the investigator) to collect the sputum from patient (deep expectorated / broncho-alveolar lavage, etc.).

Blood sample collection for bacteriological study will be done before the initiation of the therapy on Day 1 (at Visit 1, screening procedures) and before dosing on Day 4(8) of the study (at Visit 2, switch to oral therapy), within 1-2 days (Visit 3) and within 7-9 days (Visit 4) after the last dose. However blood sampling at Visit 2, 3 and 4 should not be conducted if no bacterial growth has been detected by blood cultures of samples withdrawn at Visit 1.

The results of bacteriological study will be documented in eCRF.

Causative pathogens of CAP listed below will be determined in sputum/blood samples:

- S. pneumoniae
- H. influenzae
- S. aureus
- K. pneumoniae
- P. aeruginosa
- Other.

Bacteriological study will be performed in the local laboratory of investigational site. After isolation of pathogens culture from some previously defined laboratories can be sent to a central laboratory for additional investigations by a decision of the Sponsor. Detailed information about central laboratory, conditions of culture transportation are provided in appropriate Manual. The Sponsor will use these isolates to perform additional culture (bacteriological) studies, including drug sensitivity test, etc..

10.2.4 Infection relapse assessment

Within 21-23 days after the last dose (Visit 5) the investigator will ask the patient whether he/she has any signs/symptoms of community-acquired pneumonia. In some cases the investigator may invite the patient to visit the clinic for the additional examinations:

- Physical examination
- Assessment of vital signs

- Haematology test
- Chest X ray (two-dimensional roentgenogram) or chest computed tomography
- Collection of a sputum sample for culture (if the patient has sputum)
- Collection of a blood sample for culture.

10.3 Assessment of Safety

10.3.1 Physical Examination

All physical examinations will be performed by the investigator or a sub-investigator at every visit (on each day) of the study with the exception of Long-term follow-up visit (Visit 5).

Physical examination will include the following assessments:

- performance status
- head
- eyes
- ears/nose/throat
- lymph nodes
- breast
- skin
- lungs
- heart
- abdomen
- musculoskeletal
- neurologic evaluations.

Data should be recorded in the medical history and eCRF. All clinically significant abnormal changes of physical examination results from the baseline results must be reported as AEs in the eCRF.

10.3.2 Vital Signs

The investigator or sub-investigator will assess vital signs at every visit (on each day) with the exception of Visit 5 (Long-term follow-up visit). On Day 1 of the study (Visit 1, screening procedures/initiation of therapy) all measurements will be done during screening procedures before treatment initiation and 2 hours±30 minutes after the infusion of second solution on Day 1 is finished; on each day of Days 2-3(7) of the study (Visit 1, continuation of i.v. therapy) the measurements will be done before dosing and 2 hours±30 minutes after the infusion of second solution is finished. On Day 4(8) of the study (Visit 2, switch to oral therapy) and on each day of Days 5(9)-7(14) of the study (Visit 2, continuation of oral therapy) the measurements will be done before dosing and 2 hours±30 minutes after the oral dose administration.

The following vital signs will be measured and recorded:

- pulse rate
- blood pressure (systolic and diastolic blood pressure)
- respiratory rate
- temperature.

Blood pressure, pulse and respiratory rate will be measured after the patient has been seated for at least 5 minutes.

All clinically significant abnormal changes of vital signs from the baseline results must be reported as AEs in the eCRF.

10.3.3 Electrocardiography

Electrocardiogram (ECG) will be recorded before treatment initiation on Day 1 (Visit 1, screening procedures), before dosing on Day 4(8) of the study (Visit 2, switch to oral therapy), within 1-2 days (Visit 3) and within 7-9 days (Visit 4) after the last dose. ECG should be performed before or 30 minutes after collecting blood samples for haematology test, biochemical assay and blood sample collection for culture (if needed), and should start after the patient lies supine for at least 5 minutes. ECG parameters include heart rate, RR, PR, QRS, QT, and QTc.

Results of ECG will be registered in medical records and in the eCRF. All clinically significant abnormal changes of ECG results from the baseline results must be reported as AEs in the eCRF.

10.3.4 Haematology test

Blood samples for haematology test will be withdrawn before treatment initiation on Day 1 of the study (Visit 1, screening procedures), before dosing on Day 4(8) of the study (Visit 2, switch to oral therapy), within 1-2 days (Visit 3) and within 7-9 days (Visit 4) after the last dose.

To evaluate the selection criteria of the study, the Investigator may use haematology test results obtained at the laboratory of the investigational site within 24 hours of study enrollment (Signing of the Informed Consent Form) if he / she considers that available data are sufficient to permit a decision on whether the subject meets the selection criteria. In this case, another blood sampling procedure has to be conducted in the period from the signing of the Informed Consent Form to the start of treatment in order to evaluate all other haematology test parameters that have to be determined on Day 1 in accordance with the study protocol.

Haematology test will be analyzed by the local laboratory of investigational site using standard validated methods. The following investigations will be made:

- erythrocytes
- hemoglobin
- hematocrit
- leucocytes and differential leucocyte count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
- platelets
- erythrocyte sedimentation rate (ESR).

All clinically significant abnormal changes in haematological parameters from the baseline results must be reported as AEs in the eCRF.

10.3.5 Biochemical assay

Blood samples for biochemical assay will be withdrawn before treatment initiation on Day 1 of the study (Visit 1, screening procedures), before dosing on Day 4(8) of the study (Visit 2, switch to oral therapy), within 1-2 days (Visit 3) and within 7-9

days (Visit 4) after the last dose. At Visits 1, 2, and 3, samples will be collected prior to dosing.

To evaluate the selection criteria of the study, the Investigator may use blood chemistry test results obtained at the laboratory of the investigational site within 24 hours of study enrollment (Signing of the Informed Consent Form) if he / she considers that available data are sufficient to permit a decision on whether the subject meets the selection criteria. In this case, another blood sampling procedure has to be conducted in the period from the signing of the Informed Consent Form to the start of treatment in order to evaluate all other blood chemistry test parameters that have to be determined on Day 1 in accordance with the study protocol.

Biochemical assay will be performed in the local laboratory of investigational site using standard validated methods. The following investigations will be made:

- glucose
- total bilirubin
- alanine aminotransferase (ALT)
- aspartate aminotransferase (AST)
- gamma-glutamyl transpeptidase (GGTP)
- alkaline phosphatase (ALP)
- potassium (K^+)
- sodium (Na^+)
- creatinine
- urea.

