Report on the Deliberation Results

June 12, 2007

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau

Ministry of Health, Labour and Welfare

[Brand name]	Geninax Tablets 200 mg
[Non-proprietary name]	Garenoxacin Mesilate Hydrate (JAN*)
[Applicant]	Toyama Chemical Co., Ltd.
[Date of application]	May 30, 2006

[Results of deliberation]

In the meeting held on May 30, 2007, the Second Committee on New Drugs concluded that the product may be approved and that this result was to be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

It was decided that the product is not classified as a biological product or a specified biological product, its re-examination period is 8 years, the drug substance is classified as a powerful drug and the drug product is not classified as a poisonous drug or a powerful drug.

**Japanese Accepted Name (modified INN)*

Review Report

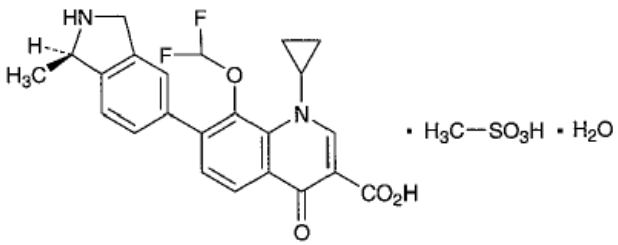
May 15, 2007

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Geninax Tablets 200 mg
[Non-proprietary name]	Garenoxacin Mesilate Hydrate
[Name of applicant]	Toyama Chemical Co., Ltd.
[Date of application]	May 30, 2006
[Dosage form/Strength]	Film-coated tablets containing 253.53 mg of Garenoxacin Mesilate Hydrate (200 mg as garenoxacin) in one tablet
[Application classification]	Prescription drug (1) Drug with a new active ingredient

[Chemical structure]



Molecular formula: $C_{23}H_{20}F_2N_2O_4 \cdot CH_4O_3S \cdot H_2O$

Molecular weight: 540.53

Chemical name:

1-Cyclopropyl-8-(difluoromethoxy)-7-[(1*R*)-1-methyl-2,3-dihydro-1*H*-isoindol-5-yl]-4-oxo-1,4-dihydroquinoline-3-carboxylic acid monomethanesulfonate monohydrate

[Items warranting special mention]	None
[Reviewing office]	Office of New Drug I

Review Results

May 15, 2007

[Brand name] Geninax Tablets 200 mg

[Non-proprietary name] Garenoxacin Mesilate Hydrate

[Applicant] Toyama Chemical Co., Ltd.

[Date of application] May 30, 2006

[Results of review]

(1) It was judged that the submitted data confirms the efficacy of the product and that there should be no major safety problems affecting approval.
(2) The dosage and administration for this product have been established from a PK/PD standpoint, taking into account MPC as well. Consequently, suppression of the emergence of drug-resistant bacteria as well as therapeutic efficacy could be expected.
(3) With respect to the issues requiring continued collection of information, appropriate measures, e.g. post-marketing surveillance and information provision to healthcare professionals and patients, have been planned for the proper use of the product, at the present stage.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indications and dosage and administration.

[Indications] <Microorganisms>
Garenoxacin-susceptible strains of *Staphylococcus* sp., *Streptococcus* sp., *Streptococcus pneumoniae* (including penicillin-resistant *Streptococcus pneumoniae*), *Moraxella (Branhamella) catarrhalis*, *Escherichia coli*, *Klebsiella* sp., *Enterobacter* sp., *Haemophilus influenzae, Legionella pneumophila, Chlamydia pneumoniae,* and *Mycoplasma pneumoniae*
<Diseases>
Laryngopharyngitis, tonsillitis (including peritonsillitis and peritonsillar abscess), acute bronchitis, pneumonia, secondary infection of chronic respiratory disease, otitis media, sinusitis

[Dosage and administration] The usual adult dosage for oral use is 400 mg of garenoxacin once daily.

Review Report (1)

March 13, 2007

I. Product Submitted for Registration

[Brand name] Geninax Tablets 200 mg

[Non-proprietary name] Garenoxacin Mesilate Hydrate

[Applicant] Toyama Chemical Co., Ltd.

[Date of application] May 30, 2006

[Dosage form/Strength] Film-coated tablets containing 253.53 mg of Garenoxacin Mesilate Hydrate (200 mg as garenoxacin) in one tablet

[Proposed indications] <Microorganisms>
Garenoxacin-susceptible strains of *Staphylococcus* sp. (including garenoxacin-susceptible MRSA), *Streptococcus* sp., *Streptococcus pneumoniae*, penicillin-resistant *Streptococcus pneumoniae* (including multi-drug resistant *Streptococcus pneumoniae*), *Moraxella (Branhamella) catarrhalis* (including β-lactamase-producing bacteria), *Escherichia coli*, *Klebsiella* sp., *Enterobacter* sp., *Haemophilus influenzae* (including BLNAR), *Legionella pneumophila, Chlamydia pneumoniae,* and *Mycoplasma pneumoniae*
<Diseases>
Laryngopharyngitis, tonsillitis (including peritonsillitis and peritonsillar abscess), acute bronchitis, pneumonia, secondary infection of chronic respiratory disease, otitis media, sinusitis

[Proposed dosage and administration]
The usual adult dosage for oral use is 400 mg of garenoxacin once daily.

II. Summary of the Submitted Data and Outline of Review by the Pharmaceuticals and Medical Devices Agency (PMDA)

1. Origin or background of discovery and usage conditions in foreign countries etc.

Garenoxacin (GRNX) is a pyridonecarboxylic acid synthetic antibacterial agent developed by Toyama Chemical Co., Ltd. Its structure lacks the 6-position fluorine, which is considered essential for fluoroquinolone antibacterial agents. The drug exhibits antibacterial activity by targeting DNA topoisomerase IV and DNA gyrase which are unique to bacteria, resulting in the inhibition of DNA replication.

