CLINICAL STUDY PROTOCOL

International, multicenter, open-label, randomized, comparative clinical study of efficiency and safety of medicinal product Uritos® (Imidafenacin, film-coated tablets; 0,1 mg, Kyorin Pharmaceutical Co. Ltd, Japan) and Urotol (tolterodinum, film-coated tablets 2 mg, Zentiva k.s., Czech Republic) for treatment of overactive bladder.

Study number:	CG04043028
Issue date:	December 26, 2016.
Version:	Final version 3.0
Phase:	III
Sponsor of the study:	R-Pharm, JSC (Russia)

Legal address:
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Moscow, ulitsa Berzarina, 19, korp. 1
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Amendments	Amendment #1 dated March 24, 2016
	Amendment #2 dated December 26, 2016

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SPONSOR SIDE SIGNATURE PAGE

Protocol title: International, multicenter, open-label, randomized, comparative clinical study of efficiency and safety of medicinal product Uritos® (Imidafenacin, film-coated tablets; 0,1 mg, Kyorin Pharmaceutical Co. Ltd, Japan) and Urotol (tolterodinum, film-coated tablets 2 mg, Zentiva k.s., Czech Republic) for treatment of overactive bladder.

Protocol number: CG04043028

I confirm that I have read and understood the protocol and approve design of the study.

[redacted]

Head of R-Pharm, JSC (Russia) Medical Department	signature	date

Telephone: [redacted]

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PRINCIPAL INVESTIGATOR SIDE SIGNATURE PAGE

Protocol title: International, multicenter, open-label, randomized, comparative clinical study of efficiency and safety of medicinal product Uritos® (Imidafenacin, film-coated tablets; 0,1 mg, Kyorin Pharmaceutical Co. Ltd, Japan) and Urotol (tolterodinum, film-coated tablets 2 mg, Zentiva k.s., Czech Republic) for treatment of overactive bladder.

Protocol number: CG04043028

I have read and understood the protocol and confirm my agreement for performance of this study according to the protocol requirements with due consideration of Good Clinical Practice requirements and according to ethical principles declared in Helsinki Declaration.

NAME of Investigator	signature	date

Number of center: _____

DESCRIPTION OF PROTOCOL CHANGES

Major changes to the Protocol introduced by Amendment #2 dated December 26, 2016 are listed below.

The requirements for ultrasound examination of kidneys, bladder and urinary tract with residual urine volume assessment were clarified. Ultrasound examination of kidneys, bladder and urinary tract with residual urine volume assessment is to be performed at screening only. After that on visits 2, 3, 4 and 6, an ultrasound examination of the bladder with residual urine volume assessment is to be performed. The clarification was made to eliminate the controversy in the requirements for those procedures in different sections of the protocol.

Section 4.5.3.1. "Visit 1 (Screening)" – clarification that a cough test is to be performed *in women* to assess the function of urethral sphincter.

Section 4.5.5.6. "Questionnaires to be filled by the patients" – a clarification was made that a questionnaire to assess overactive bladder symptoms (OAB Awareness Tool) is filled at the screening to assess the inclusion criteria and on *Visits 2, 3, 4, 5 and 6*. The clarification was made to exclude controversy with procedures description table and visit procedures description.

Section 8.3.3. "Determination of adverse events parameters" – "Unrelated" casual relationship was added:

Unrelated	- Presence of a clear alternative explanation and/or - Unreasonable temporal relationship between the drug administration and AE and/or - Implausibility

Minor formatting changes and spelling corrections were also made throughout the protocol.

Protocol changes according to administrative Amendment #1 dated March 24, 2016:

Section 4.4.4.1. Change of the study drug packaging.

Packaging:

For this clinical study, Uritos® will be supplied in bottles, each bottle containing 200 tables.

For this clinical study, Uritos® will be supplied in cardboard packs containing blisters, each blister containing 10 tablets.

Labeling:

Labeling of the clinical study drug will be performed in compliance with local rules and regulations. The drug will be labeled ~~in Russian and Belorussian languages~~ **in Russian language**, including the following data: Uritos® film-coated tablets, Manufacturer, Storage conditions, Batch No., Expiry date, Patient No., For clinical trial use, Study No., Site No., Patient No., Study Sponsor.

4.5.3.3. Visits 3, 4 and 5:

Investigator gathers packs of previously issued study product from the patient, performs calculation of returned product for assessment of compliance maintenance and gives ~~next pack of the product for further intake.~~ **a sufficient quantity of study drug for administration till the next visit. Partly used study drug packs are returned to the patient for further administration.**

1 GENERAL INFORMATION

Study number:	CG04043028
Protocol title:	International, multicenter, open-label, randomized, comparative clinical study of efficiency and safety of medicinal product Uritos® (Imidafenacin, film-coated tablets; 0,1 mg, Kyorin Pharmaceutical Co. Ltd, Japan) and Urotol (tolterodinum, film-coated tablets 2 mg, Zentiva k.s., Czech Republic) for treatment of overactive bladder.
Issue date:	December 26, 2016.
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Sponsor of the study:	**R-Pharm, JSC (Russia)** Legal address: 123154 Russian Federation, Moscow, ulitsa Berzarina, 19, korp. 1 Postal address: 119421 Russian Federation, Moscow, Leninsky Prospekt, 111 «B» Tel.: +7 (495) 956-7937, fax +7 (495) 956-7938
Amendments	**Amendment #1 dated March 24, 2016** **Amendment #2 dated December 26, 2016**

1.1 Contact information

Study Sponsor:

R-Pharm, JSC

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Sponsor contact persons:

NAME	Position	Contact information
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	Head of Medicinal Products Safety Department	Tel.: +7 (495) 956-79-37 Fax: +7 (495) 956-79-38 e-mail: safety@rpharm.ru
	Scientific consultant, medical monitor	Tel.: +7 (495) 956-7937 Fax: +7 (495) 956-7938

Contract research organization participating in the study performance within the territory of Russian Federation:

Synergy Research Group LLC

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www.unimedlab.ru

1.2 Study centers and investigators

Investigation will be performed in 15 urological centers within the territory of the Russian Federation and the Belarus Republic.

1.3 Study protocol synopsis

Sponsor:	R-Pharm, JSC	**Study product:**	Uritos® (Imidafenacin)
Clinical study title:	International, multicenter, open-label, randomized, comparative clinical study of efficiency and safety of medicinal product Uritos® (Imidafenacin, film-coated tablets; 0,1 mg, Kyorin Pharmaceutical Co. Ltd, Japan) and Urotol (tolterodinum - film-coated tablets 2 mg, Zentiva k.s., Czech Republic) for treatment of overactive bladder.		
Study type:	Investigation of efficiency and safety.		
Study protocol code	CG04043028	**Phase of the study:**	III.
Protocol version and date:	Final version 3.0 as of 26.12.2016		
Study design	International, multicenter (performed in several research centers within the territory of the Russian Federation and the Belarus Republic), open-label, randomized, comparative (parallel-group) efficiency and safety clinical study, where patients group taking Uritos® (Imidafenacin) is considered to be the test group, and the group taking Urotol (tolterodine) is considered to be the active control group (comparator product group). Non-inferiority assessment study.		
Objectives:	Assessment of clinical efficiency and safety of the medicinal product Uritos® (Imidafenacin) in comparison to the medicinal product Urotol (tolterodine) for treatment of overactive bladder (OAB).		
Study objectives:	Determination of clinical efficiency of the product Uritos® (Imidafenacin) in comparison with the product Urotol (tolterodine) according to its influence on urination frequency and number of urinary incontinence episodes. Safety assessment of the medicinal product Uritos® (Imidafenacin) in comparison to the medicinal product Urotol (tolterodine).		
Ethical considerations:	Products investigation will be performed in accordance with the protocol, ethical principles of Helsinki Declaration of World Health Organization (Fortaleza, 2013), trilateral agreement concerning Good Clinical Practice (ICH GCP) and regulated legislation of countries participating in the study.		
Patients population:	Male and female patients aging from 18 to 65 years with the symptoms of overactive bladder.		

Number of patients	Maximum of 350 scanned and 300 randomized, not less than 222 received treatment within the study according to the protocol
Number of centers planned:	Around 15 urological centers within the territory of Russian Federation and Belarus Republic
Products strengths:	Uritos® (Imidafenacin, film-coated tablets; 0,1 mg, Kyorin Pharmaceutical Co. Ltd (Japan) oral, 1 tablet BID after meals. Urotol (tolterodine, film-coated tablets; 2 mg, Zentiva k.s., Czech Republic), oral, 1 tablet BID after meals.
Study periods:	Screening period – 2 weeks (14 days) Therapy is performed during 12 weeks (84 days) Observation period after the end of treatment – 30 ± 5 days
Duration of study participation:	Maximum observation period: 136 days (screening not exceeding 14 days + therapy up to 84 days (±3 days) + observation period up to 35 days.
Visits and basic procedures of the study:	**Visit 1 (Screening): Days from -14 to -1:** • Assessment of inclusion/non-inclusion criteria • Acquirement of patient baseline information • OAB Awareness Tool Questionnaire • Physical examination with BP and HR assessment • Clinical and biochemical blood tests (ALT, AST, bilirubin, creatinine, total protein, glucose, alkaline phosphatase, cholesterol, potassium, sodium) and urinalysis will be performed in the central laboratory. Serological examination for HIV, hepatitis B and hepatitis C is performed. Moreover, PSA testing is performed in male patients. • US-examination of kidneys, bladder and urine excretory ways with residual urine volume assessment • Cough probe • 12-lead ECG • Pregnancy test using dipstick (in the research center) • Diary issue **Visit 2 (Randomization/Beginning of the therapy): Day 1**: • OAB Awareness Tool Questionnaire and Quality of life Questionnaire EQ-5D • Check up of diary filling results

	• Assessment of concomitant therapy, physical examination with BP and HR assessment, adverse events assessment and registration • Pregnancy test using dipstick (in the research center). • US examination of the bladder with residual urine volume assessment • Repetitive assessment of inclusion/non-inclusion criteria • Product issue • Diary issue **Visits 3, 4, 5 (Treatment phase visits): Days 15 (±3), 29 (±3), 57 (±3)**: • OAB Awareness Tool Questionnaire. • Assessment of concomitant therapy, physical examination with BP and HR assessment, adverse events assessment and registration • Product accounting, compliance assessment, product issue, diary filling results check up, diary return • US examination of the bladder with residual urine volume assessment (at Visits 4 and 5 only) • Clinical and biochemical blood tests (ALT, AST, bilirubin, creatinine, total protein, glucose, alkaline phosphatase, cholesterol, potassium, sodium) and urinalysis will be performed in the central laboratory (only at Visit 5). **Visit 6 (End of treatment): Day 85 (±3)** • OAB Awareness Tool Questionnaire and Quality of life Questionnaire EQ-5D • Assessment of concomitant therapy, physical examination with BP and HR assessment, adverse events assessment and registration • Clinical and biochemical blood tests (ALT, AST, bilirubin, creatinine, total protein, glucose, alkaline phosphatase, cholesterol, potassium, sodium) and urinalysis will be performed in the central laboratory. • Pregnancy test using dipstick (in the research center) • US examination of the bladder with residual urine volume assessment • 12-lead ECG • Check up of diary filling results • Product accounting, compliance assessment

	Visit 7 (Follow-up examination visit): after 30 ± 5 following end of treatment: • Assessment of concomitant therapy, physical examination with BP and HR assessment (are not performed in case of telephone contact), adverse events assessment and registration.
Inclusion criteria	1. Informed consent signed and dated; 2. Male and female patients with age range between 18 and 65 years (age at the moment of signing informed consent form). 3. Documented overactive bladder (OAB) diagnosis. OAB diagnosis is established on characteristic symptoms of the patient: a. urinary incontinence – 5 and more episodes per week; b. frequent urination – 8 and more times per day; c. Micturition urgency – 1 and more episodes per day. 4. OAB symptoms duration 3 months and more (assessment is based on patient history and medical documents). 5. Overactive bladder Awareness Tool Questionnaire (OAB Awareness Tool) score 8 and more at the screening visit and randomization visit. 6. Negative dipstick pregnancy test at screening and at randomization visit before administration of the first dose of the study product in female patients of childbearing potential. 7. Female patients of childbearing potential and male patients and their female partners should use at least two birth control methods, one of those is barrier, during the whole study period and at least 35 days following administration of the last dose of the study product. Permissible birth control methods: • oral, transdermal, implantational and injectional hormonal therapy; • efficient intrauterine devices; • double barrier contraceptive methods. 8. Willingness and ability to follow study visits schedule, treatment plan, laboratory tests and other study procedures.

Non-inclusion criteria:	1. Patient history of hypersensitivity or suspected hypersensitivity to tolterodine or imidafenacin. 2. Structural pathology of urinary bladder, including urinary bladder cancer, urinary bladder stones and interstitial cystitis. 3. Residual urea volume 100 mL and more at US-examination of urinary bladder. 4. Documented diagnosis of stress urinary incontinence. 5. Surgical interventions on urinary bladder and urethra during the previous 6 months or indications for surgical treatment due to OAB. 6. Exacerbation of gynecological diseases including endometriosis, uterine leiomyoma exceeding 3 cm in diameter. 7. Prostate carcinoma. 8. Prostate diseases with clinically significant urodynamics abnormality (benign prostatic hyperplasia, acute and chronic prostatitis, prostatic calculus). 9. Renal and urine excretory ways inflammatory disorders (pyelonephritis, bacterial cystitis, urethritis). 10. For male PSA level above 4 ng per mL. 11. Severe liver function abnormality (ALT and/or AST level 3 and more times exceeding upper limit of normal and/or total bilirubin level 1.5 times exceeding upper limit of normal). 12. Moderate or severe renal function abnormality based on medical information and/or glomerular filtration rate < 50 ml/min by Cockroft-Gault formula and/or blood creatinine level > 133 μmol during screening. 13. Positive test result for hepatitis B, hepatitis C and HIV. 14. Patients suffering from neoplastic condition without remission, at least, within 5 years from the start of administration of the study product. 15. Vascular dementia, Alzheimer disease associated dementia, dementia associated with other diseases including organic amnestic syndrome. 16. Parkinson's disease and secondary parkinsonism. 17. Nonspecific ulcerative colitis including severe stage of ulcerative colitis. 18. Thyroid gland pathology with hyperthyroidism signs. 19. Chronic heart insufficiency Stage III-IV by NYHA.

	20. Hypotension: systolic blood pressure < 90 mm Hg and/or diastolic blood pressure < 60 mm Hg. 21. Non-controlled medically induced hypertension. 22. Hemodynamically and/or clinically significant heart arrhythmias. 23. Prolongation of QTc interval up to 450 ms and more in males and 470 ms and more in females. 24. Closed-angle glaucoma. 25. Myasthenia gravis. 26. Megacolon, paralytic ileus, pyloric part of the stomach/duodenal occlusion and any other conditions associated with clinically significant gastric/intestinal passage obstruction or depressed motility. 27. Necessity of intake and/or intake of prohibited products, declared in the Section "Acceptable and prohibited recent and concomitant therapy" within 7 days before the start of therapy. 28. Drug abuse, chronic alcoholism, any psychotic disorders. 29. Participation in other studies within 3 months from the start of the current study and/or during this study. 30. Pregnancy and/or breastfeeding. 31. Female patients of childbearing potential, having unprotected sexual contact with male person, non-sterilized by vasectomy during, at least, 6 months, within 14 days before administration of the study product. 32. Inability to follow protocol procedures. 33. Any other acute or exacerbation and/or decompensation of chronic diseases at the moment of inclusion into the study. 34. Patient's behavior, any safety reasons, clinical and administrative reasons, which, according to Investigator's opinion, may potentially influence study product safety/efficiency assessment. 35. Other medical and psychiatric conditions or deviations of laboratory parameter which may increase patient risk associated with participation in the study or administration of the study product, or which can influence interpretation of the study results and, according to Investigator's opinion, make person not satisfying conditions for participation in this study. 36. Patients being employees of the research center or patients being employees of Sponsor/CRO, directly involved into performance of this clinical study.

Study premature withdrawal criteria:	1. Investigator took decision to withdraw patient according to patient's interests. 2. Sponsor's decision to exclude patient from the study due to serious protocol deviation/protocol violation. 3. Adverse event, requiring cessation of the study therapy, or prescription of prohibited products, declared in the Section "Acceptable and prohibited recent and concomitant therapy", or restricting performance of protocol procedures. 4. Significant concomitant disease that is, according to Investigator's opinion, poses risk to patient's well being. 5. Patient non-compliance with the study requirements. 6. Pregnancy. 7. Patient decision of not participating in the study (informed consent withdrawal).
Efficiency assessment criteria:	<u>Primary efficiency criteria:</u> Change of mean daily number of urination episodes at the 12 week Visit against the Visit of starting therapy. <u>Secondary efficiency criteria:</u> 1. Change of mean daily number of urinary incontinence episodes at the 12 week Visit against the Visit of starting therapy. 2. Change of mean daily number of urinary incontinence episodes during daytime (from 7 am to 11 pm) at the 12 week Visit against the Visit of starting therapy. 3. Change of mean daily number of urinary incontinence episodes during nighttime (from 11 pm to 7 am) at the 12 week Visit against the Visit of starting therapy. 4. Change of mean daily, mean daytime and mean nighttime number of urinary incontinence episodes at the weeks 2, 4, 8 Visits against the Visit of starting therapy. 5. Change of mean number of urinary incontinence episodes per week at the 12 week Visit against the Visit of starting therapy. 6. Change of mean daily number of urinary incontinence episodes at the weeks 2, 4, 8 Visits against the Visit of starting therapy.