All clinically significant abnormal changes in biochemical parameters from the baseline results must be reported as AEs in the eCRF.

10.3.6 Urinalysis

Assessments will be performed in the local laboratory before treatment initiation on Day 1 of the study (Visit 1, screening procedures), before dosing on Day 4(8) of the study (Visit 2, switch to oral therapy), within 1-2 days (Visit 3) and within 7-9 days (Visit 4) after the last dose. The following parameters will be assessed:

- color
- clarity
- specific gravity
- urine pH
- protein
- glucose
- ketones
- erythrocytes
- leucocytes
- epithelium
- bacteria
- crystals
- mucus.

To evaluate the selection criteria of the study, the Investigator may use urinalysis results obtained at the laboratory of the investigational site within 24 hours of study

enrollment (Signing of the Informed Consent Form) if he / she considers that available data are sufficient to permit a decision on whether the subject meets the selection criteria. In this case, another urine sampling procedure has to be conducted in the period from the signing of the Informed Consent Form to the start of treatment in order to evaluate all other urinalysis parameters that have to be determined on Day 1 in accordance with the study protocol.

All clinically significant abnormal changes in urinalysis parameters from the baseline results must be reported as AEs in the eCRF.

10.3.7 Documentation of adverse events

The Investigator will assess and record in the source documentation and the eCRF any non-serious AEs occurring at each visit from the moment of first IMP administration on Day 1 of Visit 1 until the last procedure at Visit 5. SAEs will be evaluated and recorded in the eCRF from the moment of signing of informed consent on Day 1 of Visit 1 until the last procedure at Visit 5.

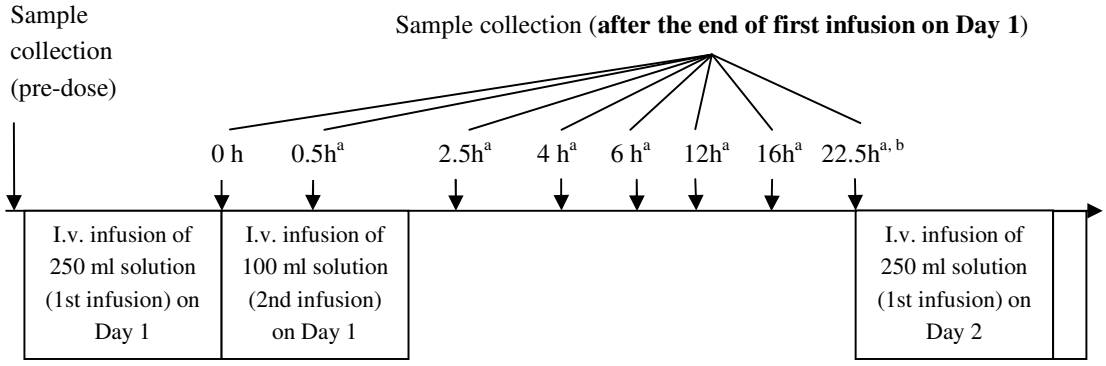
All AEs/SAEs observed or reported by the patients will be documented regardless of whether it is related to the investigational product (see Section 11.2).

10.4 Drug Concentration Measurements for Assessment of Pharmacokinetic Parameters

Blood sample collection for pharmacokinetic (PK) parameters will be withdrawn on Day 1 and 2 of Visit 1 before and after the first infusion only in 40 first patients enrolled in the investigational sites defined by the Sponsor. Blood collection will be performed via venous catheter which will be inserted into peripheral vein in the arm. Infusions of IMPs should be performed via another peripheral vein during all period of blood collection for PK parameters.

The schedule for blood sample collection for the PK is as follows: pre-dose, 0 h, 0.5 h (±3min), 2.5h (±5min), 4h (±5min), 6h (±10min), 12h (±15min), 16h (±15min) and 22.5h (±15min) after the end of first infusion (see Figure 10-1). The last blood sampling for PK (22.5h after the end of the first infusion) should be conducted just prior to the IMP infusion on study Day 2.

Figure 10-1 Schedule for blood sample collection for the PK at Visit 1



[a] - for these time points the protocol allows acceptable sampling time deviations ("sampling time windows"): 0.5 h±3min, 2.5h±5min, 4h±5min, 6h±10min, 12h±15min, 16h±15min and 22.5h±15min.
[b] - The last blood sampling for PK should be conducted just prior to the IMP infusion on study Day 2.

After the last blood sample collection catheter can be used for infusions of IMPs.

Drug concentration measurements will be performed in the central laboratory (see Contact information). Detailed information about transportation of the samples and other information are provided in the appropriate Manual.

11 ADVERSE EVENTS (AE) AND SERIOUS ADVERSE EVENTS (SAE)

11.1 Definitions

11.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding which are considered to be clinically significant), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Any worsening of symptoms of the primary disease (as compared with estimates made during the screening procedures) should also be registered as an AE.

11.1.2 Drug Relationship

The relationship between an AE and study drugs will be judged according the following categories:

1- **"Certain"**: the AE occurs in a plausible time relation to the administration of the drug and cannot be explained by a concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2- **"Probable"**: the AE occurs in a reasonable time relation to the administration of the drug, it is unlikely to be attributed to a concurrent disease or other drugs or chemicals and it follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information (AE reappearance after drug reintroduction) is not required to fulfil this definition.
3- **"Possible"**: the AE occurs with a reasonable time relation to the administration of the drug, but it could also be explained by a concurrent disease or other drugs or chemicals. Information on drug withdrawal (dechallenge) may be lacking or unclear.
4- **"Unassessable"**: The relationship cannot be judged, because of the information is insufficient or contradictory and cannot be supplemented or verified.

5- **"Unlikely"**: a causal relationship cannot be definitively ruled out, but
   - other drugs, chemicals or underlying disease provide plausible explanations and/or
   - the temporal relation to the administration of the drug makes a causal relation improbable.

6- **"Not Related":** Any of the following are present:
   - existence of a clear alternative explanation, and/or
   - unreasonable temporal relationship between Drug and Event, and/or
   - non-plausibility

11.1.3 Adverse Drug Reactions

Adverse drug reactions (ADRs) are all untoward and unintended responses to an investigational medicinal product **related** to any dose administered.