In recent years, an increase in fluoroquinolone-resistant bacteria has been reported and in particular, penicillin-resistant *Streptococcus pneumoniae* (PRSP) and multi-drug resistant *Streptococcus pneumoniae* (MDRSP) have become a serious problem. Under such circumstances, the development of a novel broad-spectrum antibacterial agent with activity against multi-drug resistant bacteria was undertaken. In the development and research of conventional fluoroquinolone antibacterial agents, they become mutagenic when their antibacterial activity is enhanced, which posed a difficulty in developing fluoroquinolones with potent antibacterial activity. However, GRNX, a safer drug with enhanced antibacterial activity, was developed as a result of substituting a methylisoindolinyl group at position 7, a difluoromethoxy group at position 8, and a hydrogen atom at position 6.

GRNX was outlicensed to Bristol-Myers Squibb Company, the U.S., in [redacted] 19[redacted], during the stage for starting clinical trials. A foreign clinical trial was started in 19[redacted] ahead of a Japanese trial, and phase I to phase III clinical trials were carried out. Afterwards, the right to develop GRNX in foreign countries was returned to Toyama Chemical Co., Ltd. in [redacted] 20[redacted] for reasons pertaining to commercial strategies. In Japan, a phase I clinical trial was initiated in collaboration with the then Bristol Pharmaceuticals, K.K. (currently Bristol Myers, K.K.) in [redacted] 19[redacted]. However, due to the return of the development right by the parent company, joint development was cancelled during a phase III clinical trial. After that, joint development with Taisho Pharmaceutical Co., Ltd. was started in [redacted] 20[redacted], in Japan, leading up to the submission of approval application.

In [redacted] 20[redacted], GRNX was outlicensed to Schering-Plough Corporation. Accordingly, in the US, Schering-Plough Corporation filed an approval application for [redacted] and [redacted] indicated for [redacted] in [redacted] 20[redacted], but withdrew the application in [redacted] 20[redacted] for commercial reasons. In Europe, the Schering-Plough Corporation submitted its approval application for [redacted] and [redacted] to the European Medicines Agency (EMEA) in May 2006, and reviews are currently ongoing.

2. Data relating to quality

<Summary of the submitted data>

(1) Formulation development

The product is a film-coated tablet containing 253.53 mg of Garenoxacin Mesilate Hydrate (200 mg as GRNX). The tablet formulation and manufacturing process were developed by Bristol-Myers Squibb Company, in the U.S., based on an exploratory investigation conducted by the applicant.

Clinical development of GRNX was initiated in foreign countries including the U.S. ahead of that in Japan. In foreign countries, the capsule formulation was used for phase I single-dose/multiple-dose studies and the tablet formulation was used for clinical pharmacology studies and phase II or later studies because the tablet is easier to take. In Japan, it was decided to progress with the development using formulations equivalent to those in foreign countries, with a view to the use of foreign clinical

data. Specifically, the capsule formulation (the same drug product as in foreign studies) was used for phase I single-dose/multiple-dose studies and the tablet formulation (a drug product with different coating components/strengths from those in foreign studies) was used for phase II or later clinical studies. [See "4. (i) Summary of results of clinical pharmacokinetic and pharmacodynamic studies"]

(2) Drug substance

The chemical structure of Garenoxacin Mesilate Hydrate has been characterized by elementary analysis, ultraviolet-visual spectrum (UV/VIS), infrared spectrum (IR), nuclear magnetic resonance spectrum (^{1}H-NMR, ^{13}C-NMR), mass spectrum, and single crystal x-ray diffraction.

Investigations have been conducted on its physicochemical properties including physical description, optical rotation, solubility, hygroscopicity, melting point, thermal analysis, pH, dissociation constant, partition coefficient, optical isomer, crystalline polymorphism, and dissolution. Garenoxacin Mesilate Hydrate occurs as white powder and the specific rotation in methanol, aqueous, and *N,N*-dimethylformamide solutions (c=1.0, 20℃) is [redacted]°, [redacted]°, and [redacted]°, respectively. It is easily soluble in *N,N*- dimethylformamide, somewhat easily soluble in methanol, and very slightly soluble in 2-propanol. As to the solubility in aqueous solutions with different pH values, it is sparingly soluble at pH2.0, pH2.9, and pH11.2, slightly soluble at pH3.8, pH4.8 and pH10.0, very slightly soluble at pH5.1, pH8.5, pH9.3, and pH9.6, and practically insoluble at pH6.6 and pH7.4. It is not hygroscopic at 22-93%RH, its melting point (decomposition point) is approximately 277℃, an endothermic peak appears at 279℃, and the pH of a 10 mg/mL solution is 3.83. Its dissociation constant is 5.6 and 9.4 and a maximum partition ratio (1-octanol/water) of 0.6-0.7 is observed at pH5.0 to pH8.8. No optical isomer is detected, and it exists in the 3 different crystal polymorphs including [redacted], of Form A ([redacted]), Form B ([redacted]), and Form C ([redacted]). Form C is [redacted] and there is no possibility that Form C occurs because [redacted] is not used in the manufacturing process. In addition, Form A and Form B can be distinguished by IR, x-ray powder diffraction patterns or a differential scanning calorimetric curve and Garenoxacin Mesilate Hydrate has been confirmed to be of Form A. There were no difference in the dissolution rate of Garenoxacin Mesilate Hydrate according to the particle size (≤[redacted]μm and ≥[redacted]μm), in any of test solutions with different pH values (pH[redacted], [redacted], and [redacted]).

The strength, description (appearance), identification (UV/VIS, IR), purity (heavy metals, related substances, residual solvents ([redacted])), water content, residue on ignition, and assay (liquid chromatography (HPLC method)) are included in the drug substance specification.

The following stability studies of the drug substance were conducted.

a. Long-term testing

・25℃/60%RH/double polyethylene bags＋fiber drum/dark place/48 months

b. Accelerated testing

・40℃/75%RH/double polyethylene bags＋fiber drum/dark place/6 months

c. Stress testing

・The effect of heat (50℃/double polyethylene bags＋fiber drum/dark place/3 months)
・The effect of humidity (40℃/75%RH/an open polyethylene bag＋fiber drum/dark place/6 months)
・The effect of light (25℃/60%RH/D65 lamp/Placed in a colorless glass petri dish and covered additionally with a polyvinylidene chloride film; the control is covered additionally with aluminum foil./Light providing an overall illumination of 1.2 million lx・hr (≥200 W・hr/m^2) or 4.2 million lx・hr)

Stress testing demonstrated that the drug substance was stable against humidity and light. Although water loss (up to [redacted]% from baseline) was noted under heat conditions, there were no changes in other attributes tested. Since the drug substance was also stable under accelerated and long-term storage conditions, the proposed re-test period for Garenoxacin Mesilate Hydrate is 48 months when stored in double polyethylene bags/fiber drum at room temperature.