	7. Changes in overactive bladder symptoms assessment parameters according to Overactive bladder Awareness Tool Questionnaire at Visits 2, 4, 8 and 12 weeks in comparison to the visit before the beginning of therapy. 8. Change of quality of life assessment using EQ-5D questionnaire (at the 12 week Visit against the Visit of starting therapy).
Safety assessment criteria:	1. Frequency for development of adverse events (AE) and serious adverse events (SAE). 2. Frequency of development of AE and SAE, depending on application of the product. 3. Frequency of development of AE and SAE, bringing to treatment cessation/withdrawal from the study. 4. Residual urine volume assessment using US-examination of the bladder at the study visits against study start visit. 5. Changes of laboratory parameters, ECG parameters and vital parameters assessment.
Justification of patient population and statistical analysis:	H_0 (null hypothesis): effect of Urotol (tolterodine) according to assessment of mean daily urination episodes exceeds effect of Uritos® (Imidafenacin) with non inferiority threshold 0.8 episodes per day. H_1 (alternative hypothesis): effect of Uritos® (Imidafenacin) according to assessment of mean daily urination episodes exceeds effect of Urotol (tolterodine) with non inferiority threshold 0.8 episodes per day. H_0: $\mu_A - \mu_B \geq \delta$ H_1: $\mu_A - \mu_B < \delta$, where μ_A, μ_B – efficiency of medicinal products Uritos® (Imidafenacin) and Urotol (tolterodine), respectively; δ – non-inferiority threshold (δ = 0,8 episodes per day) Following levels of error of the first kind = 0.025 and error of the second kind = 0.2 were taken for calculation of the study sample (that corresponds to 80% power of the study), acceptable non-inferiority threshold at the primary endpoint at Week 12 - 0.8 episodes per day; standard deviation at the primary endpoint is considered to be 2.12 episodes per day. Sample calculation pattern is bases on formula $n=f(\square,\square)x2x\square^2/\delta^2$, where $f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$ ($\Phi^{-1}(\alpha)$ and $\Phi^{-1}(\beta)$ – are the values for standard normal distribution for prescribed error of first and second kind, respectively), $\square^2$ - assumed dispersion of values , δ - non-inferiority threshold.

	Sample containing 222 patients (111 per study group) is considered to be sufficient for proof of alternative hypothesis (rejection of null-hypothesis) at the significance level 97.5% and study strength 80%. With due consideration of withdrawal during treatment total amount of patients to be randomized is about 300 (150 patients per study group). For treatment efficiency assessment (primary endpoint) one-side 97.5% confidence interval for arithmetic mean values of primary endpoint will be calculated. In other cases of comparison two-sided 95% confidence intervals will be utilized. Changes will be considered as significant at $p < 0.05$. For comparison of AE appearance in the study groups □2 test of exact Fisher test is planned to be applied, for comparison of manifestation rate Mann-Whitney U test will be applied. Laboratory parameters (total blood count and blood biochemistry, urinalysis), vital parameters will be assessed separately to each group with the following comparison using paired Student t-test for connected samples (for parameters with normal distribution) or using non-parametric Wilcoxon signed rank test for connected samples (for parameters with ordinary scale type or in case of significant distribution deviations from normal).

1.4 List of abbreviations

AUC	Area under the concentration-time pharmaceutical curve
C_{max}	Maximum plasma concentration
CYP	Cytochrome
GCP	Good Cinical Practice
EQ-5D	Quality of Life Scale EuroQol-5D
ICH	International Conference for Harmonization
MedDRA	Medical Dictionary for Regulatory Activities
M_1, M_2,M_3	Subtypes of muscarinic receptors
NYHA	New York Heart Association classification of heart insufficiency
OAB Awareness Tool	Overactive bladder Awareness Tool Questionnaire
QT	Interval between the beginning of QRS and the following T-wave peak
SD	Standard deviation
SUSAR	Suspected Unexpected Serious Adverse Reaction
$T_{1/2}$	Half-life period
C_{max}	Maximum plasma concentration time
UGT	Uridine diphosphatase glucuronil transferase
BP	Blood pressure
ALT	Alanine amintransferase
AST	Aspartate aminotransferase
HIV	Human immunodeficiency virus
WMA	World Medical Association
IUD	Intrauterine device
GGT	Gamma glutamine transferase
OAB	Overactive Bladder
CRF	Case record form
CRO	Contract research organization
LEC	Local Ethics Committee
mg	Milligram
mL	Milliliter
INN	International non-proprietary name
AE	Adverse event
pg	Picogram
PSA	Prostatic specific antigen
SAE	Serious adverse event
US	US-examination
NAME	Family name, name and second name
HR	Heart rate
eCRF	Electronic case record form
EB	Ethics Board
ECG	Electrocardiogram

2 STUDY JUSTIFICATION

Overactive bladder (OAB) is considered to be clinical syndrome with typical symptoms of frequent and urgent urination. In several cases it is characterized by urgent urinary incontinence and nicturia. Diagnosis of overactive bladder can be established symptomatically based on patient complaints for pollakiuria, urgency (severe imperative urination urge), urgency urinary incontinence, nikturia. Symptoms may appear isolated or in combinations with each other without any data of pathological conditions that can be explanations for above mentioned clinical signs (inflammatory diseases of urinary tract, kidney stone disease, interstitial cystitis). [1]

Idiopathic neurogenic detrusor hyperactivity underlies OAB pathogenesis. Despite female patients' predominance with OAB, this condition develops independently from sex, age, working conditions and life style. According to International Continence Society (ICS) data, OAB is observed in 100 millions of persons around the world. [2]

During OAB diagnostics full examination set is required with assessment of concomitant pathology and urinary tract infections. Urodynamics tests values before establishment of diagnosis are controversial therefore diagnosis is established based predominantly on clinical data. Urination diaries and patients queries are wide spread instruments for clinical symptoms specification. Urination diary allows objective assessment of the symptoms. During its filling amount of liquids intake, frequency and volume of urination, presence of micturition urgency and incontinence episodes are taken into consideration. Following filling of diary within 24 - 48 hours patient returns for discussion with attending physician which pays attention towards urination frequency, volume and description of urination process by patient. [3]

Unfortunately despite widespread distribution of the disease no optimum approaches to OAB treatment are available nowadays. This is connected, from one side, with wide spectrum of clinical manifestations of the disease, and, from other side – with insufficient efficiency of medicinal products and huge amount of side effect, caused by them. There are three main directions in OAB treatment nowadays [3]: 1) pharmacotherapy; 2) drug-free treatment; 3) surgical treatment. According to ICS recommendations, pharmacological therapy is prioritized in OAB treatment. Medical treatment of OAB patients is principally directed onto regain of control over accumulative capacity of the urinary bladder. Anticholinergic drugs (M-cholinergic antagonists) are the standard medicines for these indications because it is documented that acetylcholine-driven stimulation of postganglionic muscarinic receptors of detrusor is the main reason for both normal and involuntary constrictions of urinary bladder. [4]

Action mechanism of anticholinergic drugs consists of blocking of post-synaptic M_2, M_3) muscarinic cholinoreceptors of urinary bladder detrusor. [5]

Clinical trials indicated that anticholinergic agents bring to decreases frequency of OAB symptoms within 1-2 weeks of treatment, and maximum effect is acquired by 5-8 weeks of treatment. In the same time treatment assumes prolonged courses. Despite this in many cases of monotherapy with anticholinergic agents after their withdrawal OAB symptoms relapse is observed, that makes essential their constant intake with the object of adequate therapeutic effect maintenance. [6]

Medicinal product under brand name Uritos® (Imidafenacin) manufactured be Internal document of Kyorin Pharmaceutical Co., Ltd., was approved in Japanese pharmaceutical market in 2007 for treatment of overactive bladder in the form of film-coated tablets 0.1 mg. After the year the product was approved in South Korea. At the present time post-marketing examinations have been finished, confirming efficient application of the product for the indication of OAB and good safety profile.

Objective of this study is confirmation on non-inferiority and validation of similar safety profile of new anti-muscarinic medicinal product Uritos® (Imidafenacin) manufactured by Kyorin

Pharmaceutical Co Ltd, Japan in comparison with other product from m-cholinergic antagonists group Urotol (tolterodine) manufactured by Zentiva k.s., Czech Republic. Medicinal product Urotol is approved for application in Russian Federation.

This clinical study is developed for the further registration of the medicinal product Uritos® in Russian Federation and other countries where R-Pharm JSC is a marketing authorization holder, in accordance with regulatory requirements.

2.1 Names and description of the study products

2.1.1 Study product

Name: Uritos®

International non-proprietary name (INN): Imidafenacin (imidafenacin)

Pharmaceutical form and strength: film-coated tablets, 0.1 mg

Content per 1 tablet:

Active ingredient: imidafenacin 0.1 mg

Excipients: micro crystalline cellulose, partially pregelatinated starch, povidon, magnesium stearate, film coat (hypromellose, titanium oxide, ferrous oxide red, carnauba wax).

Description: film-coated tablets, from light red to reddish-brown or light reddish purple

Dimensions: diameter 7.1 mm, Thickness 3.5 mm, Weigh 140 mg

Pharmacotherapeutic group: M-cholinergic antagonist, selective antagonist of muscarinic receptors subtypes M_3 and M_1

ATC code: not assigned.

Manufacturer: Kyorin Pharmaceutical Co., Ltd., Japan

2.1.2 Comparator product

Trade name: Urotol **International non-proprietary name (INN):** tolterodine

Pharmaceutical form and strength: film-coated tablets, 2 mg

Content per 1 tablet:

Active ingredient: tolterodine hydrotartrate 2 mg

Excipients:

Core: micro crystalline cellulose – 146.0 mg, carboxymethyl starch sodium (Type A) – 7.0 mg; colloidal silicon dioxide – 2.0 mg, stearyl fumarate sodium – 3.0 mg.

Coating: hypromellose 2910/5 - 3.5 mg; macrogol 6000 - 0.6 mg, titanium dioxide – 0.4 mg, talc – 0.5 mg.

Description: round, biconvex, film-coated white tablets

Pharmacotherapeutic group: M-cholinergic antagonist

ATC: G04BD07

Manufacturer: Zentiva k.s., Czech Republic

2.2 Clinical and preclinical trials results

2.2.1 Pharmacodynamics

Imidafenacin refers to the M-cholinergic antagonists group highly specific towards muscarinic receptors, competitively blocking muscarinic receptors and highly selective towards urinary bladder receptors. Exerted effects:

Decreased contractility of urinary bladder detrusor, inducted by acetylcholine through intermediary of muscarinic receptors subtypes M_3. Acetylcholine release from nerve terminals of urinary bladder is secondary to stimulation of muscarinic receptors subtypes M_1. *In vitro* imidafenacin demonstrates antagonism towards muscarinic receptors subtypes M_3 and M_1. Within urinary bladder imidafenacin inhibits release of acetylcholine, blocking M_1 subtype receptors, and smooth muscles contraction, blocking M_3 subtype receptors. In comparison to inhibitory action onto salivary gland receptors, imidafenacin possesses higher selectivity for urinary bladder receptors suggesting efficiency and safety of this product in clinical practice. [7]

Impact on different subtypes of muscarinic receptors of acetylcholine (*in vitro*). Choline blocking activity of imidafenacin was assessed on muscarinic receptors of acetylcholine in seminal duct (M_1), atrium (M_2) and ileum (M_3) using tissue samples from rabbits and guinea pigs. Imidafenacin possessed high antagonistic activity in ileum (M_3) and seminal duct (M_1) in comparison to atrium (M_2). Primary metabolites in human body did not show antagonistic activity in regard to muscarinic receptors of acetylcholine. [8] Choline blocking activity of imidafenacin was evaluated on M_1, M_2, M_3 recombinant subtypes of human acetylcholine muscarinic receptors and in receptor binding test. Imidafenacin showed high selectivity towards M_3 and M_1 subtypes of cholinoreceptors. [8] Imidafenacin inhibits release of acetylcholine and urinary bladder contraction through blocking of muscarinic receptors of M_3 and M_1 subtypes in tissue samples, obtained from rats. [8, 9]

Impact on urinary bladder (*in vivo*): imidafenacin causes dose-dependent decrease in urinary bladder contractility in rats. The product dose-dependently inhibited decrease of urine bladder holding capacity inducted by carbachol in rats.

Urinary bladder selectivity: It has been established that imidafenacin possesses high selectivity towards muscarinic receptors of acetylcholine of M_3 subtype (guinea pig ileus) and M_1 (rabbit seminal duct) and causes effect of decreases contractility of guinea pig urinary bladder, caused be carbachole, in comparison to similar anticholinergic agents with high selectivity towards urinary bladder. Imidafenacin inhibits acetylcholine release in isolated rat urinary bladder in concentration, 30 times less than other anticholinergic agents, and also inhibits electrically-induced contractions at minimum concentration in comparison to other anticholinergic agents. In rats urinary bladder contractility inhibition activity coefficient in relation to carbacholine-inducted hypersalivation of imidafenacin was about 10 times higher than of propiverin hydrochloride, which is demonstrating high selectivity of imidafenacin towards urinary bladder. [10] Selectivity comparison indicated that inhibition of salivation, in comparison to decreased contractility of urinary bladder, is characterized by higher effect (i.e. high selectivity towards urinary bladder) of imidafenacin among other tested anticholinergic agents. During testing of urinary bladder contractility together with other receptors types, participating in urinary bladder contractility, administration of imidofenacin did not show inhibitory effect on contractility that allows locating its action within muscarinic receptors. Imidafenacin inhibited *in vivo* contractility of urinary bladder in rats at the minimum concentration in comparison to other anticholinergic products. The product dose-dependently inhibited carbachole-inducted hyperreflexia of urinary bladder detrusor (and urination) in rats and shortened intervals of ileus contraction in rats.

Assessment of rats' successfulness in Morris water maze showed that antagonistic activity of imidafenacin in regard of muscarinic receptors of M_1 subtype does not pose impact on spatial training and memory. [10] Imidafenacin decreases potassium ions transfer from isolated salivary

gland of rat in minimal concentration, in comparison to darifenacin. Main imidafenacin metabolites, M-2, M-4 and M-9, does not influence blocking effect towards agonist-inducted actions onto M_1, M_2 and M_3 receptors of guinea pig. Several effects were noted in general pharmacology as an aspect of safety pharmacology, however all of them were considered as being secondary to anticholinergic activity of imidafenacin. Cardiovascular and respiratory studies influence onto several parameters was observed at high doses and doses, exceeding expected clinical doses, and they included rhythm abnormalities of potassium hERG channels (determine form and duration of action potential in heart muscle cells) and action duration potential (APD) of papillary muscles *in vitro* in guinea pig and in conscious dogs – change of auditive acuity, change of QT interval (but not QTc interval) and breathing rate.

2.2.2 Pharmacokinetics

2.2.2.1 Pharmacokinetics in laboratory animals

Absorption

Radioactivity following oral administration of single dose of ^{14}C - labeled imidafenacin to rats and dogs was soon revealed in blood and reached maximum in 2 hours after administration of the product.

Following single oral administration of imidafenacin to rats urinary bladder concentration achieved maximum in an hour following administration and decreased with half-life period of 1.8 hours, more slowly than in serum. C_{max} and AUC_{0-12} in urinary bladder were 10.7 and 25.4 times higher than in serum, respectively.

Bioavailability of imidafenacin was 4.0 - 4.0% in rats and 16.6% in dogs following single dosing.

Shortly after administration of imidafenacin dose to rats and dogs product is revealed in blood and reaches maximum concentration in 0.22 hours in rats and in 1.6 hours in dogs following dosage. [^{14}C] - labeled imidafenacin quickly absorbs following oral administration in rats and dogs with blood half-life period based on radioactivity in these species 6.6 and 15 hours, respectively (with established $T_{1/2}$ in dogs 4.7 hours). Hereafter blood radioactivity in dogs demonstrated slow elimination phase with half-life period of 130 hours. Half-life period of imidafenacin in rats was 0.87 - 1.1 hours and half-life period following determination of the product form without radioactive label was 1.4 hours. C_{max} and $AUC_{0-\infty}$ serum values in rats increased proportionally to the increased doses.

Following oral administration of ^{14}C-labeled imidafenacin to rats in repeated doses during 21 days, blood radioactivity gradually decreased according to doses number and reaches plateau after 16 days of dosing. C_{max} and AUC values after 21 consecutive days of dosing were 1.5 and 2.3 times higher in comparison to values following single dose administration at the first day of dosing, respectively.

Toxicokinetic (mice, rats and rabbits) and pharmacokinetic (rats) assessment showed that plasma/serum concentrations of imidafenacin increased in dose-dependent manner in all studies. C_{max} and AUC values were proportional to doses, administered to mice, rabbits and dogs. On the other side, repeated doses, as a rule, caused less than expected C_{max} and AUC values within dose range of 30 - 500 mg/kg in mice and high values at doses 30 mg/kg and higher in rats.

Distribution

Oral bioavailability of imidafenacin was 2.5 - 5.6% in rats and 36.1% in dogs. In rats not effect of feeding onto $AUC_{0-\infty}$ was revealed during radioactivity measurement of labeled product concentration in blood.

Protein binding *in vitro* was from 55.2 to 58.4% in rats plasma, from 67.2 to 74.3% in dogs

plasma and from 87.1 to 88.8% in human plasma. Following oral administration of [^{14}C] – labeled imidafenacin to rats' radioactivity was high in liver and urinary bladder and low in cerebrum, seminal glands, bones, eye-balls and pineal gland. Radioactivity disappeared during long time period form most tissues but decreased more slowly in lungs, spleen, skin, urinary bladder, trachea and aorta. However hystopathological examination of the latter tissues did not show any significant abnormalities. In pregnant rats, on the 13th and 18th gestation day the slight radioactivity was passed to fetuses, but in lower concentration than in mother's plasma, and subsequently disappeared.

Metabolism

Imidafenacin is mainly metabolized through $CYP3A_4$ and $UGT1A_4$. Following multiple dosing of imidafenacin 30 mg/kg to rats metabolizing enzymes activity was not changed. Because inhibiting concentrations of imidafenacin and its metabolites onto human isoenzymes of cytochrome P450 were significantly higher than anticipated plasma conditions in clinical level, possibility of impact onto metabolism from the side of Imidafenacin and associated products is supposed to be low.

Excretion

Urea and feces excretion by radioactivity level following single dosing of [^{14} C] imidafenacin was 18% and 77%, respectively, in rats, and 45% and 52%, respectively, in dogs. Following repetitive dosing of imidafenacin to rats almost 100% of the total dose is excreted by kidneys and bowel within 7 days after administration of the last dose. Radioactivity content assessment in plasma, urea and bile revealed relatively low ratio of main imidafenacin form and vast majority of its metabolites. Glucuronic conjugate (M-9) was identified as metabolite in human urea.

2.2.2.2 Drugs interactions

$CYP3A_4$ inhibiting agents

Itraconazol, ketoconazol, erythromycin, clarithromycin: Following oral administration of 0.1 mg imidafenacin to healthy male adult volunteers (n = 10), oral itrakonazole was prescribed in 200 mg dose OD during 9 days. C_{max} and $AUC_{0-\infty}$ of imidafenacin increased in 1.3 and 1.8 times respectively, in comparison to administration of imidafenacin as monotherapy. [11] Theretofore is required to restrain from this combination due to possibility of increased blood serum imidafenacin concentration, that is in turn increases risk of overdose.