The definition implies a reasonable possibility of a causal relationship between the event and the Investigational Medicinal Product (IMP). This means that there are facts (evidence) or arguments to suggest a causal relationship.

11.1.4 Seriousness

An AE/ADR is considered **Serious** when:

- results in death;
- is life-threatening;

Note: Life-threatening is considered any AE in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect in children born to parents who were exposed to the drug;
- is another medically important condition that may jeopardise the patient or may require intervention to prevent one of the outcomes listed above. Any suspected transmission of an infectious agent via a medicinal product is considered serious and should be assessed under the category of medically important events in the absence of other seriousness criteria.

An AE/ADR is considered **Non-serious** when:
it does not fulfil the conditions for the definition of Serious AE/ADR.

11.1.5 Adverse Event (AE) / Adverse Drug Reaction (ADR) severity

The severity level of a Serious or a Non-serious AE or ADR is attributed according the below definitions.

- **Mild**: does not interfere with routine activities; in case of laboratory tests, when there is a mild abnormality.
- **Moderate**: interferes with the routine activities; in case of laboratory tests, when there is a moderate abnormality.
- **Severe**: makes impossible to perform routine activities; in case of laboratory tests, when there is a significant abnormality.

If the patient experiences changes in severity of an AE, the event should be captured once with the maximum severity recorded.

11.1.6 Adverse Event (AE) / Adverse Drug Reaction (ADR) expectedness

An AE/ADR is considered **Unexpected** when the nature, severity or outcome of the AE / ADR is not consistent with the information provided the Instructions for Medical Use (for marketed product) or the IB (for investigational product).

11.1.7 Suspected Unexpected Adverse Drug Reaction (SUSAR)

Any serious unexpected adverse event judged by the Investigator or the Sponsor as drug-related qualifies as suspected unexpected serious ADR (SUSAR). SUSARs are subjected to expedited reporting as specified in Section 11.3.2. Reporting duties of the Sponsor.

11.2 Monitoring and Recording of Adverse Events

At each visit during the study period the Investigator will assess and record in the eCRF any subjective or objective:

- AEs occurred after the first IMP administration on Day 1 of Visit 1 and up to the moment of last procedure at Visit 5
- SAEs occurred after the obtainment of the informed consent (after the signing of ICF) on Day 1 of Visit 1 and up to the moment of last procedure at Visit 5.

AEs communicated by the patient or by the patient's relatives or delegates through phone calls, letters or E-mails will also be recorded. In these cases the Investigator will try to obtain medical confirmation and assessment of the occurred AE.

When an AE has occurred the Investigator will record on the respective electronic Case Report Form Adverse Event (eCRF-AE) recording pages any case, Serious and Non-Serious, whether or not thought to be drug-related, observed in or reported by the patient (or relatives/delegates), specifying the judgement on the causal relationship with the study treatment.

Any available information and diagnostic measure (laboratory and instrumental tests, procedures etc.), will be recorded in the eCRF.

The Investigator is expected to follow-up any AEs occurred during the Study until the resolution of the event or permanent outcome has been determined.

11.3 Management of Serious Adverse Events (SAE)

11.3.1 Reporting duties of the Investigator

The Investigator must report any Serious AE (whether or not thought to be related to the investigational drug) sending the SAE form **no later than 24 hours** after knowledge of the event by the following e-mail or by fax number (if e-mail is not available):

24 h SAE reporting

E-mail: CJ01060044_safety@oct-clinicaltrials.com
Fax number: +7 (812) 449 86 35 (information should be marked "To the drug safety department")

When relevant, also the eCRF pages concerning medical history, concomitant medication, laboratory test should be filled.

Any further information and supporting documentation that become available (blinded copies of laboratory reports, tests, procedures, autopsy evidence of the cause of death, etc.) will be provided by the Investigator through additional written reports to the CRO and afterwards forwarded to the Sponsor.

The CRO will inform investigators about all suspected unexpected serious adverse reactions.

11.3.2 Reporting duties of the Sponsor

The Sponsor will ensure that all relevant information about any suspected unexpected serious adverse drug reaction (SUSAR), will be expeditiously reported to the competent Authorities, with these deadlines after the first knowledge (the day when the Sponsor receives the notification of the SUSAR):

- fatal and life threatening cases, no later than 7 days;
- other serious cases, no later than 15 days.

The Sponsor will ensure that all relevant information and supporting documentation that subsequently become available, will be also expeditiously reported as follow up information according to the above mentioned deadlines.

The following safety issues will be subjected to expedited management for the identification of possible adequate actions:

- SAEs associated with the trial procedures.

11.4 Management of adverse events not classified as serious

The Investigator will record all the available information on each occurring AE in the source documentation and the eCRF.

11.5 Pregnancy

All pregnancies detected in the course of the study (including pregnancies of sex partners of male study participants) should be registered in an appropriate manner. The investigator must promptly notify CRO project manager or CRA and the Sponsor using a pregnancy notification form.

If any female patient is found to be pregnant during the study, she should be withdrawn.

All reported pregnancies will be followed up to final outcome, using the pregnancy form. The outcome, including any premature termination, must be reported to the Sponsor.

Pregnancy per se is not an AE, except for the cases when the use of IMPs was

suspected to reduce the effectiveness of birth control pills. Congenital anomalies and birth defects in children are SAEs. Abortions carried out for medical reasons, as well as any serious complications during pregnancy (including spontaneous abortion) should be also reported as SAEs.

12 STATISTICAL METHODS

12.1 Analysis populations

The following populations will be identified for the statistical analyses:

- Randomized Population (RP): All subjects who were screened and randomized
- Intent-to-Treat Population (ITT): All subjects in the RT population who received at least one complete dose of the drug (Nemonoxacin or Tavanic®)
- Modified Intent-to-Treat (mITT): Subjects in the ITT population who met the minimal disease criteria (inclusion criteria 3 and 4), and was evaluated for clinical efficacy at least once
- Clinically Evaluable (CE): Per-Protocol subjects in the mITT population (i.e. patients without protocol violations and without a clinical response of "Indeterminate" in the mITT population)
- Bacteriological mITT (b-mITT): Subjects in the mITT population whose bacterial culture yielded at least one baseline bacterial isolate
- Bacteriologically Evaluable (BE): patients in the CE population who had at least one baseline bacterial isolate
- Safety Population (SP): All subjects who received at least one complete dose of the study drug (Nemonoxacin or Tavanic®) and underwent at least one safety evaluation would be included in this data population for safety analysis
- Pharmacokinetic population (PK-C): All subjects who were included in PK study and who had at least 1 measured concentration value.