(3) Drug product

The strength, description (appearance), identification (UV/VIS, qualitative tests), uniformity of the drug product, dissolution, and assay (HPLC method) are included in the drug product specification.

The following stability studies of the drug product were conducted.

・PTP sheet (10 tablets/sheet): polypropylene and aluminum sheet
・High-density polyethylene bottle (500 tablets/bottle): High-density polyethylene

a. Long-term testing
・30℃/65%RH/PTP sheet, high-density polyethylene bottle/dark place/12 months

b. Accelerated testing
・40℃/75%RH/PTP sheet, high-density polyethylene bottle/dark place/6 months

c. Stress testing
・The effect of heat (50℃/a glass petri dish (open), PTP sheet, high-density polyethylene bottle/dark place/3 months)
・The effect of humidity (40℃/75%RH/a glass petri dish (open)/dark place/6 months)
・The effect of light (25℃/60%RH/D65 lamp/Placed in a colorless glass petri dish and covered with a polyvinylidene chloride film, and the control is covered additionally with an aluminum foil. PTP sheet, the control is covered additionally with aluminium foil. High-density polyethylene bottle/Light providing an overall illumination of 1.2 million lx・hr (≥200 W・hr/m^2) or 2.4 million lx・hr)

In the stress testing, water loss under heat conditions for the drug product outside its immediate container and the drug product packaged in a PTP sheet ([redacted]% and [redacted]% from baseline, respectively), and water gain under humidity and light conditions for the drug product outside its immediate container ([redacted]% and [redacted]% from baseline, respectively) were observed while there were no changes in other attributes tested. In the accelerated testing, water gain for the drug product packaged in a PTP sheet (up to [redacted]% from baseline) was observed whereas there were no changes in other attributes tested.

In the long-term testing, water gain for the drug product packaged in a PTP sheet (up to [redacted]% from baseline) was observed while there were no changes in other attributes tested.

Based on the above, the proposed shelf life for the drug product is 1 year when the drug product is packaged in a PTP sheet or a high-density polyethylene bottle and stored at room temperature. Long-term testing (30℃/65%RH) of up to 60 months is ongoing.

(4) Reference standard

Purification process, strength, description (appearance), identification (UV/VIS, IR, ^{1}H-NMR), purity (related substances, residual solvents ([redacted])), water content, and assay (garenoxacin mesilate (potentiometric titration method), methanesulfonic acid (mesylic acid) (potentiometric titration method)) are included in the specification for reference standard.

<Outline of the review by the PMDA>

The PMDA asked the applicant to explain why chiral identity tests etc. are not included in the specification despite the fact that Garenoxacin Mesilate Hydrate is optically active.

The applicant responded as follows.

The optical activity of Garenoxacin Mesilate Hydrate is derived from [redacted] (Substance A). Thus, considering that the most appropriate method for the control of optical isomer content in Garenoxacin Mesilate Hydrate is to control the amount of the optical isomer of Substance A in Substance A, Garenoxacin Mesilate Hydrate was synthesized after the optical isomer of Substance A was added to Substance A, after which the residual amount of the optical isomer of Garenoxacin Mesilate Hydrate was determined (confirmation of the ability to remove the optical isomer of Substance A in the manufacturing process). As a result, even when [redacted]% of the optical isomer of Substance A was added to Substance A, the optical isomer content in Garenoxacin Mesilate Hydrate was less than [redacted]%, which confirmed that the optical isomer is removed in the manufacturing process. Therefore, if the amount of the optical isomer of Substance A is kept under [redacted]%, theoretically, the estimated optical isomer content in Garenoxacin Mesilate Hydrate will be not more than [redacted]%. Moreover, based on the above test results, it is considered that Garenoxacin Mesilate Hydrate does not racemize during the manufacture and since stability testing also showed no increase in the optical isomer, it seems that Garenoxacin Mesilate Hydrate does not racemize during storage, either. Therefore, even without chiral identity testing for Garenoxacin Mesilate Hydrate, adequate assurance that Garenoxacin Mesilate Hydrate is a single enantiomer can be given by controlling the amount of the optical isomer of Substance A.

The PMDA accepted the above response.

3. Non-clinical data

(i) Summary of pharmacology studies

All concentrations and doses of the product below are expressed in terms of GRNX, the active ingredient.

<Summary of the submitted data>

(1) Primary pharmacodynamics

1) *In vitro* antibacterial activity

a. Antibacterial activity against standard strains [Attachments S1 (4.2.1.1.1), S2(4.2.1.1.2), S3 (4.2.1.1.3), S4 (4.2.1.1.4), S5 (4.2.1.1.5), S6 (4.2.1.1.6)]

The MICs of GRNX and reference drugs against various standard strains were determined by the standard agar dilution method recommended by the Japanese Society of Chemotherapy (Note: *Chlamydia* spp.: standard method for MIC determination against Chlamydia, recommended by the Japanese Society of Chemotherapy, *M. pneumoniae*: microdilution method (phenol red method), *Legionella* spp.: standard method recommended by the Japanese Society of Chemotherapy, were used. The same also applies to the following studies).