Digoxin: Oral administration of 0.1 mg BID of imidafenacin concomitantly with 0.125 (0.25 mg of loading dose) digoxin OD during 8 consecutive days to healthy adult males (n = 12) revealed, that C_{max}, AUC_{0-24} and concentrations of digoxin were comparable with the identical parameters when digoxin was administered as monotherapy. [12]

Anticholinergic agents, antihistamine agent, tricyclic antidepressants, phenothiazines, monoaminooxidase inhibitors: symptoms, including thirst/dry mouth, constipation, disuria, may appear and can be severe. Anticholinergic effects of imidafenacin may escalate in case of concomitant administration of these products [13], which may increase risk of side effects.

2.2.3 Pharmacokinetics in humans

In healthy adult male Caucasians almost 100% of imidafenacin was observed from gastro-intestinal tract with absolute bioavailability of 57.8% [14].

About 40% of imidafenacin following oral administration was exposed to the first pass effect in the liver. Primary plasma metabolites included M-2 (oxidized metabolite of imidasole ring of imidafenacin), M-4 (ring of cleaved metabolite M-2) and M-9 (N-glucuronide of imidafenacine). Metabolism of M-2 and M-4 is primarily catalyzed by CYP3A4, and the same reaction with M-9 is driven by UGT1A4. Moreover, imidafenacin and its major metabolites, M-2, M-4, M-9, did not inhibit varieties of human cytochrome *in vitro* ($CYP1A_2$, $CYP2C_9$, $CYP2C_{19}$, $CYP2D_6$,

$CYP2E_1$, $CYP3A_4$). [15]

After single dosing of ^{14}C-imidafenacin to healthy adult males (non-Japanese, n = 6) at dose 0.25 mg on an empty stomach 95% of the dose was recovered by radioactivity in urea and feces not earlier than after 192 hours following administration (65.6% in urea and 29.4% in feces). Less than 10% of the dose was excreted from the body unchanged through kidneys, and no dose was excreted through intestine. [16]

2.2.4 Pharmacokinetics in special patient populations

Pediatric application: Safety of the product was not established for underweight neonates, neonates, infants, small children and older children (clinical experience is not available). [13]

Elderly age: Product should be prescribed with caution because of physiological functions declining with the aging.

Impairment of renal and liver function: Data are not available.

Pregnancy and breastfeeding: Imidafenacin is not recommended for pregnant women and women with suspected pregnancy. Product safety is not established during pregnancy. There were reports concerning animals experiments (in rats) with transmission of the product to fetus. [13]

2.2.5 Toxicology

General toxicity studies on rats and dogs showed mydriasis, lacking food consumption and decreased secretion of salivatory glands, and moreover in rats with medium and high dosage levels increased liver weight, decreased body mass and decreased food consumption were noted. Thyroid follicular hypertrophy was revealed in rats, but it is considered that is probable compensatory reaction against stimulation of thyroxin metabolism. Dogs presented with dry mouth, decreased salivation and increased weight of submandibular salivatory glands; all these signs were associated with pharmacological action of imidafanacin.

2.2.5.1 Acute and subchronic toxicity studies

Acute toxicity, intravenous dosing:

Each single dose of imidafenacin was administered intravenously at 0.03 mg/kg, 0.1 mg/kg and 0.3 mg/kg in rats and at 0.012 mg/kg, 0.04 mg/kg and 0.12 mg/kg in dogs.

The animals were then observed for the following 14 days after dosing. As a result, no abnormalities in animals' behavior, body mass change, food consumption, ophthalmoscopy, hematological parameters, blood biochemistry, necropsy (including organs weighting) and histopathology were revealed.

In case of oral administration of the product to 6-weeks old Wistar rats at 1000 mg/kg, 1500 mg/kg and 2000 mg/kg – at dose 1500 mg/kg lacrimal gland obstruction, tremor, hypothermia (females), at dose 2000 mg/kg decreased locomotor activity (males, females), soiling of lower abdominal wall, hypothermia (females), at dose 2000 mg/kg (lethal cases) on autopsy preservation of drug suspension within gastrointestinal tract (males, females). [17]

In case of oral administration to 7-weeks old Beagle dogs following abnormalities were revealed: at dose 125 mg/kg mydriasis, dry nose, decreased salivation, tachycardia, staggering, decreased locomotor activity, drowsiness, vomiting, auricular pallor, decreased body mass and food consumption, stool absence were observed. At 500 mg/kg dose: tachypnoe, tremor, hypersalivation. At dosage 500 mg/kg: Increased activity of adrenal system (autopsy, one dog) at dosage level 2000 mg/kg (lethal cases): lung congestion, liver abnormalities – jaundice, subepicardial bleeding, urinary bladder dilatation, retention of large amount of urine. [18]

Multiple dosing, oral administration:

During 4-weeks study with oral administration of imidafenacin in doses 0.5 mg/kg, 5 mg/kg, 30 mg/kg and 180 mg/kg in rats, hepatocellular hypertrophy was noted and decreased submandibular salivatory glands secretion at dose 180 mg/kg. At first two dose levels no abnormalities in behavior, weight, food consumption, laboratory parameters and histopathological values of the animals were observed. [19]

During 26-weeks study with oral administration of imidafenacin in doses 6 mg/kg, 30 mg/kg, 150 mg/kg in Wistar rats, the most significant abnormalities were observed at dose 150 mg/kg: 1 case (female) of death by asphyxia due to trachea obstruction with food clot, in survived: mydriasis, decreased food intake (females, males), failure to thrive (females, males). At the examination – increased liver mass / dark reddish liver (males). At necropsy — strongly focal liver structure (females), hepatocellular hypertrophy (females, males); brown pigmentation of hepatocytes (females); follicular hypertrophy of thyroid gland cells (females, males); increased number of microvacuoles in adrenal cortex (females); decreased secretion of submandibular salivatory glands (females, males); chronic nephropathy (males); brown pigmentation of pulmonary parenchyma (females) [20].

2.2.5.2 Cancerogenicity, reproductive toxicity and mutagenicity

In dead animals from high dose group, jaundice was revealed. Cancerogenicity study performed on mice indicated increased frequency of hepatocellular carcinoma at imidafenacin dose 300 mg/kg and, what was proposed to be secondary to induction of enzymes, metabolizing the product and not with direct cancerogenous potential [21].

One dose (0.5 mg/kg, aqueous solution) of ^{14}C-labeled imidafenacin was given on an empty stomach to female rats on 18 gestation date and afterwards maternal and fetal tissues were removed for radioactivity assessment in each sample after 1, 24 and 48 hours following administration of the product.

There was increased radioactivity in kidneys and liver of pregnant rat sobserved following one hour after dosing. Radioactivity level in placenta, ovaries, uterus was 1.3 - 2.3 times higher than in maternal plasma, and label level in amnion was equal to those in plasma. Maternal radioactivity was declining with the course of time. Radioactivity in all maternal tissues within 48 hours after administration of the product was 5% and lower from level, measured one hour following administration of the product, or lower than registration threshold.

In rat fetuses following administration of the product to mother radioactivity was registered throughout whole fetal body and in several tissues it was lower, than in maternal plasma, and hereinafter it swiftly eliminated. Therefore not tendency towards product retention within fetus body during the long time period. Total radioactivity ratio onto fetus was 0.03% of dose after one hour after dose administration and less than 0.01% dose in 24 and 48 hours following dose administration. [22]

No problematic data during toxicity assessment concerning reproductive function of rats and rabbits was revealed [23, 24], as well as in antigenicity and genotoxicity studies [25] in guinea pigs. Results taken together show that there is sufficient safety threshold for clinical doses level.

2.2.6 Clinical trials

Safety and pharmacokinetics of imidafenacin were studied in 32 healthy male volunteers which were administered imidafenacin orally in single doses of 0.025 mg, 0.05 mg, 0.1 mg, 0.25 mg and 0.5 mg. Effect of food intake was also evaluated following administration of the product at 0.1 mg dose in six healthy volunteers.

Symptoms for those casual relationship with the test product may not be excluded are listed in Table 1. All symptoms were transitory and did not pose clinical significance.

Table 1. Summary data concerning safety during single dose phase of the study

Adverse reactions	Imidafenacin (mg)				
	0.025 n = 6	0.05 n = 8	0.1 n = 6	0.25 n = 6	0.5 n = 6
Thirst				1 (1)	3 (3)
Ophthalmocopic examination (eyes tiredness)					1 (1)
Anticipated short term ventricular extrasystoles		1 (1)			
Supraventricular arrhythmia			3 (3)		
Supraventricular extrasystoles					1 (1)
Ventricular extrasystoles					2 (2)
Leucocytosis				1 (1)	
Leukocyturia		1 (1)			1 (1)

Number of cases is provided.

Pharmacokinetics

Plasma concentration: Plasma concentration and urea excretion of imidafenacin and its metabolites were determined in healthy male volunteers which took orally single dose on an empty stomach. Plasma concentration of imidafenacin promptly increases following administration of 0.025, 0.05, 0.1, 0.25 and 0.5 mg of the product. During 2 hours plasma concentration reached C_{max} 109, 180, 382, 1010 and 1940 pg/ml for doses 0.025, 0.05, 0.1, 0.25 and 0.5 mg, respectively, and swiftly decreases with $t_{1/2}$ value within the limits between 2.6 and 3.0 hours. Plasma concentration for M-2 reached C_{max} 26, 51, 110, 293 and 445 pg/ml within 2 hours after administration and swiftly decreases with $t_{1/2}$ value from 2.6 to 3.3 hours similar way to unchanged form of imidafenacin. T_{max} and $T_{1/2}$ values for imidafenacin and M-2 were approximately unchanging independently of doses levels. In contrary to this C_{max} and $AUC_{0-\infty}$ values for imidafenacin and M-2 increased proportionally to dose escalation. [26]

Food intake: Influence of food onto plasma concentration and urea excretion of imidafenacin and its metabolites were determined in 6 healthy male volunteers which took orally single dose of imidafenacin on an empty stomach and 30 minutes after food intake. However T_{max} for imidafenacin significantly elongates from 1.6 hours to 2.3 hours ($p < 0.05$) in case of oral intake, no changes were observed concerning other pharmacological parameters for imidafenacin and M-2. Imidafenacin and its metabolites M-2, M-3, M-4 excretion rate with urea and their total concentration were equal following administration on an empty stomach and after food intake, and excretion cumulativeness up to 48 hours following administration (altogether) does not interfere with food intake. These data allow to assume that there is slight effect of food intake onto imidafenacin pharmacokinetics. [27]

Double blind placebo-controlled clinical study

Patients with OAB were administered imidafenacin orally 0.1 mg of BID during 12 weeks. Change of total number of urinary incontinence episodes per week against baseline value was considered to be efficiency endpoint. Significant improvement was observed in imidafenacin group in comparison to placebo group. Moreover, significant improvement was observed concerning change in mean urination frequency per day, that means decreased micturate urge per day under the influence of the study product against baseline values in imidafenacin group in

comparison to the placebo group. [28] Results are presented in Table 2.

Table 2. Results of 12-week administration of imidafenacin at dose 0.1 mg BID in comparison with placebo group

Result	Group	Baseline	After 4 weeks	After 12 weeks and after the end of treatment
Total number of incontinence events per week (%)	Placebo	17.55 ± 11.18	-33.50 ± 51.34	-49.50 ± 57.22
	Imidafenacin	18.56 ± 14.81	-48.67 ± 44.75##	-68.24 ± 36.90###
Mean urination frequency per day (times per day)	Placebo	11.47 ± 2.50	-1.04 ± 1.74	-1.08 ± 1.62
	Imidafenacin	11.20 ± 2.28	-1.19 ± 1.58	-1.52 ± 1.70 #
Mean micturate urge frequency per day (%)	Placebo	5.42 ± 3.57	-20.83 ± 46.24	-35.63 ± 53.71
	Imidafenacin	4.87 ± 2.90	-34.58 ± 43.83##	-53.39 ± 41.35###

Placebo group: 143 cases, imidafenacin group: 318 cases, mean ± S.D., #: p<0.05, ##: p<0.01, ###: p<0.001 (vs. placebo group).

Longitudinal study

Patients with OAB were administered imidafenacin orally 0.1 mg of BID during 52 weeks. Improvement was observed concerning change of total number of incontinence episodes per week, mean frequency of urination per day and therefore micturate urge frequency per day against baseline values. [29] Study results are presented in Table 3.

Table 3. Application of imidafenacin at dose 0.1 mg BID during 52 weeks

Result	Baseline	After 12 weeks	After 28 weeks	After 52 weeks or after the end of treatment
Cases	364	355	355	363
Total number of incontinence episodes per week (%)	14.53 ± 14.47	-55.92 ± 72.52#	-70.83 ± 50.56#	-83.51 ± 35.48#
Mean urination frequency per day (changes in number)	11.56 ± 2.81	-1.65 ± 2.12#	-2.05 ± 2.26#	-2.35 ± 2.14#
Mean micturate urge frequency per day (%)	4.84 ± 3.18	-45.8 ± 53.37#	-55.67 ± 48.65#	-70.53 ± 38.37#

Mean ± SD, #: p <0.05 (against baseline values) Note: measurement parameters are provided for baseline values.

Longitudinal studies with dose increment

Patients with OAB were administered imidafenacin orally 0.1 mg of BID during 12 weeks. Afterwards the product was administered orally at 0.2 mg BID during 52 weeks in the increased dose group (0.4 mg per day) and at 0.1 mg BID during 40 weeks in maintenance dose group according to the dose escalation criteria. Improvement was observed in 0.4 mg per day group concerning change of total number of incontinence episodes per week, mean frequency of urination per day and therefore micturate urge frequency per day against baseline values, during 64 weeks after the beginning of the study (52 weeks after dose increasing) without weakening of the effect. [30] Results can be observed in Table 4.

Table 4. Application of imidafenacin with dose escalation up to 0.4 mg per day

	Baseline	**After 12 weeks**	**After 24 weeks (12 weeks of increased dose)**	**After 64 weeks (52 weeks following dose increment) or at maintenance dose**
Cases	159	159	158	159
Total number of incontinence episodes per week (%)	14.01 ± 13.29	-22.92 ± 75.22$^{###}$	-69.97 ± 42.93$^{###}$	-79.30 ± 41.01$^{###}$
Mean urination frequency per day (number)	11.86 ± 2.44	-0.82 ± 1.70$^{###}$	-2.03 ± 2.01$^{###}$	-2.11 ± 2.06$^{###}$

	Baseline	**After 12 weeks**	**After 24 weeks (12 weeks of increased dose)**	**After 64 weeks (52 weeks following dose increment) or at maintenance dose**
Mean micturate urge frequency per day (changes in %)	4.96 ± 2.99	-23.67 ± 43.29###	-58.58 ± 40.25###	-65.62 ± 38.69###

Mean ± SD, ###: p<0.001 (against baseline values)

(Notes) measurement parameters are provided for baseline values.

Dose increasing was performed according to patient request and Investigator's consideration in case when all OAB symptoms did not normalize (absence of micturition urgency [0 per day], mean urination frequency less than 8 per day and absence of urine incontinence [0 episodes per week] after 12 weeks of therapy provided that no adverse reactions of moderate/severe grade were observed.

Based on the above mentioned results correction of prescribed imidafenacin dose was performed. Amendment was applied into patient leaflet for dosing and administration in December, 2009. Standard dosage of imidafenacin for adults is 0.1 mg per os BID after breakfast and after supper. When the effect is not sufficient imidafenacin dose can be increased up to 0.2 mg BID of 0.4 mg OD.

2.3 Brief description of known and potential risks and benefits for the patients, participating in the study

2.3.1 Expected side effect of the study product [13]

Adverse reactions towards imidafenacin, including deviations of laboratory parameters, were reported in 533 (45.5%) of 1172 studied cases. Primary adverse reactions included: thirst/dry mouth in 368 cases (31.4%), constipation in 98 cases (8.4%), photophobia in 18 cases (1.5%), blurred vision in 16 cases (1.4%), drowsiness in 16 cases (1.4%), gastric discomfort in 13 cases (1.1%), increased triglycerides level in 13 cases (1.1%) and increased activity of gamma-glutamil transferase (GGT) in 12 cases (1.0%).

In additional clinical trials of dosage and application adverse reactions were reported, including deviations of laboratory parameters, in 215 (49.4%) of 435 studied cases. Primary adverse reactions included: thirst/dry mouth in 164 cases (37.7%), constipation in 59 cases (13.6%), residual urine volume in eight cases (1.8%), leukocyturia in seven cases (1.6%), gastric discomfort in six cases (1.4%), headache in five cases (1.1%) and dysuria in five cases (1.1%).

Clinically significant adverse reactions:

- Acute glaucoma (occurrence rate 0.06%). Because acute glaucoma morbidity rate due to increased intraocular pressure was reported, patients require close monitoring. In case of this event appearance product intake should be stopped and correspondent measures should be undertaken.

- Retention of urine (frequency is not known: based on spontaneous reports). Patients should be under close monitoring due to the risk of urine retention. In case of this event appearance product intake should be stopped and correspondent measures should be undertaken.

- Liver abnormality: increased level of liver enzymes (frequency is not known: based on spontaneous reports). Liver function impairment may present with increased alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin values. Patients should be closely monitored and in case of any abnormalities appearance product intake should be

stopped and correspondent measures should be undertaken.

Clinically significant adverse reactions (similar products):

- Paralytic intussusceptions: cases of paralytic ileus were reported after administration of similar products (other medicines for OAB treatment), so patients require close monitoring. In case of correspondent symptoms appearance, including constipation and abdominal distension, product intake should be stopped and correspondent measures should be undertaken.

- Hallucination/delirium: Because cases of hallucination/delirium have been reported after administration of similar products (other medicines for OAB treatment), so patients require close monitoring. In case of these events product intake should be stopped and correspondent measures should be undertaken.

- QT prolongation, ventricular tachycardia: Following symptoms, including QT interval prolongation on ECG, ventricular tachycardia, atrio-ventricular blockade, bradycardia, were reported after administration of similar products (other medicines for OAB treatment), so patients require close monitoring. In case of these events product intake should be stopped and correspondent measures should be undertaken.

Miscellaneous adverse reactions

Immune system disorders: skin rush, pruritis etc. (< 5% and ≥ 0.1%).

Nervous system disorders and psychiatric disorders: drowsiness, disgeusia, light-headedness, headache (< 5% and ≥ 0.1%), numbness, hallucinations, delirium (unknown).[1]

Gastrointestinal disorders: constipation (≥ 5%), gastric/abdominal discomfort, nausea, abdominal pain, abdominal distension, diarrhea, anorexia, dyspepsia, gastritis, vomiting, dry lips, altered defecation pattern, stomatitis (< 5% and ≥ 0.1%).

Cardiovascular disorders: increased heart rate, extrasystole, high blood pressure (< 5% and ≥ 0.1%).