12.2 Exclusion of Patients from Analysis

The investigator should not implement any deviation, except where necessary to eliminate an immediate hazard to the patient.

Data obtained from patients with protocol violations/deviations will be included into the efficacy analysis of the modified Intent-to-Treat (mITT) and bacteriological mITT (b-mITT) populations and the safety analysis (safety population, SP) (see Section 12.1). Data obtained from patients with protocol violations and major deviation will not be included into the efficacy analysis of the clinically evaluable (CE) and bacteriologically evaluable (BE) populations (see Section 12.1); however, data obtained from patients with minor deviations may be included into the efficacy analysis of the CE and BE population.

Any protocol deviations should be documented in the eCRF.

A protocol deviation is any change, divergence, or departure from the study design or procedures of a protocol that is under the investigator's control and that has not been approved by the IEC. Protocol deviations do not interfere with or may not influence significantly the trustworthiness of the obtained data and the results of the clinical study. There are major and minor protocol deviations. Major protocol deviations may lead to quality depreciation of the data for the following analysis (e.g., intake of prohibited medication, skipping TOC visit, etc.). Minor protocol deviations may decrease the data quality, but it is possible to include them in the analysis in CE and BE population (e.g., partial performance of some study procedures, etc.).

A protocol violation is a deviation from the IEC approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data. The protocol deviation should be referred to violation in the following cases:

- enrollment of patients not eligible according to the inclusion/exclusion criteria,
- enrollment of patients after the Sponsor's announcement about the enrollment termination,
- Poor compliance:
  - Patient took IMPs <80% or >120% predefined total dose (any incomplete intravenous infusion regimen will be recorded as missing 1 dose of drug), or
  - The patient took IMPs <7 days
- Patients who received the treatment different from the one they were randomized to,
- Other deviations that might affect the primary outcome assessment.

12.3 Criteria for termination of the study

Not applicable. There are no statistical criteria for termination of the study.

12.4 General considerations

Demographic and clinical characteristics at baseline, medical history, efficacy and safety data will be summarized using descriptive statistics by treatment group and by time point of assessment.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, 25^{th} and 75^{th} percentile, minimum, maximum and number of observations. In general, categorical and ordinal data will be summarized in terms of the frequency and percentage in each category.

Using explorative methods, both treatment groups will be analysed for homogeneity on the basis of patient's baseline characteristics. Analysis of variance (ANOVA) or Wilcoxon-Mann-Whitney test, as appropriate, will be used to test and compare the continuous demographic and baseline characteristics between treatment

groups. The Pearson χ^2 (or Fisher's exact test) will be used to perform between-group comparisons on categorical and binominal demographic and baseline data.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 17.1. The prior and concomitant medication will be coded using World Health Organization (WHO) Drug Dictionary (version 2013-12-19), including ATC code.

For the primary efficacy endpoint, the non-inferiority hypothesis will be tested at one-sided 0.05 significance level. For other statistical analyses statistical significance will be declared at the 2-sided 0.05-level, unless otherwise specified.

12.5 Procedure for accounting for missing, unused, and spurious data

Procedure for accounting for missing, unused, and spurious data will be described in Statistical Analysis Plan.

12.6 Efficacy evaluation

12.6.1 Efficacy endpoints

Primary endpoint:

- Proportion of patients with clinical success as judged by the investigator at the test of cure visit (Visit 4).

Secondary endpoints:

- Proportion of patients with clinical success as judged by the investigator at the Visit 2 (switch to oral therapy) and Visit 3
- Proportion of patients with infection relapse at Visit 5
- Time to switch therapy from i.v. to oral therapy
- Need for other antibiotic treatment
- Proportion of patients with microbiological responses at the Visit 2 (switch to oral therapy), Visit 3 and Visit 4.

12.6.2 Primary efficacy analysis

The percentage and the number of patients with different categories of clinical response ("clinical success", "clinical failure", "indeterminate") will be summarized by treatment group in mITT and CE populations for Visit 2 (switch to oral therapy), Visit 3 and Visit 4.

The percentage of patients with clinical success (as judged by the investigator) at the test of cure Visit 4 is defined as primary endpoint variable.

In regards to efficacy for CAP, non-inferiority of Nemonoxacin compared to Tavanic® will be evaluated for clinical response by using a one-sided 95% confidence interval for the difference in the primary efficacy endpoint (investigational drug minus comparator). Non-inferiority of Nemonoxacin will be stated if the lower boundary of the estimated one-sided 95% confidence interval for the difference in the clinical success rate of Nemonoxacin and Tavanic® is above -15% the Farrington-Manning test.

The primary analysis will be performed in the mITT population.

If non-inferiority is shown, a test on superiority will be performed in addition using the two-sided 95% confidence interval. The test on superiority is significant, if the lower two-sided 95% confidence interval limit is above "0".

12.6.3 Secondary efficacy analyses

As a supportive analysis, the primary efficacy endpoint will be analyzed in the CE population using the same method as that used for the primary efficacy analysis.

For secondary efficacy analyses, the clinical success rates of the patients in the mITT and CE populations at Visit 2 (switch to oral therapy) and Visit 3 as well as the number (proportion) of patients who needed other antibiotic treatment (treatment failure) will be analyzed using a two-sided 95% confidence interval (equality test) calculated based on the same statistical test as for the primary analysis.

Additionally, the results of statistical comparison of the clinical success rates using the logistic regression will also be provided.

Time to switch therapy from i.v. to oral therapy will be evaluated using the Kaplan – Meier survival analysis method and compared by log-rank test between treatment groups. The Kaplan-Meier curves will be presented graphically.

Microbiological efficacy endpoints will include microbiological success rates evaluated per each patient and by identified pathogens in b-mITT and BE.

The percentage and the number of patients with microbiological success and failure will be summarized by visit and treatment group. Microbiological success is defined as the assessments of eradication and presumed eradication. Other results of assessments (excluding unevaluable) will be regarded as microbiological failure. The difference between microbiological success rates and its CI will be calculated using the same method as that used for the secondary efficacy endpoints.