The MIC of GRNX was 0.025-0.78 μg/mL against aerobic and facultative anaerobic Gram-positive bacteria (10 microorganisms, 11 strains), 0.00313-12.5 μg/mL against aerobic and facultative anaerobic Gram-negative bacteria (20 microorganisms, 21 strains), 0.1-3.13 μg/mL against obligate anaerobic Gram positive bacteria (12 microorganisms, 13 strains), and 0.05-0.78 μg/mL against obligately anaerobic Gram-negative bacteria (7 microorganisms, 7 strains); as with other quinolones used as comparators, GRNX exhibited a broad antibacterial spectrum. The MIC of GRNX against *C. pneumoniae*, *C. psittaci*, *C. trachomatis, M. pneumoniae*, and *Legionella* spp., was 0.008, 0.002, 0.016, 0.0313, and 0.0039-0.0313 μg/mL, respectively, and GRNX showed antibacterial activity equal to or greater than that of reference quinolones.

b. Antibacterial activity against clinical isolates [Attachments S7 (4.2.1.1.7), S8 (4.2.1.1.8), S9 (4.2.1.1.9), S3 (4.2.1.1.3), S5 (4.2.1.1.5), S10 (4.2.1.1.10)]

The antibacterial activity of GRNX and reference drugs against various fresh clinical isolates was determined by the standard agar dilution method recommended by the Japanese Society of Chemotherapy (Note: The broth microdilution method of the CLSI was used for BLNAR).

Microorganism tested	No. of isolates	MIC (μg/mL)		
		Range	MIC_{50}	MIC_{90}
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	90	0.0125 — 1.56	0.05	0.05
Levofloxacin-susceptible methicillin-resistant *Staphylococcus aureus* (LVFX-susceptible MRSA)	45	0.0125 — 1.56	0.39	1.56
Levofloxacin-resistant methicillin-resistant *Staphylococcus aureus* (LVFX-resistant MRSA)	41	0.39 — 100	6.25	50
Methicillin-susceptible *Staphylococcus epidermidis* (MSSE)	15	0.025 — 0.1	0.05	0.1
Methicillin-resistant *Staphylococcus epidermidis* (MRSE)	15	0.05 — 1.56	0.39	1.56
Coagulase negative staphylococci	17	0.025 — 3.13	0.1	1.56
Penicillin-susceptible *Streptococcus pneumoniae* (PSSP)	76	0.025 — 0.78	0.1	0.1
Penicillin-intermediate *Streptococcus pneumoniae* (PISP)	25	0.0125 — 0.39	0.05	0.1
Penicillin-resistant *Streptococcus pneumoniae* (PRSP)	35	0.05 — 0.1	0.1	0.1
Streptococcus pyogenes	64	0.025 — 0.2	0.05	0.1
Streptococcus agalactiae	18	0.05 — 0.39	0.05	0.1
Enterococcus faecalis	103	0.025 — 25	0.39	6.25
Enterococcus faecium	70	0.1 — 100	12.5	50
Haemophilus influenzae	115	0.00313 — 0.39	0.0125	0.05
β-lactamase negative ampicillin-resistant *Haemophilus influenzae* (BLNAR)	69	≦ 0.002 — 0.0625	0.0078	0.0313
Moraxella catarrhalis	90	0.00156 — 0.05	0.025	0.025
Escherichia coli	112	0.00625 — 100	0.05	12.5
Salmonella spp.	17	0.05 — 0.78	0.05	0.2
Citrobacter freundii	35	0.05 — 3.13	0.05	1.56
Enterobacter cloacae	31	0.025 — 25	0.05	0.1
Klebsiella pneumoniae	35	0.0125 — 6.25	0.2	1.56
Extended-spectrum β-lactamase (ESBL) producing *K. pneumoniae*	13	0.1 — 6.25	0.2	0.78
Serratia marcescens	30	0.39 — 6.25	1.56	6.25
Proteus mirabilis	76	0.1 — 50	0.39	12.5
Proteus vulgaris	6	0.2 — 1.56	—	—
Providencia spp.	17	0.1 — > 100	0.39	50
Morganella morganii	70	0.2 — 50	0.39	6.25
Pseudomonas aeruginosa	54	0.025 — 12.5	0.78	6.25

Microorganism tested	No. of isolates	MIC (μg/mL)		
		Range	MIC_{50}	MIC_{90}
Imipenem-resistant *Pseudomonas aeruginosa*	16	0.05 — 25	1.56	12.5
Acinetobacter spp.	61	0.0125 — 6.25	0.05	0.39
Bacteroides fragilis	40	0.1 — 25	0.39	3.13
Prevotella spp.	38	0.0125 — 1.56	0.39	1.56
Chlamydia pneumoniae	8	0.002 — 0.008	—	—
Mycoplasma pneumoniae	50	0.0156 — 0.0625	0.0313	0.0313
Legionella pneumophila	21	0.002 — 0.0078	0.0039	0.0039

c. Antibacterial activity against resistant *Streptococcus pneumoniae* and macrolide-resistant *Streptococcus pneumoniae* isolated in Japan and overseas [Attachments S11 (4.2.1.1.11), S12 (4.2.1.1.12), S13 (4.2.1.1.13), S14 (4.2.1.1.14)]

The MIC_{90} of GRNX against penicillin-intermediate (MIC of PCG: 0.12-1 μg/mL, hereinafter referred to as "PISP") or penicillin-resistant (MIC of PCG: ≥2 μg/mL, hereinafter referred to as "PRSP") *S. pneumoniae* isolated in Japanese and foreign clinical studies was 0.06 μg/mL (MIC range: 0.03-0.13 μg/mL), and the MIC_{90} of GRNX against macrolide-resistant PRSP/PISP was 0.06 μg/mL for Japanese strains (33 strains) (MIC range: 0.03-0.06 μg/mL) and 0.06 μg/mL for foreign strains (30 strains) (MIC range: 0.03-0.06 μg/mL) and GRNX was more active by 2-4 tube dilutions than LVFX, GFLX, and MFLX.

For multi-drug resistant* *S. pneumoniae* [Multi-drug resistant*: defined as foreign isolates resistant to the 5 antibiotics of EM, CXM, PCG, TC, and SMX/TMP or Japanese isolates resistant to the 4 antibiotics of EM, CXM, PCG, and TC due to a very limited number of isolates resistant to SMX/TMP in Japan, according to the CLSI criteria], the MIC of GRNX against foreign isolates (6 isolates) was 0.03-0.06 μg/mL and the MIC_{90} against Japanese isolates (25 isolates) was 0.06 μg/mL (MIC range: 0.02-0.06 μg/mL), and GRNX was more active by 1-5 tube dilutions than LVFX, GFLX, and MFLX.

d. Antibacterial activity against quinolone-intermediate, methicillin-resistant *S. aureus* and quinolone-resistant *S. pneumoniae* [Attachments S15 (4.2.1.1.15), S16 (4.2.1.1.16)]

The MIC of GRNX against clinical isolates of quinolone-intermediate (MIC of LVFX: 6.25 μg/mL) methicillin-resistant *S. aureus* (MRSA) (15 strains: all preserved strains) was 0.39-1.56 μg/mL, and GRNX was more active by 1-3 tube dilutions than LVFX, GFLX, and MFLX.