Respiratory, thoracic and mediastinal disorders: sore throat, cough, dry throat, hoarseness (< 5% and ≥ 0.1%).

Blood and lymphatic system disorders: anemia, leucocytopenia, decreased platelets count (< 5% and ≥ 0.1%).

Renal and urinary disorders: disuria, retention of urine, residual urine presence, hematuria (presence of RBC in urea), leukocyturia, urinary tract infections (cystitis, pyelonephritis etc.), proteinuria, creatinine increased (< 5% and ≥ 0,1%).

Eye disorders: photophobia, blurred vision, abnormal sensation in eye, xerophthalmia, astenopia, eyelids edema, dyplopia (< 5% and ≥ 0.1%).

Hepatobiliary disorders: increased GGT activity, increased AST activity, increased ALT activity, increased bilirubin level (< 5% and ≥ 0.1%).

Miscellaneous: thirst/dry mouth (≥ 5%), increased triglycerides level, edema, increased lactate dehydrogenase activity, urikemia, malaise, increased cholesterol level, chest pain, back pain, weakness, dry skin (< 5% and ≥ 0.1%).

[1] based on spontaneous reports

In case of any of above mentioned symptoms product intake should be stopped and correspondent measures should be undertaken.

2.3.2 Overdose

Overdose symptoms from both study products are secondary to their excessive anticholinergic activity. The most severe overdose symptoms may include accommodation disorder and

urination difficulty, however hallucination, extreme excitation, convulsions, breathing disorders, tachycardia, retention of urine, pupillary dilation are also possible. In case of overdose symptoms product intake should be stopped and correspondent measures should be undertaken.

Recommended treatment: gastric lavage and activated charcoal administration. In case of hallucinations and extreme excitation physostigmine is recommended; in case of convulsions and extreme excitation – benzodiazepine antianxiety drugs; in case of developed respiratory failure – artificial lungs ventilation; in case of tachycardia – beta-adrenergic antagonists; in case of retention of urine – catheterization of urine bladder; in case of mydriasis – pylocarpine in the form of eye drops and/or transferral of the patient into dark room. In case of overdose essential measures due to prolonged QT should be applied. [13, 33]

2.3.3 Special warnings

You have to exercise caution while driving or participating in any other potentially hazardous activities, requiring excessive concentration of attention and prompt psychomotor reactions during Uritos® as well as Urotol course (these products may cause accommodation dysfunction and decreased rate of psychomotor reactions).

2.3.4 Description of other risk and/or discomfort sources (non related to administration of the study product)

Participation in clinical study may require more intensive, than usual, physician attendance.

Venepunction and/or veins catheterization for blood sampling may be painful and in seldom cases may bring to thromboses or trombophlebites and/or damage to peripheral nerves.

Examination procedures, such as physical examination including weight and height measurements, assessment of vital functions (blood pressure [BP], pulse), sampling (blood, urea) electrocardiogram (ECG), US-examination (US), may be associated with discomfort.

Changes of regular mode of living (including food and beverages consumption, physical activity and day schedule organization) for the patient due to his/her participation in the study are not anticipated.

2.3.5 Benefits

It is proposed that patients will gain benefits from participating in the study, particularly all patients, participating in the study, will stay under close monitoring of physician. Patients will be provided with active treatment independently of study group assignment because this study does not provide using placebo group.

2.3.6 Benefits-risks ratio

Ratio between possible benefits from participation in the study and possible risks/discomforts, connected to study participation, is considered to be beneficial.

Due to safety provision all patients before the start of participation in the study should pass physical and laboratory examination for determination of the conditions and deviations of laboratory parameters, that can cause hazardous effect to the patients during application of the product. Precautions are provided in Investigator's brochure. All patients, in whom deviations from inclusion/non-inclusion criteria were revealed, or those, that, according to investigator's point of view, are not able to participate in the study, should be excluded.

For the purpose of safety ensuring for the patients control over physical examination results and patients complaints will be performed.

Investigation is performed in specially selected clinical centers under observation of qualified medical personnel for timely medical help provision to the patients. In all cases medical care will be provided to the patient to the extent required.

2.4 Description and justification of way of administration, dosage, dosing schedule

Way of administration, dosage, dosing schedule and therapy duration using study product Uritos® correspond to results of previous clinical trials of product efficiency assessment. The product will be taken per 1 film-coated tablet (0.1 mg) BID after meals (after breakfast and after supper). This dosage regimen was established according to the results of Phase II clinical study where OAB patient got imidafenacin in different doses within 12 weeks. It has been revealed that frequency of dry mouth development in imidafenacin group increases in dose-dependent way. Moreover, percent of patients, withdrawn from the study due to this side effect in imidafenacin group in daily dose 0.5 mg/ml, was higher (8.9%), however in groups of 0.1 mg/day (1.0%), 0.2 mg/day (0%) this value was comparative to placebo group (0%). Based on balance between efficiency and safety assessment daily dose of 0.2 mg/day is considered to be recommended dose for clinical trials.

Comparator product, Urotol (tolterodine) will be prescribed according to the instructions for medical use of the product (version approved in Russian Federation) 1 film-coated tablet (2 mg) BID after meals (after breakfast and after supper). [33]

Therapy duration, equal to 12 weeks, is considered to be satisfactory period length for efficiency and safety assessment of the study product, that is confirmed by previous studies results and efficiency data of the products Uritos® and Urotol (tolterodine) applied on indication for overactive bladder.

Additionally to efficiency and safety assessment of the studied therapy, validated questionnaires will be used in the study in purpose of assessment of symptoms of the disease and quality of life of the patients:

- OAB Awareness Tool (Overactive bladder Awareness Tool Questionnaire), version OAB-V8, containing 8 questions, is considered to be simple instrument for OAB patients screening in daily clinical practice. This Questionnaire allows to select symptomatic patients.

OAB with high level of sensitivity (98.0%) and specificity (82.7%). Patient is asked to answer 8 questions concerning typical symptoms of OAB with 6-scores scale assessment by their severity. Final score by this Questionnaire equal to 8 and more is interpreted as high probability of OAB presence. [34]

- EQ-5D Questionary (version EQ-5D-5L) is considered to be validated nonspecific instrument for quality of life assessment in patients with different pathologic conditions, including OAB. [35] Three-level version (EQ-5D-3L) was developed in 1990, and five level version (EQ-5D-5L) – in 2005. The questionnary consists from two pages: descriptional part and visual analogous scale (VAS). The descriptional part includes assessment of 5 directions (mobility, self-service, daily activity, pain/discomfort, anxiety/depression), with each direction being assessed by 5-level scale from “no problems” to “significant problem” grades. Filling of EQ-5D by patient allows reception of several variants of health condition as well as conversion of results into final unified index. Health assessment results according to VAS are presented quantitatively in mm.

2.5 Regulatory framework of the study

This study will be performed according to the protocol, ethics principles outlined in Helsinki Declaration of WMA (Fortaleza, 2013) and regulations of Good Clinical Practice of International Conference on Harmonization (ICH GCP E6), and regulatory requirements of countries participating in the study, including but not limited to following documents:

In the Russian Federation

· Federal Law of 21.11.2011 No 323-ФЗ (amendment of 02.07.2013) “On fundamental healthcare principles in the Russian Federation”;

· Federal Law of April, 12, 2010 No 61-ФЗ "On Medicine Circulation" in new version of the Federal laws of 22.12.2014 No 429-ФЗ, of 13.07.2015 No 241-ФЗ;

· Ministry of Health Order of 19.09.2003 No 266 "Concerning approval of Clinical Practice regulations in Russian Federation";

· Good Clinical Practice. GOST R 52397-2005 (approved by the Order of Rostechregulirovanie [Federal agency for technical regulation and metrology] of 27.09.2005 №232-ст);

· Government Decree of September 13, 2010, No 714 "On approval of typical rules for compulsory insurance of the life and health of a patient involved in clinical trials of a medicinal product" (in accordance with amendments applied by the Government Decree of May 18, 2011, No 393),

· Order of Ministry of Health and Social Development of the Russian Federation of August 31, 2010 No 774 "On Ethics Board".

In Belarus republic:

· Belarus Republic law of June 18, 1993 No 2435-З "Concerning medicinal products" (with amendments and provisions of June 16, 2014, No 164-З);

· Belarus Republic law of June 20, 2006 No 161-З "Concerning medicinal products";

· Technical code of common practice "Good Clinical Practice", approved by government order of Ministry of Health of Belarus Republic of May, 7, 2009, No 50;

· Government order of Ministry of Health of Belarus Republic of May, 28, 2008, No 55 "On approval of Polity Statement of Ethics Board".

· Government order of Ministry of Health of Belarus Republic of August 13, 1999, No 254 "On approval of Regulations of clinical trials of medicinal products".

2.6 Study population description

Male and female patients at the age of 18 to 65 years with confirmed diagnosis of overactive bladder (OAB) with moderate symptoms and symptoms duration 3 months and more.

All patients who signed informed consent, passed screening and met criteria of participation in the study, assigned with randomization number and received at least one dose of the study products, are considered to be *included into the study.*

All patients who passed screening and met criteria of participation in the study, assigned with randomization number, are considered to be *randomized*. Patients who signed the informed consent, passed screening and subsequently stopped participation in the study for any reason before randomization and before the start of administration of the study product, are considered to be *drop out on screening*. Patients included into the study, and subsequently stopped further participation in the study due to any reason, are considered to be *withdrawn from the study.*

3 OBJECTIVES AND TASKS OF THE STUDY

Study objective:

Assessment of clinical efficiency and safety of the medicinal product Uritos® (Imidafenacin) in comparison to the medicinal product Urotol (tolterodine) for the indication of overactive bladder (OAB) treatment.

Study objectives:

- Determination of clinical efficiency of the product Uritos® (Imidafenacin) in comparison with the product Urotol (tolterodine) according to its influence on urination frequency and number of urinary incontinence episodes. Safety assessment of the medicinal product

Uritos® (Imidafenacin) in comparison to the medicinal product Urotol (tolterodine).

- Perform safety assessment of the medicinal product Uritos® (Imidafenacin) in comparison to the medicinal product Urotol (tolterodine).

4 STUDY DESIGN

4.1 Study endpoints/efficiency criteria

Primary efficiency criteria:

Change of mean daily number of urination episodes at the 12 week Visit against the Visit of starting therapy.

Secondary efficiency criteria:

1. Change of mean daily number of urinary incontinence episodes at the 12 week Visit against the Visit of starting therapy.

2. Change of mean daily number of urinary incontinence episodes during daytime (from 7 am to 11 pm) at the 12 week Visit against the Visit of starting therapy.

3. Change of mean daily number of urinary incontinence episodes during nighttime (from 11 pm to 7 am) at the 12 week Visit against the Visit of starting therapy.

4. Change of mean daily, mean daytime and mean nighttime number of urinary incontinence episodes at the weeks 2, 4, 8 Visits against the Visit of starting therapy.

5. Change of mean number of urinary incontinence episodes per week at the 12 week Visit against the Visit of starting therapy.

6. Change of mean daily number of urinary incontinence episodes at the weeks 2, 4, 8 Visits against the Visit of starting therapy.

7. Changes in overactive bladder symptoms assessment parameters according to Overactive bladder Awareness Tool Questionnaire at Visits 2, 4, 8 and 12 weeks in comparison to the visit before the beginning of therapy.

8. Change of quality of life assessment using EQ-5D questionnaire (at the 12 week Visit against the Visit of starting therapy).

4.2 Justification and brief description of the study design.

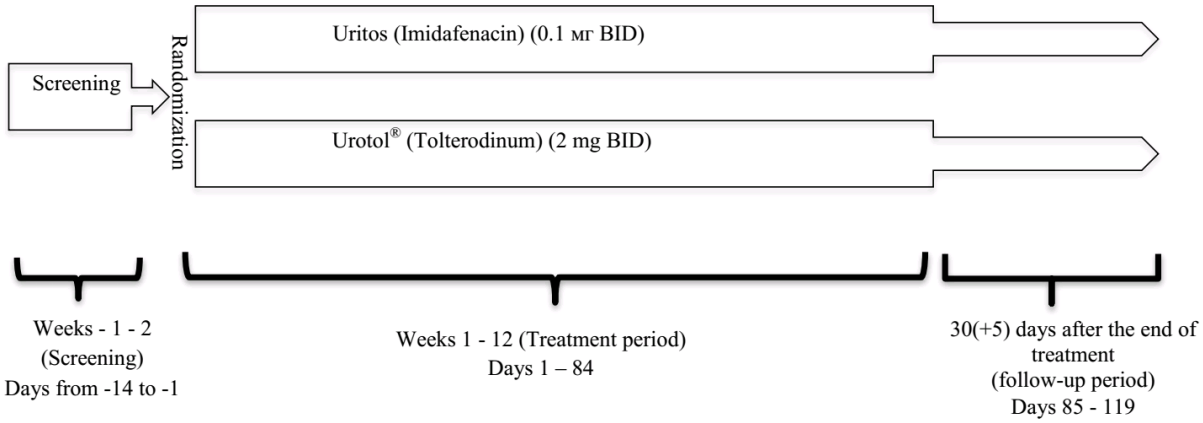
International multicentral (performed in several research centers within the territory of Russian Federation and Belarus Republic), open-label, randomized comparative (parallel-group) efficiency and safety clinical study, where patients group, taking medicinal product Uritos® (Imidafenacin), is considered to be test group, and group, taking medicinal product Urotol (tolterodine) is considered to be active control group (comparator product group). Non-inferiority assessment study.

No more than 350 patients are planned to be screened and 300 patients are planned to be randomized (150 per study group), that, with due consideration of assumed withdrawal during treatment period, will give at least 222 patients completely finished the study (111 patients per study group).

Parallel study design was selected in scientific purposes.

Study design is presented on the Figure 1. and detailed description is presented in the Section 4.5.3.

Fig. 1 Study scheme



4.3 Description of measures providing subjectivity minimization

4.3.1 Randomization

For exception of subjectivity in study product prescription randomization process is provide with use of envelops without any additional stratification.

Overall 300 patients are planned to be randomized, that will give at least 222 patients completely finished the study (111 patients per study group).

Patients will be randomly assigned into two groups:

1. Uritos® (Imidafenacin, film-coated tablets; 0,1 mg, Kyorin Pharmaceutical Co. Ltd., Japan), oral, 1 tablet BID after meals (after breakfast and after supper).

2. Urotol® (tolterodine, film-coated tablets; 2 mg, Zentiva k.s., Czech Republic), oral, 1 tablet BID after meals (after breakfast and after supper).

Randomization is performed in 1:1 ratio. List of randomization numbers will be generated beforehand by Sponsor's data processing department or designated Contract research organization (CRO) using correspondent software package.

Sponsor will provide all research centers with the set of enumerated sealed envelopes. Each envelop contains randomization number and prescribed medicinal product. Envelopes will be sequentially numbered.

Patients, familiarized with the Patient's information list and signed Informed consent form, will be assigned numbers in order of research center visiting for screening procedures performance. During randomization visit (treatment start visit) each patient following screening and satisfying inclusion/non-inclusion criteria will be assigned unique randomization number: Investigator takes the subsequent envelop (sequentially at order of magnitude) and assigns randomization number to the patient according to the number contained in the envelope with correspondent fixation in primary documentation, CRF and Screening/patients inclusion log. Hereafter list of randomization numbers will be included into primary study file and final study report.

Randomization will be balanced around research centers so that one center would contain approximately equal number of patients, receiving test product and comparator product.

Randomization number, as well as product assigned to the patient, should not be changed during the study. If patients prematurely withdraws from the study, **his/her randomization number never used again**, and patients does not have an ability to return to the study. For patients, prematurely withdrawn from the study, Investigator should fill out correspondent CRF section – Study termination.

4.3.2 Treatment blinding

This study is performed as open-label so that investigators and participating patients will be aware of the product administered to the patients.

4.4 Description of treatment method applied within the study, dosage and administration schedule of the study product. Description of pharmaceutical form, package and labeling of the study product

4.4.1 Study product description

Name: Uritos®

International non-proprietary name (INN): Imidafenacin (imidafenacin)

Pharmaceutical form and strength: film-coated tablets, 0.1 mg

Content per 1 tablet:

Active ingredient: imidafenacin 0.1 mg

Excipients: micro crystalline cellulose, partially pregelatinated starch, povidon, magnesium stearate, film coat (hypromellose, titanium oxide, ferrous oxide red, carnauba wax).

Description: film-coated tablets, from light red to reddish-brown or light reddish purple

Dimensions: diameter 7.1 mm, Thickness 3.5 mm, Weigh 140 mg

Pharmacotherapeutic group: M-cholinergic antagonist, selective antagonist of muscarinic receptors subtypes M_3 and M_1

ATC code: not assigned.

Manufacturer: Kyorin Pharmaceutical Co., Ltd., Japan

Storage conditions: Store at the temperature not exceeding 25°C.

4.4.2 Description of comparator product

Trade name: Urotol **International non-proprietary name (INN):** tolterodine

Pharmaceutical form and strength: film-coated tablets, 2 mg

Content per 1 tablet:

Active ingredient: tolterodine hydrotartrate 2 mg

Excipients:

Core: micro crystalline cellulose – 146.0 mg, carboxymethyl starch sodium (Type A) – 7.0 mg; colloidal silicon dioxide – 2.0 mg, stearyl fumarate sodium – 3.0 mg.

Coating: hypromellose 2910/5 - 3.5 mg; macrogol 6000 - 0.6 mg, titanium dioxide – 0.4 mg, talc – 0.5 mg.

Description: round, biconvex, film-coated white tablets

Pharmacotherapeutic group: M-cholinergic antagonist

ATC: G04BD07

Manufacturer: Zentiva k.s., Czech Republic

Storage conditions: Store in dry place, protected from light, at the temperature not exceeding 25°C. Keep out of reach of children.

4.4.3 Application of the study products

Prescription of test product/comparator product is performed on Visit 2 (randomization visit/visit of therapy start) after finishing of screening procedures, assessment of eligibility of the patient towards inclusion/non-inclusion criteria and randomization number assignment.

First administration of the product is performed at the day of randomization.

Uritos® and Urotol are taken **orally, 1 tablet BID after meals after breakfast and after supper).**

It is recommended to keep 12-hours interval between administrations of the study product. In case of missing dose of the product it should be taken as quickly as possible, however if less than 6 hours left from planned dose, dose is considered to be missed, the next dose should be taken as usual, without doubling dose.

Patients should be instructed and reminded to return all empty packages of study products (including empty and partially used) during each visit to the study physician.

4.4.4 Package and labeling of the study products

Tested product and comparator product will be prepared and provided by Sponsor. Sponsor will provide clinical centers with the test product and comparator product.