The percentage and number of the baseline-identified strains (sputum and blood culture) with microbiological success and failure will be summarized by visit and treatment group. The frequency of each category and sample source (sputum and blood culture) will be presented separately and by treatment group. Microbiological data by identified pathogens will be analyzed descriptively.

Microbiological efficacy evaluation

Based on the results of culture (bacteriological) study the microbiological response will be assessed. Microbiological response is defined as:

1. Eradication (admission pathogen[s] is absent),
2. Presumed eradication (if no material available for culture because of clinical success)
3. Persistence (admission pathogen[s] is present),
4. Presumed persistence (no material available for culture for patients with clinical failure),
5. Unevaluable (assessment is not possible because the patient was lost to follow-up after the treatment or posttherapy culture was not obtained).

6. Superinfection is defined as the appearance of a new pathogen in patients with clinical failure.

The eradicated and presumed eradicated microbiological responses will be combined and classified as microbiological success. Other results of assessments (excluding unevaluable) will be regarded as microbiological failure.

12.7 Safety evaluation

Safety evaluation will include assessment of AEs, vital signs, ECG, physical examination data and laboratory assessment in the safety population. All safety statistical analyses will be performed descriptively.

AEs/ADRs/SAEs will be analyzed descriptively, the evaluation of adverse events will comprise various frequency tabulations by system organ class and preferred term coded according to MedDRA. The AEs will be will be tabulated for each treatment group separately on a patient basis (counting each preferred term once per patient). Descriptive statistics will be also tabulated by relation to study drugs and severity by treatment group. The tables for AEs will present the number of patients with an event within each preferred term as a percentage of the number of treated patients. The number of events within each preferred term will also be reported. For each patient and each adverse event, the worst severity category recorded will be used in the by-severity summaries. The worst causality category (most related to treatment) will be used in the by-causality summaries.

Blood count, biochemistry and urinalysis data as well as change from baseline in laboratory data will be tabulated descriptively by treatment group and by visit. Frequency tables of laboratory shifts with respect to the reference range will also be presented. Clinically relevant abnormalities will be listed individually.

Vital signs data and change from baseline values will be summarized descriptively by treatment group and by visit.

The baseline and postbaseline ECG as well as physical examination data will be summarized descriptively by visit and by treatment group.

12.8 Pharmacokinetic parameters

The non-compartment method will be used to analyze the Nemonoxacin concentration-time data after the first intravenous infusion in adult patients with CAP.

The following pharmacokinetic parameters will be estimated from the measured concentrations: the peak drug concentration (C_{max}), 22.5-h drug concentrations ($C_{22.5h}$), areas under the concentration-time curve from 0 to 22.5 h, and 0 h to infinity ($AUC_{0-22.5}$, $AUC_{0-\infty}$), total systemic clearance (CL), volume of distribution at steady state (V_{ss}), and terminal elimination half-life ($T_{1/2}$).

Plasma concentrations will be plotted graphically versus time for all subjects on both linear and semilogarithmic scales. The mean profile will also be presented. The planned blood sampling times will be used for PK concentration summaries and plots. The actual sampling times will be recorded and used for determination of pharmacokinetic parameters.

Descriptive summary will be provided for the plasma concentration-time data of each time point and for the calculated PK parameters.

12.9 Procedures for reporting any deviations from the original statistical plan.

The statistical analysis will be performed under supervision of the responsible biostatistician. The statistical analysis will be described in detail in the statistical analysis plan in accordance with GCP requirements and other applicable requirements and laws. The statistical analysis plan will be finalized prior to the database close-out. All deviations from the original statistical analysis plan will be justified in the final clinical study report.

12.10 Sample size calculation

The primary efficacy objective is to show that Nemonoxacin is not inferior to Levofloxacin (Tavanic®) for the treatment of CAP, on the basis of the primary efficacy endpoint - clinical success at Visit 4 (Test of cure visit) in the mITT population. The sample size calculation for this endpoint is based on assuming a clinical success rate of 82% in the treatment and in the active control group, and an eligibility of 80% of the randomized patients for mITT population. Non-inferiority margin is chosen to be 15% (i.e., δ= -15%), a one-sided significance level α is set at 5%. Then, to achieve power of 80%, the sample size for equal allocation is estimated as 171 randomized patients in each group (342 patients totally) that provides about 137 patients in each group (274 patients totally) in the mITT population.

Presumably screening of 382 patients will allow enrollment and randomization of 342 patients.

13 ETHICAL AND LEGAL CONSIDERATIONS

The study will be conducted in accordance with the principles of the World Medical Association Declaration of Helsinki, Good Clinical Practice of the International Council on Harmonisation (ICH GCP) and all requirements of the local national legislation.

The clinical study will be conducted in accordance with the Protocol. Protocol, as well as the patient information and informed consent form will be approved/endorsed by the Institution Review Board/ Independent Ethics Committee before the start of the study.

The Protocol amendments should also be approved/endorsed by the Institution Review Board/ Independent Ethics Committee.

13.1 Informed Consent Form

Before enrollment into the study the patient or his legal representative are provided with oral information and written materials about the aims and methods of the study, as well as the anticipated benefits and possible risks associated with participation in the study. In addition, the patient or his legal representative should be notified of the voluntary nature of participation in the study and that the patient has the right to refuse to participate in the study at any time, and this refusal will not affect the quality of medical

care provided to him/her. Although the patient is not obligated to disclose his reasons to interrupt the participation in the study, the investigator should try to find out the reasons, without violating the rights of the patient of the study. Written consent of the patient should be obtained before conducting any research procedures, the second original and signed copy of the Informed Consent Form is handed to the patient.

Processing of data collected in the course of the study is carried out in compliance with confidentiality of study patients. Patients should be informed about the purpose of the planned data processing and the terms of the publication of these data (e.g., for presentation at medical conferences). The patient or his legal representative must provide consent for the data processing and publication of information in case it does not identify his/her personality.

Patients should be made aware that the authorized representatives of health authorities and the sponsor have access to their confidential medical information for purposes of audit. Patients or their legal representatives should provide written consent for the access to this information by these persons. However, in this case patients should be guaranteed strict confidentiality of all information which may identify patient and non-disclosure of such information.

13.2 Information Confidentiality

The information contained herein is the property of the Sponsor and transfer to third parties is allowed only with written permission from the Sponsor. The right to become acquainted with this information is granted only to the investigator(-s) and the staff of the research center(-s) participating in the study, members of an Ethics Council and health care officials, authorized to monitor the trial conduct. Information about the study to the extent necessary for making a decision on granting consent to participate is provided to patients whom the investigator plans to treat with the investigational drug.