The MIC of GRNX against clinical isolates of quinolone-resistant *S. pneumonia* (MIC of LVFX: ≥6.25 μg/mL) (7 strains: among which, 5 strains were isolated in clinical studies conducted for this regulatory submission) was 0.2-3.13 μg/mL, and GRNX was more active by 1-6 tube dilutions than LVFX, GFLX, and MFLX.

e. Antibacterial activity against vancomycin-resistant enterococci [Attachment S17 (4.2.1.1.17)]

The MIC of GRNX against vancomycin-resistant enterococci isolated in the US (VanA-containing

strains) was 0.1-3.13 μg/mL, which was 1/4 to 4 times that of LVFX and 1/2 to 4 times that of GFLX. The MIC of T-3811ME against VanB- and VanC-containing strains was 0.1-3.13μg/mL, which was 1/8-1/16 of that of LVFX and 1/2-1/4 of that of GFLX.

f. Investigation of various factors affecting antibacterial activity [Attachments S18 (4.2.1.1.18), S19 (4.2.1.1.19)]

Using *S. aureus* IFO 12732, *S. pneumoniae* ATCC 49619, *K. pneumoniae* ATCC 10031, and *P. aeruginosa* ATCC 27853, the effects of various factors on the antibacterial activity of GRNX were investigated. As a result, there were little effects of the type of medium, pH of the medium, or addition of human serum, whereas the addition of calcium/magnesium resulted in 2-16 times higher MIC values and an increase in the inoculum concentration ($3.2\text{-}4.8\times10^{6}\rightarrow3.2\text{-}4.8\times10^{8}$) resulted in a 2 times higher MIC value, showing decreased antibacterial activity.

g. Bactericidal activity [Attachment S20 (4.2.1.1.20)]

Using *S. aureus* IFO 12732, *S. pneumoniae* ATCC 49619, *K. pneumoniae* ATCC 10031, and *P. aeruginosa* ATCC 27853, the MIC and MBC of GRNX were determined. As a result, the MIC and MBC values were the same for all strains.

h. Emergence of resistant bacteria [Attachments S25 (4.2.1.1.25), S26 (4.2.1.1.26)]

Frequency of spontaneous resistance

The frequencies of spontaneous resistance to GRNX at 4, 8, and 16 times the MIC were determined. As a result, at all concentrations, the frequencies were $<4.6\times10^{-11}$ for *S. aureus* IFO 12732 and $<9.8\times10^{-10}$ for *S. pneumoniae* ATCC 49619. The spontaneous resistance frequency for *K. pneumoniae* ATCC 10031 was 3.8×10^{-9}-4.2×10^{-9} at 4 times the MIC of GRNX and $<3.5\times10^{-11}$ at both 8 and 16 times the MIC.

***In vitro* resistance acquisition**

A culture of the maximum drug concentration macroscopically showing a bacterial growth to a similar extent as that in a well containing no drug was diluted with sterile physiological saline to about 10^{7} CFU/mL, in order to prepare a bacterial suspension for inocula, and MIC was determined by the broth microdilution method. The same procedure was repeated 7 times and the MIC for bacteria passaged up to 7 times was determined and a rise in MIC for each drug was investigated. As a result, a 2-fold rise for *S. aureus* IFO 12732, *S. pneumoniae* ATCC 49619, and *K. pneumoniae* ATCC 10031 and a 4-fold rise for *P. aeruginosa* ATCC 27853 were noted with GRNX, which were similar to a 2-4 fold rise with LVFX and GFLX.

i. Mutant Prevention Concentration (MPC) [Attachment S27 (4.2.1.1.27)]

The MPC of T-3811ME against quinolone-intermediate [with mutations in the quinolone resistance determining region (QRDR) of DNA gyrase or topoisomerase IV] and quinolone-susceptible *S. aureus* and *S. pneumoniae* was 0.08-1 μg/mL, which was lower than those of LVFX (0.5-30 μg/mL) and

GFLX (0.3-7 μg/mL).

j. Intracellular distribution [Attachment S28 (4.2.1.1.28)]

Using human polymorphonuclear leukocytes (PMNs) and a cell line, HeLa229, intracellular distribution of T-3811ME was measured together with those of LVFX and GFLX. As a result, the ratio of intracellular concentration (C) to extracellular concentration (E) (C/E ratio) was 9.39±1.20 for PMNs and 11.2±0.964 for HeLa229, which were both higher than those with LVFX and GFLX.

k. Mode of action

The inhibitory effect of T-3811ME on DNA gyrase and topoisomerase IV derived from *S. aureus* ATCC 25923 and *S. pneumoniae* R6 and on human topoisomerase II was investigated using agarose electrophoresis. As a result, T-3811ME selectively inhibited bacterial topoisomerase IV.