Study product Uritos® is manufactured by Kyorin Pharmaceutical Co. Ltd (Japan). Sponsor of the study (R-Pharm JSC), according to licensing agreement with manufacturer of the study product Kyorin Pharmaceutical Co Ltd (Japan), possesses the rights development, authorization and commercial promotion of the drug product Uritos®.

Within the frames of the study Sponsor is responsible for provision of package, labeling, shipping of the study products dedicated for the clinical study in accordance with shelf life and expiration date.

4.4.4.1 Study product

Dosage form: Film-coated tablets; 0,1 mg.

Package:

Uritos® for this clinical study will be provided in bottles, each bottle containing 200 tablets.

Labeling:

Study products labeling will conform to the local regulations and requirements. Study product will be labeled in Russian language with designation of the following information: Uritos®, film-coated tablets, Manufacturer, Storage conditions, Batch No; Expiration date; Patient No; For clinical trials; Study No; Center No, Patient No, Sponsor of the study.

4.4.4.2 Comparator product

Dosage form: Film-coated tablets; 2 mg.

Package:

Urotol for this clinical study will be provided in blister pack with 14 tablets per pack made of PVC/PVDC/AI. 2 or 4 blisters per carton pack together with package insert.

Labeling:

Study products labeling will conform to the local regulations and requirements. Study product will be labeled in Russian language with designation of the following information: Urotol, film-coated tablets, Manufacturer, Storage conditions, Batch No; Expiration date; Patient No; For clinical trials; Study No; Center No, Patient No, Sponsor of the study.

4.5 Duration of patients' participation in the study, description of visits order and duration of all study periods, including follow-up period visit

The study provides:

- Screening period – up to 2 weeks (14 days)
- Treatment period – therapy is performed during 12 weeks (84 days), including randomization visit (Day 1), 3 treatment phase visits on Weeks 2, 4 and 8 and end of the study visit on Week 12 (Day 85). Permissible variation during treatment visits ± 3 days.
- Follow-up period visit – 30 (+5) days after the end of study treatment, finishes with follow-up period visit and end of participation of the patient in the study (Days 114 - 119).

Maximum observation period of the patients within the study is 136 days (screening not exceeding 14 days + therapy up to 84 days (±3 days) + observation period up to 35 days.

4.5.1 Beginning of the study

- Beginning of the study is considered to be opening visit in the first research center. In Russian Federation, according to the Federal law "On Medicine Circulation", head of medical institution within terms, not exceeding 3 business days from the start of clinical study of the medicinal product for medical use informs about this authorized federal authority of the executive branch of the government, approved performance of this study, according to the established form (part 3.1 was introduced by the Federal law of 29.11.2010 No 313-ФЗ).

- Before the start of any procedures and actions connected with the study, patients should be provided with comprehensive and reliable information concerning any aspects of the preformed study. Each potential participant of the study should be informed of its objectives, methods, anticipated benefits and risks/ inconveniences associated with the study. All information concerning study course, benefits and possible risks is presented in Patient information list with form of informed consent, dated and signed by patient in two copies. One copy is provided to the participant of the study (see Section 12.4).

- Before the start of participation in the study all patients are discussed with and being warned about necessity to use reliable birth control methods during whole study period and, within at least 30 days, after the end of study (see Section 4.5.3.1).

- Before the start of participation in the study patient should be informed that he/she will receive qualified medical health as appropriate, as well as that information of the patient derived during study, will be confidential, that is stated in Patient's information list.

- According to Article 5.3 of Order No 266 of Ministry of Health of the Russian Federation, Investigator and/or healthcare institution are oblige to inform patient concerning requirement of treatment of the diseases, revealed during the course of the clinical study. This information should be recorded in the source documents and Sponsor should be informed about these cases (newly discovered disease within the clinical study is classified as adverse event).

- Each research center will be keeping record of the List of identification codes of the patients with full patient name, initials, date of birth, identification code, assigned during screening, status (unsuccessful screening, finished the study, prematurely withdrawn from the study). This list is stored in the center and is not subject to transfer to sponsor.

- Moreover, Patients screening and inclusion log will be filled where data of informed consent signing, screening visit date, identification code, assigned during screening, initials, failed screening (yes/no), randomization date and randomization number will be included.

4.5.2 Determination of the end of study

Finishing of the study for the patient is considered to be the last examination/procedure, performed during follow-up visit for safety parameters assessment.

4.5.3 Study visits and assessments

Screening procedures will be undertaken following signing of Informed consent form.

Graphical scheme of the scheduled procedures for each visit are presented in the Table 5.

4.5.3.1 Visit 1 (Screening): Days from -14 to -1

Screening period should not exceed 14 days before randomization visit/beginning of therapy.

During the screening patient's conformity towards inclusion/non-inclusion criteria is verified.

During screening visit following receipt of informed consent from the patient acquisition of baseline information of the patient, including demographic data (sex, date of birth, race, body mass, height), medical anamnesis, diagnosis, concomitant pathology and previous and concomitant therapy with designated date of start of product administration and doses within 30

days before screening visit; for female and male patients – birth control methods, for female patients – terms of menopause beginning.

Patient fills out OAB Awareness Tool Questionnaire for assessment of overactive bladder symptoms severity.

Physical examination with BP and HR assessment is performed.

Assessment and registration of adverse events starts from the moment of signing of informed consent form.

Clinical and biochemical blood tests (ALT, AST, bilirubin, creatinine, total protein, glucose, alkaline phosphatase, cholesterol, potassium, sodium) and urinalysis will be performed in the central laboratory. Serological examination for HIV, hepatitis B and hepatitis C is performed. Moreover, PSA testing is performed in male patients.

US-examination of kidneys, bladder and urine excretory ways with residual urine volume assessment is performed for exclusion of bladder structural pathology.

Cough probe is performed for assessment of urethral sphincter capability in women.

12-lead ECG is performed.

Female patients of childbearing potential undertake pregnancy test using dipstick (in the research center).

- <u>All patients should be discussed with efficient birth control issues</u>:

Female patients of childbearing potential and male patients and their female partners should use at least two birth control methods, one of those is barrier, including double barrier contraception method (condom in combination with intravaginal spermicide, cervical caps with spermicide, diaphragms with spermicide) during the whole study period and at least 30 days following administration of the last dose of the study product. Moreover, in addition to barrier contraception method, female patients of childbearing potential may use other approved birth control method:

- Oral, transdermal, implantational and injectional hormonal therapy;
- Intrauterine device (IUD).
- Partner's vasectomy (if patient was exposed to vasectomy, nevertheless barrier contraception method should be applied).

Female patients of childbearing potential before the start of the study should be informed about importance of birth control measures during the study, potential risk factors associated with pregnancy occurrence and, moreover, that in case of pregnancy occurrence they should immediately inform investigator physician. Female patients, not having menstruations for 2 years and more before inclusion into the study, as well as female patients subjected to surgical intervention (surgical sterilization, bilateral ovariectomy, hysterectomy etc) are considered as female patients without childbearing potential. These patients may be free from requirements concerning contraception described above.

Male patients, participating in the study, should be also informed, that in case of pregnancy appearance in their female partners they have to notify Investigator physician about this circumstances.

Patient is issued the diary where he/she should make notes concerning number of urination episodes, number of incontinence episodes at daytime (from 7 am to 11 pm) and nighttime (from 11 pm to 7 am), number of awakenings, number of micturition urgency episodes, as well as administration/missing doses of the study product and adverse events.

Investigator explains to the patients rules for diary filling, schedules next visit date and requests for daily filling of diary and reminds to take the diary to the next visit.

4.5.3.2 Visit 2 (Randomization/Beginning of the therapy): Day 1

During the Visit 2 patient's conformity towards inclusion/non-inclusion criteria is repeatedly verified by Investigator. Patient, conforming to the inclusion criteria and not possessing non-inclusion criteria, randomly assigned into correspondent therapy group by randomization procedure (according to Section 4.3.1).

Randomization day and day of start of therapy are designated to be Day 1 and is considered to be baseline point for calculation of following visits schedule.

Prior to randomization:

Patient fills out OAB Awareness Tool Questionnaire and Quality of life Questionnaire EQ-5D.

Check up of diary filling results is performed.

Assessment of concomitant therapy, physical examination with BP and HR assessment, adverse events assessment and registration is performed.

Female patients of childbearing potential undertake pregnancy test using dipstick (in the research center).

US examination of the bladder with residual urine volume assessment is performed.

If patients is recognized to be fully conforming to inclusion/non-inclusion criteria, randomization procedure is performed with following assignment into treatment group (according to Section 4.3.1).

Following randomization:

Investigator provides patient with comparator product according to randomization result in amount, sufficient for administration before the next visit, and explains how to take the product and reminds to return all packs from the product at the following visit.

First administration of the study product is performed at the day of randomization.

Patient is issued diary for the following filling. Investigator explains to the patients rules for diary filling, schedules next visit date and requests for daily filling of diary and reminds to take the diary to the next visit.

4.5.3.3 Visits 3, 4, 5 (Treatment phase visits): Days 15 (±3), 29 (±3), 57 (±3)

Visit 3 takes place after 2 weeks ± 3 days after beginning of therapy (Day 15 ± 3).

Patient fills out OAB Awareness Tool Questionnaire.

Assessment of concomitant therapy, physical examination with BP and HR assessment, adverse events assessment and registration is performed.

Investigator gathers packs of previously issued study product from the patient, performs calculation of returned product for assessment of compliance maintenance and gives next pack of the product for further intake.

Check up of diary filling results is performed; afterward diary is returned to the patient for further filling. Investigator explains to the patients rules for diary filling, schedules next visit date and requests for daily filling of diary and reminds to take the diary to the next visit.

Visit 4 takes place after 4 weeks ± 3 days after beginning of therapy (Day 29 ± 3).

Patient fills out OAB Awareness Tool Questionnaire. Assessment of concomitant therapy, physical examination with BP and HR assessment, adverse events assessment and registration is

performed.

US examination of the bladder with residual urine volume assessment is performed.

Investigator gathers packs of previously issued study product from the patient, performs calculation of returned product for assessment of compliance maintenance and gives next pack of the product for further intake.

Check up of diary filling results is performed; afterward diary is returned to the patient for further filling. Investigator explains to the patients rules for diary filling, schedules next visit date and requests for daily filling of diary and reminds to take the diary to the next visit.

Visit 5 takes place after 8 weeks ± 3 days after beginning of therapy (Day 57 ± 3).

Patient fills out OAB Awareness Tool Questionnaire. Assessment of concomitant therapy, physical examination with BP and HR assessment, adverse events assessment and registration is performed.

Clinical and biochemical blood tests (ALT, AST, bilirubin, creatinine, total protein, glucose, alkaline phosphatase, cholesterol, potassium, sodium) and urinalysis will be performed in the central laboratory.

US examination of the bladder with residual urine volume assessment is performed.

Investigator gathers packs of previously issued study product from the patient, performs calculation of returned product for assessment of compliance maintenance and gives a sufficient quantity of study drug for administration till the next visit. Partly used study drug packs are returned to the patient for further administration..

Check up of diary filling results is performed; afterward diary is returned to the patient for further filling. Investigator explains to the patients rules for diary filling, schedules next visit date and requests for daily filling of diary and reminds to take the diary to the next visit.

4.5.3.4 Visit 6 (End of treatment) Day 85 (±3)

Visit 6 takes place after 12 weeks ± 3 days after beginning of therapy – at the next day following intake of the last dose of the study product (Day 85 ± 3).

Patient fills out OAB Awareness Tool Questionnaire and Quality of life Questionnaire EQ-5D.

Assessment of concomitant therapy, physical examination with BP and HR assessment, adverse events assessment and registration is performed.

Clinical and biochemical blood tests (ALT, AST, bilirubin, creatinine, total protein, glucose, alkaline phosphatase, cholesterol, potassium, sodium) and urinalysis will be performed in the central laboratory.

Female patients of childbearing potential undertake pregnancy test using dipstick (in the research center).

US examination of the bladder with residual urine volume assessment is performed.

12-lead ECG is performed.

Diaries are taken from the patients with the following check of diary filling results.

Investigator gathers packs of previously issued study product from the patient, performs calculation of returned product for assessment of compliance maintenance.

Decision is taken concerning further patient management.

4.5.3.5 Visit 7 (Follow-up examination visit): after 30 ± 5 following end of treatment

Visit 7 should take place after 30 ± 5 following end of treatment for assessment of safety of the

treatment performed (days 114 - 119). Visit can be performed through telephone connection without need for physician appointment by patient.

Assessment of concomitant therapy, physical examination with BP and HR assessment (are not performed in case of telephone contact), adverse events assessment and registration are performed.

4.5.3.6 Unplanned visit

If patient prematurely withdraws from the study at any stage, it is required, if possible, to perform all procedures associated to premature withdrawal from the study visit within one week following decision of patient withdrawal. Procedures of this visit are identical to the procedures of the end of treatment visit (Visit 6).

Table 5 Timetable of basic procedures of the study

	Visit 1	Visit 2	Visit 3 (2 weeks ± 3 days)	Visit 4 (4 weeks ± 3 days)	Visit 5 (8 weeks ± 3 days)	Visit 6 (12 weeks ± 3 days)	Visit 7 (30 + 5 days after end of treatment)
Days (D)	D from -14	D1	D15 (±3)	D29 (±3)	D57 (±3)	D85 (±3)	D114 -
Reception of the informed consent	X						
Demographic data[1]/patient history acquirement	X						
Previous and concomitant therapy assessment	X	X	X	X	X	X	X
Assessment and registration of AE	X	X	X	X	X	X	X
Physical examination[2]	X	X	X	X	X	X	X[3]
Complete blood count[4]	X				X	X	
Blood chemistry[5]	X				X	X	
Urinalysis[6]	X				X	X	
Serological							
examination (HIV, Hep B and C)	X						
PSA level assessment (male only)	X						
Pregnancy test (only women with child-bearing potential)	X	X				X	

US-examination of kidneys, bladder and urine excretory ways (residual urine volume assessment)	X						
US examination of the bladder with residual urine volume assessment		X		X	X	X	
Cough probe	X						
12-lead ECG	X					X	
Assessment with OAB Awareness Tool Questionnaire	X	X	X	X	X	X	
Quality of Life assessment with EQ5D Questionnaire		X				X	
Issue/return and assessment of the diary	X	X	X	X	X	X	
Randomization		X					
Study product issue:		X	X	X	X		
Study product return, compliance assessment			X	X	X	X	

[1] Sex, date of birth, race, body mass, height

[2]Physical examination includes vital parameters assessment

[3]Is not conducted in case of telephone contact with the patient

[4]Hemoglobin, hematocrit, white blood cells and differential blood count, platelets.

[5] ALT, AST, bilirubin, creatinine, total protein, glucose, alkaline phosphatase, cholesterol, potassium, sodium

[6] Specific gravity, pH, protein, urinary sediment

4.5.4 End of the study

Clinical center should entirely finish the study and fill out all required documentation in accordance with protocol. The study may be suspended before its official finish in case of appearance of objective reasons, either by Sponsor, or by clinical center. Notifications concerning study cessation should be submitted to all parties, taking part in the study within the shortest possible time. Any extension of study terms should be coordinated between Sponsor and clinical center with corresponding documentation.

4.5.5 Description of several study procedures

4.5.5.1 Physical examination and vital parameters assessment

Full physical examination of all organs and systems will be performed at screening visit (Visit 1) and before randomization (Visit 2). During all following visits abbreviated physical examination is permitted with determination of significant deviations from baseline conditions (deviation-associated data are recorded as AE/SAE). Physical examination during every visit includes assessment of vital parameters (arterial pressure [BP], heart rate [HR]). BP and HR should be

assessed at resting state in sitting position.

4.5.5.2 Laboratory parameters

Following laboratory rests will be performed in central laboratory.

- **Complete blood count:** Hemoglobin, hematocrit, WBC and full blood count, platelets count – during screening, on Week 8 of treatment (Visit 5) and after the end of therapy (Week 12, Visit 6).

- **Blood serum biochemistry:** ALT, AST, bilirubin, creatinine, total protein, alkaline phosphatase, cholesterol, potassium, sodium – at screening on Week 8 (Visit 5) at the end of therapy (week 12, Visit 6). Before blood sampling for biochemical analysis patient should refrain from food and drink only water for, at least, 8 hours.

- **Urinalysis:** Specific gravity, pH, protein, urinary sediment – during screening, on Week 8 of treatment (Visit 5) and after the end of therapy (Week 12, Visit 6).

- **Serological testing for infections:** Blood analysis for presence of antibodies to HIV, antibodies to Hepatitis C virus, Hepatitis B virus (HBsAg) is performed during screening only.

- **Total prostatic specific antigen (PSA) level:** Assessment is performed in all male patients only during screening. Assessment result is used for validation of patient's conformity to inclusion/non-inclusion criteria (PSA exceeding 4 ng/ml is considered to be non-inclusion criteria).

Detailed description of laboratory probes acquirement, handling, storage and shipping, materials (tubes and labels) as well as normal values range of laboratory parameters will be provided in laboratory manual. Laboratory examinations results, performed in central laboratory, will be sent to Investigator by e-mail.

Investigator should validate results and assess remarks (notes) in laboratory tests prints. In case of deviations clinically significant changes should be emphasized. Investigator should sign and date the laboratory tests prints approving their verified status.

Following laboratory rests will be performed in the research center:

- Urine pregnancy test should be performed with use of dipsticks for female patients of childbearing potential – during screening visit, before randomization (Visit 2) and after finishing of the therapy (Visit 6). Test result has to be negative during screening visit and randomization visit for inclusion into study. For dipstick pregnancy test performance Sponsor of the study will be supplying centers with dipsticks for human chorionic gonadotropin (hCG) level evaluation in urea. Test results are fixed in the source documents. Dipsticks are not entitled to storage and should be discarded after results record following local practices.

4.5.5.3 US-examination of kidneys, bladder and urine excretory ways

US-examination of kidneys, bladder and urine excretory ways is performed according to local research center practice by functional diagnostics specialist during screening, uUS examination of the bladder with residual urine volume assessment is performed before randomization (Visit 2), at week 4 of treatment (Visit 4), at week 8 of treatment (Visit 5) at the end of therapy (week 12, Visit 6). Abdominal access is preferable. This examination is directed towards exclusion of organic pathology of urinary system before prescription of the study therapy and residual urine volume assessment (in ml) before the start of the study and during the study course. US-examination is performed on filled urinary bladder. Patient should not take diuretics the day before examination. Following measurement of full urinary bladder patient is asked to empty it and US-examination is performed second time for measurement of residual urine volume.