13.3 Financing and Insurance coverage

This study is sponsored and financed by R-Pharm JSC. The Study Sponsor R-Pharm JSC has concluded a license agreement with the manufacturer of the investigational product TaiGen Biotechnology Co. Ltd., according to which R-Pharm JSC is entitled to perform development, registration, and commercial promotion of the medicinal product Nemonoxacin.

The insurance against the risk of life and health injury is guaranteed to the patients participating in clinical study. The investigator should inform the patient about the provision of such insurance, as well as to explain to the patient that the conduct of other forms of treatments and concomitant therapy during the study (except emergency care) is possible only with the permission of the investigator.

All risks associated with the conduct of this clinical study are insured by ‘Alliance Insurance Company’ OJSC in accordance with the current legislation (Federal Law No. 61 “On the circulation of medicinal products” and Decree No. 714 of the Government of the Russian Federation dated 13 September 2010 “On approval of the typical rules for mandatory insurance of the life and health of patients participating in clinical studies of medicinal products”).

14 ADMINISTRATIVE OBLIGATIONS

14.1 Data collection

All clinical data will be documented in the eCRF after recording in the source documents. The investigator is responsible for ensuring that all sections of the eCRF are completed correctly and that the entries can be verified against source data whenever applicable.

14.2 Data handing

After completion of data entry checks for plausibility, consistency, and completeness of the data will be performed. All missing data or inconsistencies will be reported back to the site as queries and clarified by the responsible person. If no further corrections are to be made in the database it will be declared closed and used for statistical analysis.

All data management activities will be done according to the current Standard Operating Procedures (SOPs) of the OCT.

14.3 Storage and archiving of Data

According to the regulations all important trial documents (e.g. eCRF) will be archived for at least 15 years after the final study termination. Before disposing of any documents the investigational site should contact the Sponsor and receive written approval for disposal of the documents.

The Sponsor is responsible for archiving of trial master file including all essential trial documents. Furthermore, the Principal Investigator will archive all trial-specific data (source data and Investigator Site File (ISF) including participant identification list and relevant correspondence).

15 QUALITY CONTROL AND QUALITY ASSURANCE

The representative of the sponsor/CRO (the CRA) together with the investigators and staff of the site will conduct the discussion of the Protocol and eCRF prior at the beginning of the study during the initiating visit in the site and/or at an investigators' meeting. During the study the CRA will regularly attend the site and check the completeness of source documentation and accuracy of patient records in eCRF (100% source data verification), the implementation of protocol requirements and Good Clinical Practice, the course of patient recruitment into the study, as well as conditions of study medication storage, dispense and accounting. During these visits the core investigational staff should provide the CRA with necessary assistance.

The investigator should store the source documentation for each patient

participating in the study which contains the patient's personal data of (hospitalization and medical history), and notes made during visits, including demographic and medical information, lab tests data and all other tests and procedures. Any information that the eCRF contains should have the original source in the source documents. The investigator also should store the original Informed Consent Form signed by the patient.

The investigator must provide the CRA an access to all the patients' source documents to confirm the accuracy of the data entered in the eCRF. No source document that identifies the patient's personality is to be disclosed.

The representatives of the Sponsor should be given an opportunity to conduct periodic visits to all the sites involved in the study to test the quality of the study. At site they will check records on the study and compare them with the source documents as well as discuss the course of the study with the investigators and check if the equipment complies with the Protocol.

In addition, the study may be inspected by the internal auditors of the Sponsor and persons authorized by the Sponsor, as well as by state inspectors, who should be granted an access to eCRFs, source documents, other study files and research equipment. Audit reports from the Sponsor are confidential.

16 PUBLICATIONS

The clinical study center is not allowed to publish the trial results without obtaining an approval by the sponsor.

17 REFERENCES

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APPENDIX 1: CRITERIA FOR HOSPITALIZATION*

Criteria for hospitalization in patients with a confirmed diagnosis of community-acquired pneumonia*

Patients require hospitalization if they comply with **at least one** of the following criteria:

1. Physical examination data:
   - Respiratory rate ≥ 30 breaths per minute
   - Diastolic blood pressure ≤60 mm Hg
   - Systolic blood pressure <90 mm Hg
   - Heart rate ≥125 beats per minute
   - Temperature < 35.5°C or ≥39,9°C
2. Laboratory data and X-ray findings:
   - WBC count of < 4.0 x 10^9/L or >20.0 x 10^9/L
   - SaO_2 <92% (measured by pulse oximetry)
   - PaO_2 <60 mm Hg and/or $PaCO_2$ >50 mm Hg while breathing room-air
   - Serum creatinin >176.7 µmol/l or blood urea nitrogen >7.0 mmol/l (blood urea nitrogen = urea, mmol/l/2.14)
   - Pneumonic infiltration, involving more than one lobe
   - Cavitation in a lung
   - Pleural effusion
   - Rapid progression of focal-infiltrative lesions in the lungs (> 50% increasing of infiltration size within the previous 2 days)
   - Hematocrit <30% or hemoglobin <90 g/l
   - Extrapulmonary site of infection (meningitis, septic arthritis and other)
   - Sepsis or multiple organ failure, manifested as metabolic acidosis (pH <7.35), coagulopathy
3. Impossibility of adequate care and fulfillment of all medical prescriptions at home

Criteria for preferred inpatient treatment for patients with a confirmed diagnosis of community-acquired pneumonia*

Preferred in-patient treatment may also be considered in the following cases:

1. Older than 60 years of age
2. Concomitant diseases (chronic bronchitis, chronic obstructive pulmonary disease, bronchiectasis, malignancies, diabetes mellitus, chronic renal insufficiency, congestive cardiac failure, chronic alcoholism, drug abuse, significant weight deficit, cerebrovascular diseases)
3. Treatment failure after starting treatment with antibiotics
4. The desire of the patient and/or his/her family.