2) *In vivo* antibacterial activity

a. Investigation of a relationship between AUC/MIC and the bactericidal effect [Attachment S32 (4.2.1.1.32)]

Using quinolone-resistant *S. pneumoniae* D-1687, a relationship between serum concentrations over time that are equivalent to those observed after a single oral dose of 200 mg or 400 mg in Japanese subjects and bacterial growth, was investigated by an *in vitro* pharmacokinetic model (IVPM). As a result, an adequate effect was obtained at Free AUC_{24}/MIC $\geq$26.3.

b. Bactericidal effect in a model of rats subcutaneously infected with *S. aureus* in the back [Attachments S33 (4.2.1.1.33), S34 (4.2.1.1.34)]

In a rat infection model in which a paper disk impregnated with *S. aureus* SA113 suspension (2.0-12.0 $\times 10^6$ CFU/disk) was inserted into a pouch under the skin on the back of rats, 1.25, 2.5, 5, and 10 mg/kg of GRNX and LVFX were administered orally (immediately after the disk was implanted). After the administration of the drugs, the disks were collected repeatedly and the viable cell count was measured. As a result, with all doses, the viable cell count in the disk (effusion) at 24 hours after the administration of GRNX was lower as compared with the administration of LVFX. In addition, with regard to the PK/PD parameters after the oral administration of 5 mg/kg of GRNX and LVFX, C_{max}/MIC and AUC/MIC of GRNX were 3.1- to 4.4-fold and 6.0- to 7.4-fold greater than those of LVFX, respectively, in terms of total concentration, and 0.54- to 0.59-fold and 0.98- to 1.0-fold greater than those of LVFX, respectively, in terms of free drug concentration. GRNX exhibited a potent *in vivo* bactericidal effect at serum free AUC/MIC $\geq$23.2.

c. Therapeutic efficacy in an experimental systemic infection model of mice [Attachments S35 (4.2.1.1.35), S36 (4.2.1.1.36), S37 (4.2.1.1.37), S38 (4.2.1.1.38)]

Each bacterial suspension was inoculated into the peritoneal cavity of mice and GRNX, LVFX, or GFLX was orally administered at 1 hour post-inoculation. Based on the number of surviving mice at 7 days post-infection, the ED_{50} value was calculated using the Probit method. The ED_{50} values of

GRNX against methicillin-resistant *S.aureus* F-1479, penicillin-resistant *S.pneumoniae* D-979, *E.coli* TK-16, and *P.aeruginosa* S-1295 were 0.00593, 0.555, 0.0111, and 0.913 mg/mouse, respectively, which were lower than or equal to those of LVFX and GFLX.

d. Therapeutic efficacy in an experimental pneumonia model of mice [Attachment S39 (4.2.1.1.39)]

After penicillin-resistant *S. pneumoniae* D-979 was transnasally inoculated into mice, 5 mg/kg of GRNX, LVFX, or GFLX was orally administered three times daily at 4 hour intervals for 2 days to these mice starting 18 hours post-inoculation. Then, the mortality and viable cell count in the lungs were determined. While the mortality in the control group was 70%, the mortality was 0% in all of the GRNX, LVFX, and GFLX groups. The viable cell counts in the lungs were < 2.68±0.83 Log_{10} CFU/g of lung in the GRNX group, 5.30±0.88 Log_{10} CFU/g of lung in the LVFX group, and 4.15± 0.74 Log_{10} CFU/g of lung in the GFLX group.

e. Therapeutic efficacy in an experimental chlamydial pneumonia model of mice [Attachment S40 (4.2.1.1.40)]

C. pneumoniae TW-183 was transtracheally inoculated into mice that were intraperitoneally administered 250 mg/kg of cyclophosphamide and GRNX, LVFX, or AZM was orally administered twice daily at 8 hours intervals for 3 days starting the day after inoculation. Then, the ED_{50} value and 95% confidence limits were calculated based on the number of surviving mice 14 days after the last dose (Probit method, calculated as the dose per administration). The ED_{50} value of GRNX was 0.0286 mg/body, which was lower than those of LVFX and AZM.

f. Therapeutic efficacy in a hamster mycoplasmal pneumonia model [Attachments S41 (4.2.1.1.41), S5 (4.2.1.1.5)]

M. pneumoniae FH was intratracheally inoculated into hamsters and 10, 20, and 40 mg/kg of GRNX, LVFX, or CAM were orally administered once daily for 2 or 5 days starting 7 days after infection. Then, the viable cell count in bronchoalveolar lavage fluid (BALF) was determined on the following day of the last dose (9 and 12 days after infection). The viable cell count in BALF at 12 days post-infection in the GRNX 10 mg/kg group was lower compared with the control group and lower than in the LVFX and CAM groups. The viable cell count in BALF at 12 days post-infection was <2.90±0.71 Log_{10} CFU/mL in the GRNX 20 mg/kg group and <2.30 Log_{10} CFU/mL in the GRNX 40 mg/kg group, which were lower compared to the control group and the LVFX group, and lower than in the CAM group.

g. Therapeutic efficacy in a guinea pig legionella pneumonia model [Attachments S42 (4.2.1.1.42), S6 (4.2.1.1.6)]

L. pneumophila ATCC 33152 was intratracheally inoculated into guinea pigs and 5 mg/kg of GRNX, LVFX, CPFX, RFP, and CAM was orally administered once daily for 2 or 7 days from 24 hours post-infection. Then, the viable cell count was determined at 24 hours post-infection and at 24 hours

after the last dose (3 days and 8 days post-infection). The viable cell count in the lungs at 3 days post-infection in the GRNX group was lower compared with the control group and was similar to that in the CAM group. The viable cell count in the lungs at 8 days post-infection in the GRNX group was lower compared with the control group and lower than in the CPFX and CAM groups and similar to that in the RFP group.

(2) Secondary pharmacodynamics

1) Effects on GABA receptor binding [Attachment S47 (4.2.1.2.1)]

Using rat brain synaptic membrane, the effects of GRNX on [^{3}H]GABA receptor binding were measured by the filtration method. As a result, the addition of GRNX alone up to 100 μmol/L did not inhibit GABA receptor binding. Also in the presence of aspirin, mefenamic acid, diclofenac, indomethacin, ibuprofen, ketoprofen, naproxen, piroxicam, or biphenylylacetic acid (the applied concentration: 100 μmol/L), GRNX did not show the inhibitory effect up to 100 μmol/L. On the other hand, the addition of ENX, NFLX, CPFX, OFLX, or trovafloxacin alone up to 100 μmol/L did not inhibit GABA receptor binding, but inhibition occurred in the presence of biphenylylacetic acid.