4.5.5.4 Cough probe

Cough probe is one of the most wide-spread functional probes performed in patients with urinary incontinence symptoms. This examination is performed according to local research center practice by functional diagnostics specialist. Probe is performed on filled urinary bladder. Female take the probe in gynecological examination chair. For probe performance patient has to cough 3 times with series of 3-4 cough impulses (with intervals between cough impulses for full inhale). When involuntary urea leaking is observed following coughing the probe is considered to be positive. Positive result designates internal sphincter failure and is typical for stress urinary incontinence diagnosis.

4.5.5.5 12-lead ECG

12-lead ECG is performed according to local practice – at screening and after the end of the study (Week 12, Visit 6). ECG copies are applied to patient's CRF. Standard ECG registration will be performed at the lying position following 5-minutes rest period. Results will be registered in the correspondent CRF pages. Primary ECG registration and/or its high-quality copy (in case of thermal paper application) should be applied to CRF. HR and PQ, QRS and QTc (Frederichi method based correction) as well as deviations of ECG outlines from normal values will be assessed.

4.5.5.6 Questionnaires, filled up by the patients

Questionnaire for hyperactive bladder symptoms assessment (OAB Awareness Tool) and health assessment questionnaire EQ-5D are to be filled by patients. EQ-5D questionnaire is to be completed during randomization (Visit 2) and after the end of therapy (Week 12, Visit 6). Questionnaire for hyperactive bladder symptoms assessment (OAB Awareness Tool) is filled out during screening for verification of inclusion criteria and during Visits 2, 3, 4, 5 and 6.

These questionnaires are required to be filled out at the beginning of the visit before discussion with the patient and performance of other visit procedures. Patient should be provided with sufficient amount of time for answers to the questions. Questionnaires should be filled out in quite place without any distracting factors. Completed questionnaire is passed from the patient to Investigator, then Investigator verifies comprehensiveness and accuracy of it filling. The investigator transfers the filled questionnaires data into the CRF.

4.6 Description of "rules for study cessation" and "inclusion criteria" for individual subjects, parts of the study and study in a whole.

Sponsor of the study, R-Pharm JSC, shall reserve the right for termination of the study anytime for reasons, including but not limited to safety problems, ethical aspects or major protocol violations (see also Section 5.3).

Moreover, R-Pharm JSC, shall reserve the right to stop the study anytime if study goals are considered to be inaccessible.

However, the Sponsor shall notify the Principal Investigator and the Head of Medical Institution concerning premature termination of the study in written form.

If the study is terminated for reasons connected to safety problems, R-Pharm JSC shall immediately notify about these circumstances all Principal Investigators and regulatory authorities and ethical boards as well.

In cases when the Principal Investigator prematurely terminates the study before its end in his/her clinical center, he or she shall immediately notify the Sponsor concerning its ceasing with explanation provided.

Moreover, the study may be terminated under requirement of regulatory authorities or ethics board for reasons, including but not limited to safety problems, in accordance to the Russian Federation and the Belarus Republic legislation.

4.7 Study products accounting procedure

The test product and the comparator product for the study will be supplied to the study organizer (CRO) by the Sponsor with correspondent acceptance and transfer certificate, analysis certificate. The responsible center employee (Investigator or authorized representative) should acquire and handle all the product supplies from the Sponsor (CRO). The product storage will be performed in locked case (applicable for storage of medicinal products) at the temperature not exceeding 25° C in a dry place protected from light, before its dispensing in specially equipped rooms with restricted access.

The Sponsor will provide research centers with the test product and comparator product in sufficient amount for performance of the study.

Control, accounting and storage of the products within research center is performed by responsible person, authorized by Principal Investigator in accordance to in-house center order and instructions from the Sponsor of the study. Study products should be stored in accordance with instructions, provided by the Sponsor, and applicable regulatory requirements.

Accounting of the test product and comparator product is performed by Investigator in Product accounting, storage and issue log. Prescription of the study product to the patients will be documented in Investigator's file (patients won't get the product personally). Investigator bears responsibility for application of study products in strict compliance with approved protocol. Any discrepancies should be provided with explanations and appropriately documented.

The Investigator will be maintaining accounting of the prescribed product for each patient, recording number and initials of patients, acquired this product, issue date, amount of issued product and date of product return by patient. Person, responsible for accounting and storage of the products and Principal Investigator draw and sign the report.

After the end of the study all unused or partially used study products should be returned to Sponsor with correspondent delivery and acceptance certificate.

4.8 Storage of randomization codes

Randomization process description is provided in Section 4.3.1.

List of randomization numbers, generated before the start of the study, will be stored in the study file in center, as well as by Sponsor or his/her Representative. Investigator bears responsibility for randomization performance (assignment of randomization number to the patient) according to this list. Randomization number, assigned to the patient, is recorded in the Screening/patients inclusion log.

Randomization numbers list will be known to investigators, Sponsor, regulatory authorities (in case of serious adverse event recognition).

4.9 List of data registered directly in CRF.

Primary data (source data) contains all information, recorded in original medical documents and approved copies, describing results of clinical observations, investigations and other activity, allowing to reconstruct clinical study course and perform its assessment. Source data are contained in primary documents (original documents or certified copies).

For each patient, participating in this study, electronic case report form (eCRF) is created, containing basic information, associated with the study.

The Sponsor will provide a separate manual (guidance) concerning eCRF handling.

This study does not provide any data that would be included into eCRF without reflection of this information in primary documents. All data, associated with this study, will be originally recorded in primary documents and then in the eCRF.

5 PATIENTS SELECTION AND EXCLUSION

5.1 Inclusion criteria

For participation in the study patient should satisfy all the listed criteria:

1. Informed consent signed and dated;

2. Male and female patients with age range between 18 and 65 years (age at the moment of signing informed consent form).

3. Documented overactive bladder (OAB) diagnosis. OAB diagnosis is established on characteristic symptoms of the patient:

a. urinary incontinence – 5 and more episodes per week;

b. frequent urination – 8 and more times per day;

c. Micturition urgency – 1 and more episodes per day.

4. OAB symptoms duration 3 months and more (assessment is based on patient history and medical documents).

5. Overactive bladder Awareness Tool Questionnaire (OAB Awareness Tool) score 8 and more at the screening visit and randomization visit.

6. Negative dipstick pregnancy test at screening and at randomization visit before administration of the first dose of the study product in female patients of childbearing potential.

7. Female patients of childbearing potential and male patients and their female partners should use at least two birth control methods, one of those is barrier, during the whole study period and at least 35 days following administration of the last dose of the study product. Permissible birth control methods:

- oral, transdermal, implantational and injectional hormonal therapy;
- efficient intrauterine devices;
- double barrier contraceptive methods.

8. Willingness and ability to follow study visits schedule, treatment plan, laboratory tests and other study procedures.

5.2 Non-inclusion criteria

For participation in the study patient should be free from all the following criteria:

1. Patient history of hypersensitivity or suspected hypersensitivity to tolterodine or imidafenacin.

2. Structural pathology of urinary bladder, including urinary bladder cancer, urinary bladder stones and interstitial cystitis.

3. Residual urea volume 100 mL and more at US-examination of urinary bladder.

4. Documented diagnosis of stress urinary incontinence.

5. Surgical interventions on urinary bladder and urethra during the previous 6 months or indications for surgical treatment due to OAB.

6. Exacerbation of gynecological diseases including endometriosis, uterine leiomyoma exceeding 3 cm in diameter.

7. Prostate carcinoma.

8. Prostate diseases with clinically significant urodynamics abnormality (benign prostatic

hyperplasia, acute and chronic prostatitis, prostatic calculus).

9. Renal and urine excretory ways inflammatory disorders (pyelonephritis, bacterial cystitis, urethritis).

10. For male PSA level above 4 ng per mL.

11. Severe liver function abnormality (ALT and/or AST level 3 and more times exceeding upper limit of normal and/or total bilirubin level 1.5 times exceeding upper limit of normal).

12. Moderate or severe renal function abnormality based on medical information and/or glomerular filtration rate < 50 ml/min by Cockroft-Gault formula and/or blood creatinine level > 133 μmol during screening.

13. Positive test result for hepatitis B, hepatitis C and HIV.

14. Patients suffering from neoplastic condition without remission, at least, within 5 years from the start of administration of the study product.

15. Vascular dementia, Alzheimer disease associated dementia, dementia associated with other diseases including organic amnestic syndrome.

16. Parkinson's disease and secondary parkinsonism.

17. Nonspecific ulcerative colitis including severe stage of ulcerative colitis.

18. Thyroid gland pathology with hyperthyroidism signs.

19. Chronic heart insufficiency Stage III-IV by NYHA.

20. Hypotension: systolic blood pressure < 90 mm Hg and/or diastolic blood pressure < 60 mm Hg.

21. Non-controlled medically induced hypertension.

22. Hemodynamically and/or clinically significant heart arrhythmias.

23. Prolongation of QTc interval up to 450 ms and more in males and 470 ms and more in females.

24. Closed-angle glaucoma.

25. Myasthenia gravis.

26. Megacolon, paralytic ileus, pyloric part of the stomach/duodenal occlusion and any other conditions associated with clinically significant gastric/intestinal passage obstruction or depressed motility.

27. Necessity of intake and/or intake of prohibited products, declared in the Section "Acceptable and prohibited recent and concomitant therapy" within 7 days before the start of therapy.

28. Drug abuse, chronic alcoholism, any psychotic disorders.

29. Participation in other studies within 3 months from the start of the current study and/or during this study.

30. Pregnancy and/or breastfeeding.

31. Female patients of childbearing potential, having unprotected sexual contact with male person, non-sterilized by vasectomy during, at least, 6 months, within 14 days before administration of the study product.

32. Inability to follow protocol procedures.

33. Any other acute or exacerbation and/or decompensation of chronic diseases at the

moment of inclusion into the study.

34. Patient's behavior, any safety reasons, clinical and administrative reasons, which, according to Investigator's opinion, may potentially influence study product safety/efficiency assessment.

35. Other medical and psychiatric conditions or deviations of laboratory parameter which may increase patient risk associated with participation in the study or administration of the study product, or which can influence interpretation of the study results and, according to Investigator's opinion, make person not satisfying conditions for participation in this study.

36. Patients being employees of the research center or patients being employees of Sponsor/CRO, directly involved into performance of this clinical study.

5.3 Exclusion criteria

This study provides premature withdrawal of the patients from the protocol due to different reasons, that include but not limited to the following:

1. Investigator took decision to withdraw patient according to patient's interests.

2. Sponsor's decision to exclude patient from the study due to serious protocol deviation/protocol violation.

3. Adverse event, requiring cessation of the study therapy, or prescription of prohibited products, declared in the Section "Acceptable and prohibited recent and concomitant therapy", or restricting performance of protocol procedures.

4. Significant concomitant disease that is, according to Investigator's opinion, poses risk to patient's well-being.

5. Patient non-compliance with the study requirements.

6. Pregnancy.

7. Patient decision of not participating in the study (informed consent withdrawal).

5.4 Follow up observation of the patients withdrawn from the study

If patient withdraws from center prematurely it is required to ask him to visit center and, if possible, to complete all visit procedures of the end of the study (Visit 6, Week 12).

Investigator should designate the reason for preterm withdrawal in primary documents and CRF. Whether patient is willing to withdraw from the study of one's own free will, Investigator should try to reveal the reason for his/her decision. If preterm withdrawal is associated with adverse event, Investigator should apply all possible efforts for collection of information concerning his/her outcome and record this information in CRF in adverse events section. If withdrawal from the study is secondary to serious adverse event (SAE), immediate notification of Sponsor about SAE procedure should be followed.

Patients, prematurely withdrawn from the study after the start of receiving of the study therapy, will not be substituted by new patients, and their data will be taken into consideration during final assessment.

When patient withdraws from the study due to SAE, patients is observed during the whole period up to resolution of SAE.

6 PATIENTS MANAGEMENT

6.1 Description of study products, including name, dosage, frequency and way of administration, treatment duration and follow-up examination

The study will assess following doses and administration schedules of the products (see also Section 4.4):

- Uritos® (Imidafenacin, film-coated tablets; 0,1 mg, Kyorin Pharmaceutical Co. Ltd., Japan), oral, 1 tablet BID after meals (after breakfast and after supper).

- Urotol® (tolterodine, film-coated tablets; 2 mg, Zentiva k.s., Czech Republic), oral, 1 tablet BID after meals (after breakfast and after supper).

Distribution will be performed according to 1:1 randomization.

Investigator's file will contain batch numbers of the study product and comparator product.

First dose of the product will be issued to the patients at the day of randomization. Administration of this dose will be performed during research center visit. Products will be issued directly to patients, which should hereinafter take the product by their own and record information concerning intake of the study product into diary.

It is recommended to keep 12-hours interval between administrations of the study product. In case of missing dose of the product it should be taken as quickly as possible, however if less than 6 hours left from planned dose, dose is considered to be missed, the next dose should be taken as usual, without doubling dose.

Patients should be instructed and reminded to return all empty packages of study products (including empty and partially used) during each visit to the study physician.

6.2 Medicines allowed and not allowed before and/or during the study.

During the whole study period patient are allowed to receive therapy for primary and concomitant diseases, in case of correspondent indications and absence of significant changes in administration schedule of the existent medicinal therapy within the last month after the study.

During the whole period of administration of the study therapy and following groups of medicines are prohibited for OAB syndrome treatment (except the following):

- M-cholinergic antagonists, including those with selective action, except topic and inhalatory products
- Agents, decreasing urinary bladder activity (toxins)
- All antidepressants
- Alfa-1-adrenergic blocking agents
- Urine formation diminishing agents (vasopressin analogs)
- Prostaglandins synthesis inhibiting agents

Moreover, concomitant prescription of medicinal products from the following groups with possible pharmacokinetic and pharmacodynamic interaction is prohibited.

- Antibiotics from macrolides group (erythromycin, clarithromycin)
- Antifungal agents (ketokonazole, intrakonazole, mikonazole)
- Neuroleptics, barbiturates and other psychotropic agents
- Other medicines strong inductors or inhibitors of cytochromes P450 2D6 and 3A4.
- M-cholinergic agents

Drug-free management of OAB:

Drug-free methods of OAB treatment (e.g. behavioral therapy, Kegel exercises) – are allowed during the study.

Surgical treatment of OAB:

When surgical intervention is required, patient with OAB should be excluded from the study.

No other restrictions concerning daily life, physical activity and diet were not prescribed.

6.3 Measures for control over patients' compliance with study procedures

Compliance assessment will be performed by diary where patient should record data concerning product receipt, as well as be control of amount of product, issued at visits 2, 3, 5 and 5 and returned at visits 3, 4, 5 and 6.

Before participation in the study patients will be informed about risks and restrictions associated with the study. Investigator possesses the right to deny patient's participation in the study in case of his/her suspicion of further study procedures violation from the patient's side.

Compliance will be calculated according to the following formula:

К (%) = N (actual administrations) / N(scheduled administrations) x 100%.

Compliance not lower than 95% will be considered as satisfactory.

Control over compliance will be performed by the diary records.

Patient's diary will be issued to patients not only for assessment of efficiency endpoints, but also for additional control over investigation procedures compliance. Diary, among OAB symptoms (number of urinations, incontinence episodes, micturition urgency) should include information concerning administration of the study product and any adverse events. Patient should take his diary with him/her for each visit. Investigator checks regularity and accuracy of diary filling by the patient. When necessary patients can be instructed repeatedly concerning diary filling rules.

7 EFFICIENCY ASSESSMENT

7.1 Set of efficiency parameters:

Primary efficiency criteria:

Change of mean daily number of urination episodes at the 12 week Visit against the Visit of starting therapy.

Secondary efficiency criteria:

1) Change of mean daily number of urinary incontinence episodes at the 12 week Visit against the Visit of starting therapy.

2) Change of mean daily number of urinary incontinence episodes during daytime (from 7 am to 11 pm) at the 12 week Visit against the Visit of starting therapy.

3) Change of mean daily number of urinary incontinence episodes during nighttime (from 11 pm to 7 am) at the 12 week Visit against the Visit of starting therapy.

4) Change of mean daily, mean daytime and mean nighttime number of urinary incontinence episodes at the weeks 2, 4, 8 Visits against the Visit of starting therapy.

5) Change of mean number of urinary incontinence episodes per week at the 12 week Visit against the Visit of starting therapy.

6) Change of mean daily number of urinary incontinence episodes at the weeks 2, 4, 8 Visits against the Visit of starting therapy.

7) Changes in overactive bladder symptoms assessment parameters according to Overactive bladder Awareness Tool Questionnaire at Visits 2, 4, 8 and 12 weeks in comparison to the visit before the beginning of therapy.

8) Change of quality of life assessment using EQ-5D questionnaire (at the 12 week Visit against the Visit of starting therapy).

7.2 Methods, terms of assessment, registration and analysis of efficiency parameters

Calculation of urination episodes number and urinary incontinence episodes number will be performed on basis of data recorded be patients into their diaries.

Mean daily number of urination episodes is calculated as total number of episodes during the day (from 7 am to 7 am of the next day) for the study period (between visits) divided into number of days in period.

Average daily number of incontinence episodes is calculated the same way.

Mean daytime number of urinary incontinence episodes is calculated as total number of episodes during the period from 7 am to 11 pm for the study period (between visits) divided into number of days in period.

Mean nighttime number of urinary incontinence episodes is calculated as total number of episodes during the period from 11 pm to 7 am for the study period (between visits) divided into number of days in period.

Mean number of urinary incontinence episodes per week is calculated as total number of episodes during the study period (between visits) divided into number of days in period.

During randomization visit, treatment visits (Visits 3, 4, 5) and end of treatment visit (Visit 6) investigator will summon diary from patient, verify comprehensives of its filling, record results in CRF with further automatic calculation of mean values.

8 SAFETY ASSESSMENT

8.1 List of safety parameters

1) Frequency for development of adverse events (AE) and serious adverse events (SAE).

2) Frequency of development of AE and SAE, depending on application of the product.

3) Frequency of development of AE and SAE, bringing to treatment cessation/withdrawal from the study.

4) Residual urine volume assessment using US-examination of the bladder at the study visits against study start visit.

5) Changes of laboratory parameters, ECG parameters and vital parameters assessment.

8.2 Methods, terms of assessment, registration and analysis of safety parameters

8.2.1 Vital parameters assessment:

Vital parameters assessment (systolic and diastolic BP, HR) will be assessed following 5 minutes resting period at the sitting position.

All visits include physical examination with vital parameters assessment

8.2.2 Clinical and laboratory examinations

Total blood count and blood biochemistry and urinalysis will be performed during screening visit, Visit 5 and Visit 6 (see Section 4.5.5.2).