Criteria for Intensive Care Unit treatment for patients with a confirmed diagnosis of community-acquired pneumonia**

The patients require hospitalization in an intensive care unit (in that case the patient will not be enrolled in the study) **if one of** the following major criteria is met:

- Severe respiratory insufficiency requiring mechanical ventilation;
- Septic shock requiring the administration of vasopressors;

OR if the patient meets **three** of the following minor criteria at the same time:

- Respiratory rate ≥ 30 breaths per minute;
- Multilobar pneumonic infiltration;
- Impairment of consciousness;
- Uraemia (residual urea nitrogen ≥ 20 mg/dL);
- Leukopenia (white blood cell count < 4 x 10^9/L);
- Thrombocytopenia (platelet count < 100 x 10^{12}/L);
- Hypothermia (< 36 °C);
- Hypotension requiring intensive infusion therapy.

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**Чучалин А.Г., Синопальников А.И. и соавт. Клинические рекомендации по диагностике, лечению и профилактике тяжелой внебольничной пневмонии у взрослых, 2014

APPENDIX 2: ASSESSMENT OF CLINICAL STABILITY (POSSIBILITY OF SWITCH TO ORAL TREATMENT)*

1. Cough and shortness of breath improving.
2. Patient afebrile for ≥24 hours (axillary temperature <37.2°C, or equivalent for oral, tympanic, or rectal temperature), on 2 or more measurements at least 24 hours apart, with no known spiking of temperature during that interval.
3. Possibility of oral intake and gastrointestinal tract absorption adequate.

* Ramirez J.A., Cooper A.C., et al. Switch therapy in hospitalized patients with community-acquired pneumonia: Tigecycline vs. Levofloxacin, BMC Infectious Diseases, 2012, 12:159 (with modifications)
Чучалин А.Г., Синопальников А.И. и соавт. Внебольничная пневмония у взрослых: практические рекомендации по диагностике, лечению и профилактике, пособие для врачей, Москва, 2010 (with modifications)

APPENDIX 3: DRUGS THAT MAY PROLONG THE QT INTERVAL WITH KNOWN RISK OR POSSIBLE RISK OF TORSADES DE POINTES (TDP)

Generic Name	Drug Class	Therapeutic Use	TdP Risk Category
Azithromycin	Antibiotic	Bacterial infection	Drugs with possible TdP risk
Alfuzosin	Alpha1-blocker	Benign prostatic hyperplasia	Drugs with possible TdP risk
Amiodarone	Anti-arrhythmic	Abnormal heart rhythm	Drugs with known TdP risk
Anagrelide	Phosphodiesterase 3 inhibitor	Thrombocythemia	Drugs with known TdP risk
Apomorphine	Dopamine agonist	Parkinson's disease	Drugs with possible TdP risk
Aripiprazole	Anti-psychotic, atypical	Psychosis, Adjunct for Depression	Drugs with possible TdP risk
Astemizole	Antihistamine	Allergic rhinitis	Drugs with known TdP risk
Atazanavir	Anti-viral	HIV/AIDS	Drugs with possible TdP risk
Bedaquiline	Antibiotic	Tuberculosis, drug resistant	Drugs with possible TdP risk
Bepridil	Anti-anginal	Angina Pectoris (heart pain)	Drugs with known TdP risk
Bortezomib	Proteasome inhibitor	Multiple Myeloma, lymphoma	Drugs with possible TdP risk
Bosutinib	Tyrosine kinase inhibitor	Leukemia	Drugs with possible TdP risk
Vandetanib	Anti-cancer	Thyroid cancer	Drugs with known TdP risk
Vardenafil	Phosphodiesterase inhibitor	Vasodilator	Drugs with possible TdP risk
Vemurafenib	Kinase inhibitor	Anti-cancer	Drugs with possible TdP risk
Venlafaxine	Anti-depressant, SNRI	Depression	Drugs with possible TdP risk
Vorinostat	Anti-cancer	Lymphoma	Drugs with possible TdP risk
Halofantrine	Anti-malarial	Malaria infection	Drugs with known TdP risk
Haloperidol	Anti-psychotic	Schizophrenia, agitation	Drugs with known TdP risk
Gatifloxacin	Antibiotic	Bacterial infection	Drugs with possible TdP risk
Gemifloxacin	Antibiotic	Bacterial infection	Drugs with possible TdP risk

Generic Name	Drug Class	Therapeutic Use	TdP Risk Category
Granisetron	Anti-nausea	Nausea, vomiting	Drugs with possible TdP risk
Grepafloxacin	Antibiotic	Bacterial infection	Drugs with known TdP risk
Dabrafenib	Anti-cancer	Melanoma	Drugs with possible TdP risk
Dasatinib	Tyrosine kinase inhibitor	Leukemia	Drugs with possible TdP risk
Dexmedetomidine	Sedative	Sedation	Drugs with possible TdP risk
Dihydroartemisinin+piperaquine	Anti-malarial	Malaria	Drugs with possible TdP risk
Disopyramide	Anti-arrhythmic	Abnormal heart rhythm	Drugs with known TdP risk
Dolasetron	Anti-nausea	Nausea, vomiting	Drugs with possible TdP risk
Domperidone	Anti-nausea	Nausea	Drugs with known TdP risk
Dofetilide	Anti-arrhythmic	Abnormal heart rhythm	Drugs with known TdP risk
Dronedarone	Anti-arrhythmic	Atrial Fibrillation	Drugs with known TdP risk
Droperidol	Anti-psychotic / Anti-emetic	Anesthesia adjunct, nausea	Drugs with known TdP risk
Ziprasidone	Anti-psychotic, atypical	Schizophrenia	Drugs with possible TdP risk
Ibutilide	Anti-arrhythmic	Abnormal heart rhythm	Drugs with known TdP risk
Iloperidone	Anti-psychotic, atypical	Schizophrenia	Drugs with possible TdP risk
Isradipine	Anti-hypertensive	High blood pressure	Drugs with possible TdP risk
Quetiapine	Anti-psychotic, atypical	Schizophrenia	Drugs with possible TdP risk
Clarithromycin	Antibiotic	Bacterial infection	Drugs with known TdP risk
Clozapine	Anti-psychotic, atypical	Schizophrenia	Drugs with possible TdP risk
Cocaine	Local anesthetic	Topical anesthetic	Drugs with known TdP risk
Crizotinib	Kinase inhibitor	Anti-cancer	Drugs with possible TdP risk
Lapatinib	Anti-cancer	Breast cancer, metastatic	Drugs with possible TdP risk
Levomethadyl	Opiate	Pain control, narcotic dependence	Drugs with known TdP risk
Levofloxacin	Antibiotic	Bacterial infection	Drugs with known TdP risk
Lithium	Anti-mania	Bipolar disorder	Drugs with possible TdP risk
Mesoridazine	Anti-psychotic	Schizophrenia	Drugs with known TdP risk