2) Convulsion-inducing effect [Attachments S68 (4.2.1.4.1), S69 (4.2.1.4.2)]

Nonsteroidal antiinflammatory drugs (aspirin 300 mg/kg, mefenamic acid 200 mg/kg, diclofenac 17.5 mg/kg, fenbufen 100 and 200 mg/kg, indomethacin 12.5 mg/kg, ibuprofen 100 mg/kg, ketoprofen 25 mg/kg, naproxen 100 mg/kg, piroxicam 3.5 mg/kg) or biphenylylacetic acid 50 mg/kg were orally administered to mice (male, 7 animals/group). 30 minutes later, whether or not convulsions were induced was observed following the intravenous administration of 15, 30, or 60 mg/kg of GRNX. GRNX did not induce convulsions at any dos or with any concomitant drug, whereas reference fluoroquinolones induced clonic convulsions in combination with fenbufen (200 mg/kg): ENX at doses $\geq$1.88 mg/kg, NFLX at doses $\geq$7.5 mg/kg, CPFX at doses $\geq$15 mg/kg, OFLX at a dose of 60 mg/kg, and alatrofloxacin at a dose of 60 mg/kg. While no convulsions were induced in combination with aspirin, ENX at 60 mg/kg in combination with naproxen induced clonic convulsions.

Whether or not a convulsion occurred was observed after the intracerebroventricular administration of GRNX 12.5, 25, 50, and 100 μg to mice (male, 10 animals/group). As a result, GRNX induced clonic convulsions at 50 μg or more. Meanwhile, NFLX at 3.13 μg or more, CPFX at 12.5 μg or more, STFX at 25 μg or more, trovafloxacin at 25 μg or more, OFLX at 50 μg or more, and olamufloxacin at 50 μg or more induced clonic convulsions.

3) Effects on righting reflex and other general symptoms [Attachment S48 (4.2.1.2.2)]

Following the intravenous administration of GRNX 15, 30, and 60 mg/kg to mice (male, 10 animals/group), righting reflex and other general symptoms were observed. As a result, there were no effects at any dose. On the other hand, trovafloxacin caused decreased alertness and response, relaxation of posture, and decreased respiration rate at 15 mg/kg or more, and an increase in the number of animals with righting reflex loss at 30 mg/kg or more. Although CPFX did not affect

righting reflex at any dose, decreased passivity, decrease in grooming, and relaxation of posture were noted at 15 or 30 mg/kg.

4) Effects on motor coordination [Attachment S49 (4.2.1.2.3)]

GRNX 15, 30, and 60 mg/kg were intravenously administered to mice (male, 7 animals/group) and the motor coordination at 5 and 30 minutes post-dose was assessed by the Rotarod method. Fluoroquinolones (NFLX, CPFX, and alatrofloxacin) were used as reference drugs.

Intravenous T-3811ME up to 60 mg/kg did not affect the motor coordination in mice. As to the reference drugs, intravenous NFLX or CPFX up to 60 mg/kg had no effects, but intravenous alatrofloxacin at 60 mg/kg caused impaired motor coordination (an increase in the number of animals falling off the rotating rod) at 30 minutes post-dose.

(3) Safety pharmacology [Attachments S50 (4.2.1.3.1), S52 (4.2.1.3.3), S53 (4.2.1.3.4), S54 (4.2.1.3.5), S55 (4.2.1.3.6)]

The effects of GRNX on the central nervous system, cardiovascular system, respiratory system, renal/urinary system, autonomic nervous system, gastrointestinal system, etc. were investigated.

1) Effects on the central nervous system

Although intravenous GRNX at 60 mg/kg caused a decrease in spontaneous locomotor activity in mice, there were no effects on general symptoms/behaviour (mice), hexobarbital-induced sleep (mice), nociceptive reaction (mice), or body temperature (rats) at doses up to 60 mg/kg. In addition, GRNX did not show anticonvulsive action (maximal electroshock seizures and pentylenetetrazol-induced seizures) or an effect synergistic with the convulsive activity of pentylenetetrazol (both in mice).

2) Effects on the cardiovascular system

After single intravenous administration of GRNX 30, 50, and 75 mg/kg/12min to conscious dogs (3 males and 3 females), a transient decrease in blood pressure, increase in heart rate, and elevation of plasma histamine levels were noted in a dose-dependent manner. This decrease in blood pressure was reduced by the pretreatment with antihistamines (diphenhydramine hydrochloride 4 mg/kg and cimetidine hydrochloride 20 mg/kg). With regard to ECGs, dose-related QTc interval prolongation at 30 and 75mg/kg (about 20 and 40 msec, respectively) and a prolongation of the PR interval (about 10 msec) were observed. In addition, following repeated intravenous administration of GRNX 50 and 75 mg/kg/12min, a transient decrease in blood pressure was observed after the first dose of 50 mg/kg while there were no effects on blood pressure after the 2nd to 4th doses of GRNX 50 mg/kg and after the first and second doses of GRNX 75 mg/kg. Elevations of plasma histamine levels were noted also during repeated-dose administration. When the same doses were administered over 1 hour, there was no decrease in blood pressure or elevation of plasma histamine levels in females and a decrease in blood pressure was seen in males, which was milder as compared with administration over 12 minutes.

Following the intravenous administration of 80 and 160 mg/body of CPFX, elevations of plasma histamine levels and flush in the pinna and oral region were observed, whereas intravenous GRNX did not affect plasma histamine levels or general condition at doses up to 320 mg/body.

After a single intravenous dose of GRNX 75 and 112 mg/kg over 1 hour to conscious monkeys (male, 5 animals/group), there were no changes in blood pressure, but a dose-unrelated slow decrease in heart rate (a decrease of 35-67 beats/min, persisted until 1 hour after the end of administration) was observed and at the same time, there was an ECG QT interval prolongation (42-57 msec), QTc interval prolongation (29-44 msec), and PR interval prolongation (8-20 msec).

3) Effects on the respiratory system

Following the intravenous administration of GRNX up to 60 mg/kg to anesthetized dogs, there were no effects on respiratory rate.

4) Effects on the renal/urinary system

After the intravenous administration of GRNX to rats, there were increased urinary excretion of potassium and a decrease in the urinary sodium/potassium ratio at 20 mg/kg or more, and increased urinary excretion of creatinine, increased urine osmolarity, and decreased urinary pH at 60 mg/kg.

5) Effects on the autonomic nervous system

GRNX 100 μg/mL inhibited the spontaneous motility of the rabbit isolated ileum and suppressed the contractions of the guinea pig isolated ileum induced by agonists (acetylcholine, histamine, barium, and serotonin).