Blood count includes determination of hemoglobin, hematocrit, WBC and full blood count, platelets count.

Blood biochemistry includes determination of ALT, AST, bilirubin, creatinine, total protein, glucose, alkaline phosphatase, cholesterol, potassium, sodium values.

Serological examination will include testing for HIV, hepatitis B and hepatitis C.

Urinalysis includes determination of specific gravity, pH, protein and urea sediment examination.

All assessments will be performed in central laboratory. Total volume of blood, sampled from patients during the study, will be approximately **35 ml.**

Dipstick pregnancy test should be performed for female patients of childbearing potential – during screening visit, before randomization (Visit 2) and after finishing of the therapy (Visit 6).

Investigator should validate results and assess remarks (notes) in laboratory tests prints. In case of deviations clinically significant changes should be emphasized. Investigator should sign and date the laboratory tests prints approving their verified status.

8.2.3 Electrocardiogram assessment

During ECG study following parameters would be registered: HR and PQ, QRS and QTc (Frederichi method based correction) as well as deviations of ECG outlines from normal values (see Section 4.5.5.5).

8.2.4 US-examination

US-examination of kidneys, bladder and urine excretory ways includes residual urine volume assessment.

8.3 Adverse events and intercurrent diseases reporting

8.3.1 Serious adverse event definition

Adverse event is considered to be any untoward medical occurrence in a patient or clinical study

subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. Therefore AE can be attributed to adverse and unintentional signs (including deviations of laboratory parameters), symptoms and diseases, demonstrating temporal relationship with application of medicinal (test) product, independently from causal relationship with medicinal (test) product.

Following issues are considered to be AE:

- Laboratory parameters, exceedint the threshold of normal values and clinically significant.
- Laboratory parameters, changed against baseline parameters of the patient and clinically significant.
- Preexisting findings on physical examination, deteriorated in comparison to baseline parameters, and considered to be clinically significant.
- Physical examination findings (including vital parameters) which are considered to be clinically significant.

8.3.2 Adverse events reporting

Investigator-physician and medical center employees bear responsibility for detection, provision of essential medical care, documentation and reporting concerning cases, corresponding to AE and Serious adverse events (SAE) definitions.

Any AE not considered to be serious, will be reported from the moment of start of administration of the study products and before the end of follow-up period (30-35 days after the last receipt of the products). SAE will be registered up to the moment of informed consent signing and will be followed up to their resolution or stabilization of patient condition.

Investigators should document in patients' records and CRF any AE, appeared in patient during the study period. Patient is warned that he/she has to inform his attending physician about any new symptoms evolving.

AE are registered base on complaints, provided by patient personally, results of conversations between investigator and patient, physical examination results and laboratory assessments. Investigator should phrase the questions to the patients not to instigate to presentation of false information.

AE are recorded in the correspondent sections of CRF as well as primary medical documents of the patient.

Following information should be provided during registration of the AE:

- Patient identification code;
- AE classification according to CTC AE V4 classification (if applicable).
- AE features (diagnosis is preferable, not the symptoms list);
- Date of development and resolution of AE (and time, if applicable);
- AE severity:
- Actions taken in respect to the AE:
- Actions, taken in respect to the study product;
- Correspondence of AE to serious adverse event criteria;
- Presence on interrelation between AE and application of the study product (according to Investigator's assessment);

- Outcome of the AE.

Additional procedure is required for SAE (see Section 8.3.5).

8.3.3 Determination of adverse events parameters

In accordance with the current guidances, AE parameters concerning seriousness, foreseeness, severity grade, outcome and causal relationship will be assessed the following way:

Seriousness:

An adverse event is considered to be any adverse medical event, which:

- Resulted in death;
- Was life-threatening;
- Resulted in persistent or significant disability or incapacity;
- Required in-patient hospitalization or prolongation of existing hospitalization;
- Was a congenital anomaly/birth defect;
- Was medically significant event (required measures for prevention of the above mentioned outcomes).

Foreseeness:

"Unintentional" adverse event/reaction does not comply by its nature and severity grade those AE, which are listed in the current version of Investigator's Brochure or instructions for medical use of the product.

Severity grade:

AE severity is assessed according to the following criteria:

- Mild: Non-interfering with daily activity
- Moderate: Interferes with daily activity
- Severe: Patient is unable to manage with daily activity

Serious AR may not be serious and, conversely, serious AE is not obligatory serious.

In case of AE "dry mouth" severity of this event will be interpreted the following way:

- Mild: Dry mouth presents but scarcely bothers.
- Moderate: Dry mouth is tolerable after water/other liquid intake.
- Severe: Dry mouth is intolerable even after water/other liquid intake; requires therapy withdrawal

Outcome:

AE outcome is assessed following way:

Death	Patient died due to AE (death is considered to be outcome, not AE)
Deterioration	AE deterioration
Unchanged	AE not resolved
Resolved with consequences	AE resolved, but several residual effects continue to persist
Resolved without consequences	AE entirely resolved without any residual effects
Not known	AE outcome is not known because patient did not appear for

	visit of the follow-up examination and attempts to obtain information are fruitless (inaccessibility for further observation).

Causal relationship:

Causal relationship between each AE, according to WHO criteria, is determined by the following nomenclature:

Unrelated	– Presence of a clear alternative explanation and/or – Unreasonable temporal relationship between the drug administration and AE and/or – Implausibility
Inaccessible/ Unclassifiable	– report contains proposal concerning adverse reaction, however it is impossible to consider relationship because information is not sufficient or contradictory, data cannot be completed or validated.
Conditional/Unclassified	– events including deviation of laboratory parameter – more data are required for appropriate assessment – additional data are pending issue at the present time
Unlikely related	event including deviation of laboratory parameter with inconclusive (implausible) temporal connection with administration of the product, which, however, does not exclude possibility of this connection other factors, e.g. primary and concomitant diseases, or other medicinal products, could be more probable reasons for AE
Possible	event including deviation of laboratory parameter possess strong temporal connection with administration of the product AE may also be associated with concomitant diseases or any other medicinal products of chemical substances. Information concerning product withdrawal is not available or requires and upgrade.

Probable/Likely	– event including deviation of laboratory parameter possess strong temporal connection with administration of the product – AE is unlikely associated with concomitant diseases or any other medicinal products of chemical substances. – clinically significant response on product dechallenge – repetitive prescription of the product was not performed
Certain	event including deviation of laboratory parameter possess strong temporal connection with administration of the product AE is not explainable by concomitant diseases or application of other medicinal products or chemical substances. causal relationship with administration of the study product and its withdrawal is justified from biological point of view AE is considered to be identified risk for application of the product AE appears again following repetitive administration of the product (if applicable)

Actions, that should be taken in case of AE appearance:

- change of study product dose
- revocation or suspension of the study product
- prescription of additional medicines (which, what dose, how long) for AE treatment;
- no actions taken

8.3.4 AE follow up observation period

All AE should be followed up to their resolution or up to the moment when physician considers them as “chronic” or “stable”.

In case of serious AE patient observation is performed up to its resolution, using telephone calls with requirement for complains and history taking, as well as during unplanned visits required from patient’s safety point of view.

In case when, according to Investigator physician opinion, AE, not considered to be serious, requires further observation of the patient, this observation may be also performed by telephone calls and visits with inquiry of complaints and patient’s history.

In case of SAE appearance, according to investigator physician assessment, with possible connection with administered product, observation and required treatment is performed dependent on SAE development terms; patient observation is also performed before resolution of SAE.

All additional information concerning AR should be recorded in the correspondent pages of eCRF in the form of additional reports.

8.3.5 SAE report

8.3.5.1 Investigator’s responsibility

AE seriousness assessment is performed by Investigator or his/her authorized representative.

Investigator should inform about any SAE independently from assessment of causal relationship with the study product to the Sponsor’s authorized pharmacovigiliance representative (contact information see below) by fax or by e-mail within 24 hours after their development or receiving information concerning SAE.

Primary contact person for SAE cases reporting is Sponsor of the study (R-Pharm JSC).

Authorized pharmacovigilance representative of the Sponsor company will obtain from investigator completed SAE forms, verify their comprehensiveness and specify missing data (whether required). Sponsor may delegate several procedures to CRO including checking CRF and refinement of missing data from investigators. Interaction between CRO and the Sponsor, submission of SAE cases to the Regulatory authorities will be performed in accordance with Standard operational procedures of the Sponsor.

Contact information for safety issues reporting: **Sponsor:**

Head of Medicinal Products Safety Department of R-Pharm JSC[redacted]
Tel.: +7 (495) 956-7937 ext.[redacted] Fax: +7 (495) 956-7938

e-mail: safety@rpharm.ru;[redacted]

Contract research organization:

Authorized person on pharmaceutical safety

Synergy Research Group OOO

Tel.: +7 (495) 600-4445 Fax: +7 (800) 700-1164

e-mail: safety@synrg-pharm.com

In case of additional questions Investigators should get in contact with monitor of the corresponding center or Medicinal Products Safety Department of R-Pharm JSC.

SAE report should be prepared independently from assessment of causal relationship with the study product.

If SAE, associated with application of study product, is registered in patient, correspondent report should be submitted even in case when the study has been finished.

Observation over SAE and AE of special interest, as well as AE, causing withdrawal from the study, is performed up to their resolution or stabilization of patient's condition.

8.3.5.2 Notification of regulatory authorities about serious adverse reactions cases

Reporting about suspected unexpected serious adverse reactions (SUSAR)

Authorized pharmacovigilance representative of the Sponsor company will submit information concerning SUSAR towards regulatory authorities of the countries, participating in the study.

Authorized pharmacovigilance representative of the Sponsor company will also inform investigators concerning any SUSAR, reported during the study course.

Investigator will send all information, obtained from Sponsor, about SUSAR, into Local Ethics Board (LEB) of the research center and will store all information, associated with safety report, into Investigator's file.

SUSAR reports, caused death or life-threatening for the patient, should be submitted to regulatory authorities within 7 consecutive days after receipt of information by authorized pharmacovigilance representative of the Sponsor company, and further reports with additional information – within 8 consecutive days. Similar terms for non-life threatening SUSAR are considered to be 15 consecutive days.

Other safety reports application

Authorized pharmacovigilance representative of the Sponsor company will submit to the regulatory authorities reports concerning other safety aspects entitled to immediate notification of these authorities in case they are having an impact on assessment of benefit-risk ratio, connected with treatment applied or may require application of significant corrections into treatment performed under the study conditions, or into study methodology.

Besides immediate reporting, Sponsor company will be preparing annual safety reports for the study product, including all new information, obtained within report period. during the whole study period. These reports will be annually submitted be Sponsor to the regulatory authorities or in different terms on remand of these authorities.

8.3.6 Pregnancy

Pregnancy itself is not considered to be AE, excluding the cases where it is reasonable to presume that application of the study product brought to decreased efficiency of birth control measures. Congenital anomalies/birth defects in patients' children are considered to be SAE. Scheduled abortions, performed for medical indications, with complications, as well as any serious complications during pregnancy (including miscarriages), should be recorded as SAE. Non-complicated scheduled artificial abortions are not considered as AE.

All pregnancy cases occurred within the study period (including pregnancy cases of sexual partners of male patients, participating in the study), should be recorded in an appropriate manner. In case of confirmed pregnancy Investigator should inform authorized pharmacovigilance representative of the Sponsor company through special report form for pregnancy occurrence. Then Investigator should render information to the Sponsor company concerning pregnancy outcome. Female patients and patients' female partners pregnancy cases are recorded from the start of administration of the study product and up to the last study procedure.

Outcomes of all pregnancy cases (spontaneous abortion, elective artificial abortion, healthy child birth or birth of child with congenital anomaly/birth defect) should be recorded.

9 STATISTICS

Statistical analysis will be performed by CRO. Any deviations from assessment order should be included into the Plan to be submitted within the Clinical study report.

Interim analysis during the study is not scheduled. Statistical analysis will be performed using software packet SAS® 9.3 or other commercially available software.

9.1 Statistical methods

All values of analyzed parameters will be provided in Tables and graphically represented.

9.1.1 Data description

All registered characteristics of the patients, including demographic data, will be provided in tables as frequency-based and/or percent-based parameters, or using mean, standard deviation, median, minimum and maximum, upper and lower quartiles dependent on variable type. Data will be provided for all patients from the studied population according to the treatment groups. Validation of variables distribution for normality using Kolmogorov-Smirnov test will be performed for assessment of possibility for application of parametric methods.

9.2 Patient population justification

H_0 (null hypothesis): effect of Urotol (tolterodine) according to assessment of mean daily urination episodes exceeds effect of Uritos® (Imidafenacin) with non inferiority threshold 0.8 episodes per day.

H_1 (alternative hypothesis): effect of Uritos® (Imidafenacin) according to assessment of mean daily urination episodes exceeds effect of Urotol (tolterodine) with non inferiority threshold 0.8 episodes per day.

$H_0: \mu_A - \mu_B \geq \delta$ $H_1: \mu_A - \mu_B < \delta$,

where μ_A, μ_B – efficiency of medicinal products Uritos® (Imidafenacin) and Urotol (tolterodine), respectively; δ – non-inferiority threshold (δ = 0,8 episodes per day)

Following levels of error of the first kind = 0.025 and error of the second kind = 0.2 were taken for calculation of the study sample (that corresponds to 80% power of the study), acceptable non-inferiority threshold at the primary endpoint at Week 12 - 0.8 episodes per day; based on results of previous examination of imidafenacin, standard deviation at the primary endpoint is considered to be 2.12 episodes per day on sample consisting from 355 patients.

Sample size calculation is based on formula from [36]:

$$n_A = \frac{(r+1)\sigma^2(Z_{1-\beta}+Z_{1-\alpha})^2}{r((\mu_A-\mu_B)-\delta)^2}$$

Where $r = n_A/n_B$,

σ – assumed standard deviation for change in mean daily number of urination episodes.

n_A, n_B – study group and control group sizes, respectively.

μ_A, μ_B – assumed mean change of mean daily urination episodes in study group and control group, respectively.

$Z_{1-\alpha}, Z_{1-\beta}$ – cumulative function parameters of normal standard distribution for first (α) and second (β) types of errors, respectively.

δ - non-inferiority threshold.

With due consideration of homogeneous distribution of patients among treatment groups ($n_A = n_B$ и $r = 1$), , in each treatment group will be randomized

$$n = \frac{2 \cdot 2{,}12^2 (0{,}84 + 1{,}96)^2}{0{,}8^2} = 111$$

Sample containing 222 patients (111 per study group) is considered to be sufficient for proof of alternative hypothesis (rejection of null-hypothesis) at the significance level 0.025% and study strength 80%. With due consideration of withdrawal during treatment total amount of patients to be randomized is about 300 (150 patients per study group).

9.3 Significance level applied

All analysis types used in the study will be performed at the statistical significance level < 0.05 if overwise noted.

During assessment of significance of discrepancies in primary endpoint access one-sided 97.5% confidence interval will be applied.

Two-sided 95% confidence intervals will be applied during description and testing of other data.

9.4 Interim analysis and study cessation criteria.

Not applicable

9.5 Accounting procedures for missing, non-assessable and equivocal data

Missing, non-assessable and equivocal data will not be substituted and considered to the frames of statistical analysis of the results. All missing or equivocal data as well as data, not included into statistical analysis, will be registered according to CRO procedures. All data unaccounted during analysis will be described and justified in final study report.

Before taking decision concerning inclusion of data, obtained during clinical study, into assessment, patients compliance will be evaluated.

Following indicators will be applied:

Taking Compliance (CC) reflects relationship between number of the product doses taken within defined period and doses, prescribed by attending physician.

Formula: TC = number of doses taken: number of prescribed doses x 100%.

Timing Compliance (TiC).

Formula: TC = number of doses taken in the right time: number of prescribed doses x 100%.

Data would not be taken into consideration when “Product receiving compliance” indicator is less than 90%, and “Accuracy compliance” is less than 90%.

9.6 Reporting procedures concerning any deviations from primary statistical plan

In case of minor deviations from primary statistic analysis plan all deviations will be justified and described in final report for performance of the study. In case of changing of the statistical analysis plan correspondent amendment to the protocol will be issued.

9.7 Patients selection for assessment

Efficiency analysis will be performed on FAS population (Full Analysis Set), including all randomized patients taken at least one dose of the study product and having at least one efficiency assessment after Visit 2. Efficiency analysis in this population will be performed according to the assigned treatment.

Per protocol population (PP) includes all FAS population patients, went through all planned visits up to Visit 6, observing protocol conditions, namely patients, eligible to inclusion/non-inclusion criteria and finished participation in the study in accordance with all protocol requirements (except slight deviations from the protocol, which are not a cause for withdrawal from the study). Efficiency analysis in this population will be performed for confirmation of the

conclusions, obtained after efficiency assessment in FAS population.

List of major deviations from the protocol, caused patient withdrawal from the study or from PP population during statistical analysis, will be finalized by Sponsor before completion of statistical analysis and consequently will be presented in final study report. These protocol deviations may include but not limited to the following:

- Non-compliance with inclusion or non-inclusion criteria by the patient participating in the study.
- Participation of the patient in the study having exclusion criteria according to the study protocol;
- Incorrect study product administration schedule and dosage;
- Administration of the medicines, forbidden by the protocol

All randomized patients, receiving test product/comparator product, at least once, will constitute population for safety assessment. Safety assessment will be performed based on the actual treatment received by the patients. All AE revealed during the study should be included into analysis.

9.8 Efficiency assessment

Efficiency assessment of mean daily, mean daytime and mean nighttime number of urinary incontinence episodes / urination at the Week 2, 4, 8 and 12 Visits, including analysis based on primary efficiency criteria, as well as mean number of urinary incontinence episodes per week at the Week 12 – will be performed with the use of covariance analysis (ANCOVA). Number of urinary incontinence episodes / urination at the Vistit of start of therapy will be used as covariate, and therapy group will be used as factor. Primary efficiency analysis according to primary efficiency criteria will be performed in FAS and PP populations. For evaluation of hypothesis of "non-inferior" efficiency upper border of one-side 95% confidence interval for difference in evaluation of mean daily number of urinations among test product and control product tolteroine will be calculated. During comparison of therapy groups according to other efficiency criteria two-sided 95% confidence intervals will be built. Comparison of therapy groups on efficiency criteria: change in Overactive Bladder Awareness Tool Questionnaire (OAB Awareness Tool) and change in Quality of life by Quality of life Questionnaire EQ-5D will be performed following data validation concerning their normality, distribution using Kolmogorov-Smirnov criteria. In case of normal distribution data will be compared using Student's t-test, overwise non-parametric Mann-Whitney criteria will be used.