Generic Name	Drug Class	Therapeutic Use	TdP Risk Category
Methadone	Opiate	Pain control, narcotic dependence	Drugs with known TdP risk
Mirabegron	Beta3 adrenergic antagonist	Overactive bladder	Drugs with possible TdP risk
Mirtazapine	Anti-depressant, Tetracyclic	Depression	Drugs with possible TdP risk
Moxifloxacin	Antibiotic	Bacterial infection	Drugs with known TdP risk
Mifepristone	Progesterone antagonist	Pregnancy Termination	Drugs with possible TdP risk
Moexipril/HCTZ	Anti-hypertensive	High blood pressure	Drugs with possible TdP risk
Nicardipine	Anti-hypertensive	High blood pressure	Drugs with possible TdP risk
Nilotinib	Anti-cancer	Leukemia	Drugs with possible TdP risk
Norfloxacin	Antibiotic	Bacterial infection	Drugs with possible TdP risk
Oxytocin	Oxytocic	Labor stimulation	Drugs with possible TdP risk
Olanzapine	Anti-psychotic, atypical	Schizophrenia, bipolar	Drugs with possible TdP risk
Ondansetron	Anti-emetic	Nausea, vomiting	Drugs with known TdP risk
Ofloxacin	Antibiotic	Bacterial infection	Drugs with possible TdP risk
Pazopanib	Tyrosine kinase inhibitor	Anti-cancer	Drugs with possible TdP risk
Paliperidone	Anti-psychotic, atypical	Schizophrenia	Drugs with possible TdP risk
Pasireotide	Somatostatin analog	Cushings Disease	Drugs with possible TdP risk
Pentamidine	Antibiotic	Pneumocystis pneumonia	Drugs with known TdP risk
Perflutren lipid microspheres	Imaging contrast agent	Echocardiography	Drugs with possible TdP risk
Pimozide	Anti-psychotic	Tourette's tics	Drugs with known TdP risk
Pipamperone	Antipsychotic	Schizophrenia	Drugs with possible TdP risk
Probucol	Antilipemic	Hypercholesterolemia	Drugs with known TdP risk
Procainamide	Anti-arrhythmic	Abnormal heart rhythm	Drugs with known TdP risk
Promethazine	Anti-psychotic / Anti-emetic	Nausea	Drugs with possible TdP risk
Ranolazine	Anti-anginal	Chronic angina	Drugs with possible TdP risk
Rilpivirine	Anti-viral	HIV/AIDS	Drugs with possible TdP risk

Generic Name	Drug Class	Therapeutic Use	TdP Risk Category
Risperidone	Anti-psychotic, atypical	Schizophrenia	Drugs with possible TdP risk
Roxithromycin	Antibiotic	Bacterial infection	Drugs with possible TdP risk
Saquinavir	Anti-viral	HIV/AIDS	Drugs with possible TdP risk
Sevoflurane	Anesthetic, general	Anesthesia	Drugs with known TdP risk
Sertindole	Anti-psychotic, atypical	Anxiety, Schizophrenia	Drugs with possible TdP risk
Sorafenib	Tyrosine kinase inhibitor	Anti-cancer	Drugs with possible TdP risk
Sotalol	Anti-arrhythmic	Abnormal heart rhythm	Drugs with known TdP risk
Sparfloxacin	Antibiotic	Bacterial infection	Drugs with known TdP risk
Sulpiride	Anti-psychotic, atypical	Schizophrenia	Drugs with known TdP risk
Sunitinib	Anti-cancer	Renal cell cancer, GIST	Drugs with possible TdP risk
Tacrolimus	Immunosuppressant	Immune suppression	Drugs with possible TdP risk
Telavancin	Antibiotic	Bacterial infection	Drugs with possible TdP risk
Telithromycin	Antibiotic	Bacterial infection	Drugs with possible TdP risk
Tamoxifen	Anti-cancer	Breast cancer	Drugs with possible TdP risk
Terfenadine	Antihistamine	Allergic rhinitis	Drugs with known TdP risk
Tetrabenazine	Monoamine Transporter Inhibitor	Chorea (Huntington's disease)	Drugs with possible TdP risk
Tizanidine	Muscle relaxant	Spasticity	Drugs with possible TdP risk
Thioridazine	Anti-psychotic	Schizophrenia	Drugs with known TdP risk
Tolterodine	Muscle relaxant	Bladder spasm	Drugs with possible TdP risk
Toremifene	Estrogen agonist/antagonist	Anti-cancer	Drugs with possible TdP risk
Arsenic trioxide	Anti-cancer	Leukemia	Drugs with known TdP risk
Famotidine	H2-receptor antagonist	Peptic ulcer/ GERD	Drugs with possible TdP risk
Felbamate	Anti-convulsant	Seizure	Drugs with possible TdP risk
Fingolimod	Sphingosine phospate receptor modulator	Multiple Sclerosis	Drugs with possible TdP risk
Flecainide	Anti-arrhythmic	Abnormal heart rhythm	Drugs with known TdP risk

Generic Name	Drug Class	Therapeutic Use	TdP Risk Category
Foscarnet	Anti-viral	HIV/AIDS	Drugs with possible TdP risk
Fosphenytoin	Anti-convulsant	Seizure	Drugs with possible TdP risk
Quinidine	Anti-arrhythmic	Abnormal heart rhythm	Drugs with known TdP risk
Chloroquine	Anti-malarial	Malaria infection	Drugs with known TdP risk
Chlorpromazine	Anti-psychotic / Anti-emetic	Schizophrenia/ nausea	Drugs with known TdP risk
Cisapride	GI stimulant	Heartburn	Drugs with known TdP risk
Citalopram	Anti-depressant, SSRI	Depression	Drugs with known TdP risk
Eribulin	Anti-cancer	Metastatic breast neoplasias	Drugs with possible TdP risk
Erythromycin	Antibiotic	Bacterial infection; increase GI motility	Drugs with known TdP risk
Escitalopram	Anti-depressant, SSRI	Major depression/ Anxiety disorders	Drugs with known TdP risk

APPENDIX 4: DECLARATION OF HELSINKI

WMA DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods,

sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as

positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.