Primary efficiency analysis according to secondary efficiency criteria will be performed in FAS and PP populations.

Kolmogorov-Smirnov test for normal distribution and heterogeneous dispersion test using Leven criteria will be also performed during every visit as additional assessments in FAS population for mean daily, mean daytime and mean nighttime number of urinations and urinary incontinence episodes at Weeks 2, 4, 8 and 12. In case when one of these tests is apparently statistically significant ($p < 0.05$), comparison between therapy groups will be performed using non-parametric Mann-Whitney criteria.

9.9 Safety assessment

For longitudinal safety variables (laboratory analysis data) mean, standard deviation, median, minimum and maximum should be provided. For nominal variable group frequencies and percent of patient for each demographic category should be provided.

All AE should be presented as a list an coded in accordance to the MedDRA terminology of lower grade (version on data lock point). AE started before administration of the study product

should not be included into analysis.

Frequency of all AE should be summarized (number and percent of patients in which AE were reported at least once during the study) concerning interaction with the study product, assessed by investigator, and by severity grade.

For comparison of AE appearance in the study groups □2 test of exact Fisher test is planned to be applied, for comparison of manifestation rate Mann-Whitney U test will be applied.

Laboratory parameters (total blood count and blood biochemistry, urinalysis), vital parameters will be assessed separately to each group with the following comparison using paired Student t-test for connected samples (for parameters with normal distribution) or using non-parametric Wilcoxon signed rank test for connected samples (for parameters with ordinary scale type or in case of significant distribution deviations from normal).

10 DIRECT ACCESS TO THE SOURCE DATA/DOCUMENTS

Investigator and institution should provide direct access towards source documents and documents for monitoring and audit of the study, Ministry of Health of the Russian Federation inspections, and authorized regulatory bodies inspections.

During research center visit eCRF should be completed and direct access to the source documents for accuracy of filling validation should be provided. Each eCRF should be signed and dated by Investigator of responsible employee, approved be Investigator, for verification of correspondence of source data with data imported into eCRF.

11. QUALITY CONTROL AND ASSURANCE

11.1 Selection of centers for conducting of the study

Selection of centers for the study performance is approved by Sponsor before the start of the study in order to provide availability of all necessary for the study personnel and assess of possibility to perform the study by this personnel in accordance with Good Clinical Practice requirements of the International Conference on Harmonization and requirements of regulatory authorities of the Russian Federation and Belarus Republic (see section **Ошибка! Источник ссылки не найден. Ошибка! Источник ссылки не найден.**).

11.2 Conducting of the study

All protocol details should be followed during the study conduction. In case any amendments are required, they should be immediately discussed among Investigator, Monitor and Sponsor. Amendments to the protocol should be made in written form with detailed justification of the amendments applied. Amendments should be submitted into Ethical board, performing ethics review of the study, and into the regulatory authorities.

Every deviation from the study protocol should be documented and justified be Investigator (or person, approved by Investigator) in correspondent section of CRF.

All other persons, participating in clinical study process, will be instructed by Investigator and monitor concerning their tasks. Responsibility for this rests with the Investigator.

11.3 Monitoring

Monitoring – control process for clinical study course, intended to guarantee that it is performed, documented and information is transmitted into correspondent board according to the Protocol and Good Clinical Practice requirements. Person responsible for monitoring is approved by the Sponsor of the study. Monitor is the main liaison between Sponsor and Investigator. Monitor, in accordance with Sponsor's requirements, should provide appropriate performance and documentation of the study.

Quality control of the study conduction is provided by the Principal Investigator and quality control is performed by monitoring visits, with terms established by Sponsor.

Sponsor representative or authorized person will perform monitoring of the study guaranteeing the following:

- data are authentic, accurate and comprehensive;
- study patients safety and rights are protected;
- study is performed in accordance with currently approved protocol variant and any other agreements concerning the study, ICH Guidance "Good Clinical Practice" and all applicable regulations.

Monitor will periodically get into connection with Investigator and perform visits aimed in assessment of all source data/records associated with the study, verification of protocol adherence, as well as comprehensiveness, accuracy and precision of all records in CRF in comparison to the source data. Investigator will cooperate with Monitor for elimination any deviations revealed.

11.4 Data identification

All data before inclusion into CRF should be designated in primary documents. Primary documents and data include but not restricted to laboratory tests and instrumental investigations prints as well as documents, filled out during physical examinations (e.g. patient's history, adverse events, demographic data).

11.5 Audit and inspection

In case of situation, requiring targeted inspection during the study, Sponsor initiates audit to be performed by his/her representatives and independent auditors. Audit remarks and conclusions should be documented.

The study may be also subject to inspection from the regulatory organs side.

Sponsor has to warn Investigator concerning audit and inspection perspective. Conversely, if Investigator receives notification concerning planned inspection of the center from the side of healthcare authorities, he/she should immediately inform about this Sponsor of the study.

Investigator during inspection of the research center should allow to the persons, responsible for audit/inspection, to perform an inspection of the center, equipment and materials, used during the study, provide access to source documents of the patients an allow meeting with all investigation team members.

11.6 Principal Investigator responsibilities

Principal Investigator before the start of the study is ought to:

- Sign final version of the study protocol, approved by authorized regulatory authorities.
- Provide the list of employees with correspondent qualification which will be delegated several investigator duties. The list should include description of the delegated responsibilities. Investigator should guarantee storage of this list with actual data during the study, as well as full awareness of these employees concerning study goals and his responsibilities.
- Provide to Sponsor any documents concerning approval of the study from the side of local ethics board/institutional review board.
- Investigator should, on request of Sponsor, provide actual curriculum vitae of all employees, those are requested to perform several duties and those names are declared in signature transfer forms and delegation of authority.
- On demand present to the Sponsor copies of samples of all forms which are used within the frames of the study.
- Provide no request of Sponsor normal values range of laboratory tests performed in local laboratory.

Principal Investigator during the study is ought to:

- Perform the study in the research center in accordance with conditions, instructions and limitations, designated in this Study protocol.
- Provide sufficient time and appropriate conditions for performance of the study during the whole study course.
- Guarantee handling of all material, provided to Sponsor or by Sponsor (study protocol, products, CRF, Investigator's brochure etc) in strict confidentiality conditions. Content of any of these documents should not be disclosed to other parties not involved into this study.
- Guarantee satisfactory storage conditions for all study materials.
- Guarantee reception of written informed consent from patient before the start of any study procedures.
- Insert comprehensive and accurate data and sign CRF.

- Guarantee understanding of the patient importance of strict adherence to their study protocol requirements and Investigator's instructions.
- Provide ability to identify all data belonging to each patients using unambiguous identified code stored in confidential documents.
- Meet the Study monitor or any other Sponsor company employees at the scheduled time.
- Immediately inform Sponsor and Ethics board about any serious adverse events
- Guarantee storage of all individual randomization numbers in safe place and their return to Sponsor after the end of the study.
- Guarantee free possession of the data reporting system during the whole study period within this study.
- Not to apply amendments into the study without prior coordination with the Sponsor.

11.7 Protocol amendments

Changes in protocol would influence legal and ethical status of the investigation and may influence statistical assessment of sample size and probability of achievement of main study goal.

All protocol requirements including amendments should be rigorously followed except emergency cases. In case when amendment is required, it should be presented in written form and should be approved according to standard operational procedures. All protocol amendments, except those related to logistics and administrative procedures, should be submitted to Ethics board (EB) for review and approval before their implication, and into authorized bodies for approval/notification, if required.

In emergency cases or in cases of any other medical events requiring protocol deviation Investigator of authorized representative should get in contact with the Sponsor at the earliest opportunity for resolution of the issue concerning prolongation of participation in the study for this patient. Protocol deviation should be recorded.

11.8 Protocol adherence

Investigator should perform the study according to the protocol, coordinated with Sponsor and approved by regulatory authorities and ethic board, which is confirmed be signing of the protocol by Investigator before the start of the study.

Investigator should not deviate from protocol or apply changes into protocol without Sponsor's consent and without preliminary approval from ethic committees and regulatory health authorities. Investigator may deviate from protocol or apply amendments into protocol without approval in case when it is required to preclude safety risks and for study subject well-being; in this case Sponsor and local ethics board should be notified within the preset shortest terms.

Investigator or authorized person should explain and document any deviations from the approved protocol. List of serious deviations from the protocol will be provided in the final study report.

In case of non-compliance with protocol or ICH GCP by Investigator, research center employees or Sponsor's employees, Sponsor will take necessary measures directed towards enforcement. Sponsor's employee (Monitor) during center visits will discuss with the investigator any revealed cases of deviations from protocol and take actions for their prevention in the future.

In case of detection of serious or repetitive cases of protocol and ICH GCP principles violation from Investigator's side during monitoring or audit, Sponsor ceases participation of Investigator/Research center in the study and notify about these circumstances regulatory bodies in accordance to local legislation.

12 ETHICAL CONSIDERATIONS

12.1 General requirements

Participation in the study is voluntary. Patient has the right to refuse from participation in the study during any stage. Ethical considerations for clinical trials of medicinal products performance are brought under regulations of the following document: Article 21 of Constitution of the Russian Federation, Article 25 of Constitution of Belarus Republic, ICH Guidance "Good Clinical Practice", Helsinki Declaration of World Medical Association etc.

Investigation is performed in accordance with principles outlined in Helsinki Declaration of WMA (approved on 18 Assembly of WMA in Helsinki in June 1964, last redaction 2013).

Investigators, involved in the clinical study, before its start provide to sponsor signed and dated resume, containing description of clinical study performance experience, data concerning professional and scientific activity.

12.2 Ethics Board (EB)

Ethics review of the clinical trials of medicinal products is performed be Ethics board of Ministry of Health of the Russian Federation, correspondent local Ethics boards (LEB) at clinical centers within Russian Federation and Belarus Republic. EB is intended to protect the rights, safety and well-being of the patients, participating in the study. EB should assess correspondence of Investigator's qualification towards proposed study based on his/her scientific biography (curriculum vitae). Full list of EB (for each participating center), as well as Head(s) of Committee will be included into study final report.

Investigators should provide the start and performance of the clinical study under inspection and approval of EB, in accordance with current requirement of Good Clinical Practice and legislation of the Russian Federation and Belarus Republic. Before the start of the study investigators should submit copies of all study documents, including protocol, informed consent form, Investigator's brochure, Investigator's curriculum vitae into LEB for review and approval.

Before the start of the study in the center Investigator should receive from LEB full confirmation of protocol approval and other provided documents in written form with designated date.

Investigators should not apply and corrections into the study or performance of the study without EB approval except the cases when changes are required for amendment of apparent direct hazards for patients' well-being. Amendments of slight inaccuracies in protocol or change of study plan without ethical significance will be submitted to EB with notifying purposes.

Investigator should report to LEB about any changes in the investigation and unexpected problems, including risks for patients or other persons, as well as any deviations from protocol aiming on elimination of direct hazard to patients.

Investigator should provide final report to LEB after finishing of the study as a part of requirements for LEB for continuation of review of approved trials.

12.3 Approval from regulatory authorities

Permission for performance of the clinical study is issued by Ministry of Health of the Russian Federation and Ministry of Health of Belarus Republic based on results of expertise of the documents required for approval of the study performance, as well as ethics review, performed by the order, established by legislation (Article 20 of the Federal Law of April, 12, 2010 No 61-ФЗ "On Medicines Circulation" and Article 15 of the Belarus Republic Law of July 20, 2006 No 161-З "On medicinal products").

All approved documents should be collected before the patients start to fulfill any study procedures.

12.4 Informed consent

Informed consent of the patients should be obtained and documented in accordance with requirements of Russian Federation and Belarus Republic legislation, ICH regulations on Good Clinical Practice, international regulations and ethical principles outlined in Helsinki Declaration.

Before receiving of informed consent investigator or authorized person should provide information to the patient on language, with difficulty level, understandable to the patients both in oral and in written form. All patients have and ability to discuss the study and its alternatives with the investigators.

Before the start of participation in the study informed consent form should be signed in two copies by patient and person, performing discussion of informed consent (investigator of authorized person) with date stated. Patient should be provided with one informed consent original with designated date. Second original should be included into main study file by the Investigator. In case of presentation of informed consent. patient should provide consent for direct access to his/her medical documents for monitoring and audit during the study and EB inspections by authorized legal bodies.

Amendments and provisions are applied to the informed consent form whenever new information, significant to the patient, appears. Afterwards patient should sign up the informed consent original with designated date.

Investigator will explain that all patients possess the right to abstain from participation in the study and withdraw their informed consent any time without any consequences for their further treatment and without explanation of the reasons.

13 DATA HANDLING AND RECORD MAINTENANCE

13.1 Data management

All documents, associated with the study, as well as information concerning patients, participating in the study, is strictly confidential.

Investigator bears responsibility for presentation of accurate, comprehensive and reliable information in CRF and all required reports.

All patient's information, obtained during the study course, is originally recorded in the source documents (documents from medical institution of attending physician records in the research center) and afterwards is passed into patient's CRF. Data contained in the CRF should be the same as primary documents data. CRF should be filled at the day of patient visit to the research center.

eCRF handling instructions will be presented in a separate manual (guidance).

Information is articulately imported into the Study database directly or indirectly from source documented data, by specially assigned and trained for these goal investigation team members with use of single import of the data with electronic confirmation. Sponsor employees/CRO perform data assessment in the context of their comprehensiveness and accuracy and provide center employees instructions concerning amendments and expansion of the information. Requests for missing data and equivocal data are sent to the research center using electronic request form, automatically controlling amendments, applied by investigators.

Principal Investigator bears ultimate and personal responsibility for accuracy and reliance of the clinical and laboratory data included into CRF. Principal investigator should confirm comprehensiveness and accuracy of the provided data with following approval by electronic signature in the electronic report form. Later he/she receives CDROM and hard copies with patients data for archivation in the research center. All report forms submitted to the Sponsor from clinical centers are verified upon admission for the presence of serious adverse events.

13.2 Data storage

All records and documents, associated with clinical study, including completed CRF, Patient information lists with Informed consent forms, lists of patients are stored in clinical institutions where clinical study is performed, for 15 years after finishing of the examination.

Investigator should take any available measures to prevent occasional or premature destruction of the documents. In case when archive storage of documents within research center becomes impossible, Investigator should notify Sponsor.

14 FINANCING AND INSURANCE

This study is sponsored and funded by R-Pharm JSC. The Sponsor of the study, R-Pharm JSC, has concluded the licensing agreement with the manufacturer of the study product Kyorin Pharmaceutical Co Ltd (Japan), according to which R-Pharm JSC possesses the rights for development, registration and commercial promotion of the drug product Uritos®.

According to current regulatory requirements (including Article 44 of the Federal Law of the Russian Federation "On Medicines Circulation" No 61-ФЗ of April, 12, 2010, Order of the President of the Belarus Republic of August 25, 2006 No 530 "On insurance activity", Governmental regulation of Ministry of health of Belarus Republic of May 7, 2009 No 50 "On several questions concerning performance of clinical trials of medicinal products"), health insurance procedure of the patients shall be performed before the start of the study. In case of hazard to patient's health due to clinical study, insurance company contracted with Sponsor shall compensate all expenses for required medical examination and treatment, demand for which may arise following the direct action of the tested product and/or medical manipulations applied according to the Study protocol.

15 DATA REPORTING, PUBLICATIONS, PRESENTATIONS

15.1 Publications

All information, not published previously, concerning investigation of the product and procedures, used by Sponsor, is considered to be confidential. All rights for this information belong exclusively to Sponsor company. Investigator is obliged to use confidential information only within the frames of the study; in all other cases – only under written consent of Sponsor.

Investigator should be aware that data, acquired during the study, may used by Sponsor or his/her representative for assignment to other investigator or health governmental authorities. It is required to acknowledge that all data obtained during the study should be presented at first demand of the Sponsor.

Sponsor's representative and healthcare health governmental authorities should have access to the source documents, however study patients anonymity should be observed as professional norm.

15.2 Final report

Final report will be prepared after data base lock and statistical analysis performance. Final report and other documents concerning the study are considered to be confidential information, not intended for disclosure from the side of Investigator without specific permission from Sponsor company. Report will be prepared in accordance with ICH Guidance "Good Clinical Practice" and ICH E3 Guidance "Structure and content of clinical trials reports".

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17 ADDENDUMS

17.1 Russian version of the OAB Awareness Tool

RUSSIAN VERSION OF THE OAB AWARENESS TOOL

The questions below ask about how bothered you may be by some bladder symptoms. Some people are bothered by bladder symptoms and bay not realize that there are treatments available for their symptoms. Please circle that number that best describes how much toy have been bothered by each symptom. Add the numbers together for a total score and record the score in the box provided at the bottom.

How bothered you have been by…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**A great deal**	**A very great deal**
1. Frequent urination during the daytime hours?	0	1	2	3	4	5
2. An uncomfortable urge to urinate?	0	1	2	3	4	5
3. A sudden urge to urinate with little or no warning?	0	1	2	3	4	5
4. Accidental loss of small amounts of urine?	0	1	2	3	4	5
5. Nighttime urination?	0	1	2	3	4	5
6. Waking up at night because you had to urinate?	0	1	2	3	4	5
7. An uncomfortable urge to urinate?	0	1	2	3	4	5
Urine loss associated with a strong desire to urinate?	0	1	2	3	4	5
Are you male? If male, ❑ add 2 point to your score						

Please add all your responses in the question above ❑ ❑

Please hand this page to your healthcare provider when you see him/her for your visit.

If score is 8 or greater, you may have overactive bladder. There is effective treatments for this condition. You may want to talk with a healthcare professional about your symptoms.

Note: You may be asked to give an urine sample. Please ask before going to the bathroom.

Russian OAB Awareness Tool, ver. 1.0 2004

17.2 Quality of Life Questionnaire EQ-5D-5L

EQ-5D-5L

Health Questionnaire

Russian version for Russia

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Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

We would like to know how good or bad your health is TODAY.

• This scale is numbered from 0 to 100.

• 100 means the best health you can imagine.

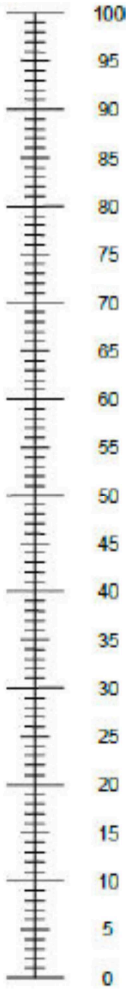
0 means the worst health you can imagine.

• Mark an X on the scale to indicate how your health is TODAY.

• Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐

The best health you can imagine



The worst health you can imagine