6) Effects on the gastrointestinal system

Intravenous administration of GRNX up to 60 mg/kg did not affect the intestinal transport in mice (charcoal transportation).

7) Effects on general conditions

Single intravenous doses of GRNX 30, 50, and 75 mg/kg/12min were administered to conscious dogs (3 males and 3 females). Decreased spontaneous locomotor activity, vomiting, circling, salivation, and shivering were observed during the administration of 30 mg/kg. In addition to these symptoms, ptosis, nausea, restlessness, swelling (nose and mouth, eyes, ears), decreased respiratory rate, lateral position, erythema, dyspnea or pale mucous membrane were observed at 50 and 75 mg/kg.

8) Effects on various receptors, ion channels, and enzymes [Attachments S56 (4.2.1.3.7), S57 (4.2.1.3.8), S58 (4.2.1.3.9), S59 (4.2.1.3.10)]

The effects of GRNX on adrenaline receptors (α_1, α_2, and β_2), angiotensin II receptors (AT_1 and AT_2), dopamine receptors (D_1 and D_2), endothelin receptor (ET_A), histamine receptors (H_1 and H_2), L-type

calcium channel, dopamine transporter, protein kinase C (refer to Attachments 4.2.1.3.7), adenosine receptors (A_1, A_{2A}, and A_{2B}), bradykinin receptors (B_1 and B_2), vasopressin receptors (V_{1a} and V_2), and phosphodiesterase 3 (refer to Attachment 4.2.1.3.8) as the receptors, ion channels, and enzymes related to the cardiovascular system, were investigated. As a result, GRNX 10 μmol/L inhibited α_2, β_2 and protein kinase C and the IC_{50} value were >100 μmol/L, 21 or 40 μmol/L, and >100 μmol/L, respectively. The IC_{50} value for β_1 was >300 μmol/L. Inhibition of other receptors, ion channels and enzymes was not observed.

9) Effects on hERG currents [Attachment S60 (4.2.1.3.11)]

hERG currents in hERG gene (human ether-a-go-go related gene) expressed HEK293 cells were measured using the whole-cell clamp technique. As a result, GRNX inhibited hERG currents in a concentration-dependent manner and the IC_{50} value was about 300 μmol/L. The potency of inhibiting hERG currents was ranked in the following order: SPFX > GPFX > CAM > GRNX ≒ gemifloxacin > EM ≒ AZM.

10) Effects on myocardial action potential [Attachment S61 (4.2.1.3.12)]

Using rabbit Purkinje fibers, action potential was measured by the microelectrode method. As a result, GRNX prolonged the action potential duration (APD_{90}: action potential duration at 90% repolarization) in a concentration-dependent manner and the potency of this effect was ranked in the following order: SPFX > EM > CAM > GPFX > GRNX.

11) Effects on calcium currents [Attachment S62 (4.2.1.3.13)]

T-type and L-type calcium currents in human calcium channel gene (CACNA1H and CACNA1C) expressed HEK293 cells were measured using the whole-cell clamp technique. As a result, GRNX and CPFX 300 μmol/L inhibited T-type and L-type calcium currents in a dose-dependent manner (GRNX: 41.8% and 27.9% inhibitions, respectively, CPFX: 15.5% and 23.6% inhibitions, respectively).

12) Effects on isolated blood vessels [Attachment S63 (4.2.1.3.14)]

Isolated aortas with endothelial cells removed were prepared from male rats (4 rats/group) and the inhibitory effects on contractions induced by various drugs were evaluated. As a result, GRNX suppressed contractions induced by phenylephrine (0.03 μmol/L) and potassium chloride (80 mmol/L) at 100 μmol/L or more and contractions induced by prostaglandin $F_{2\alpha}$ at 300 μmol/L. GRNX did not affect the contractions induced by serotonin (10 μmol/L) or phorbol-12, 13-dibutyrate (3 μmol/L) at concentrations up to 300 μmol/L and enhanced contractions induced by endothelin-1 (0.1-316 nmol/L) and angiotensin II (0.1-100 nmol/L) at 100 μmol/L. CPFX showed the same effects as GRNX except that CPFX did not affect the contraction induced by potassium chloride.

13) Effects on isolated hearts [Attachment S64 (4.2.1.3.15)]

Langendorff isolated perfused hearts were prepared from male rats (8 or 15 rats/group). By measuring changes in the volume of the left ventricular lumen, its relationship with heart rate, coronary blood

flow volume, and left ventricular pressure, was evaluated. As a result, GRNX decreased heart rate by 12% at 100 μmol/L and caused increases in relative end-systolic pressure and relative end-diastolic volume or a decrease in relative end-systolic volume at 1 μmol/L or higher, which was not concentration-dependent. As with GRNX, CPFX did not affect heart rate but caused increases in relative end-systolic pressure and relative end-diastolic volume or a decrease in relative end-systolic volume at 1 μmol/L or higher, which was not concentration-dependent.

(4) Pharmacodynamic drug interactions

1) Effects on the anticoagulant effect of warfarin [Attachments S70 (4.2.1.4.3)]

Repeated oral dose of warfarin 0.3 mg/kg was administered once daily for 5 days to male rats (6 or 7 rats/group), and GRNX (6, 20, and 60 mg/kg, intravenous administration) was administered once daily for 3 days concurrently with warfarin starting the 3rd day of warfarin administration. Then, coagulation parameters (prothrombin time and activated partial thromboplastin time) at 24 hours after the last dose were measured. As a result, GRNX, CPFX, or OFLX did not affect the anti-coagulant effect of warfarin at doses up to 60 mg/kg.

<Outline of the review by the PMDA>

The PMDA concluded that GRNX has activity against the proposed bacteria, based on the results from pharmacology studies. As decreased blood pressure etc. associated with histamine release has been noted in a safety pharmacology study, it should be necessary to pay an adequate attention to possible reactions associated with histamine release also in clinical use. The PMDA is currently asking the applicant whether there is any plan to investigate (a) the effects of GRNX on insulin secretion and (b) the function of pigmented organs.

(ii) Summary of pharmacokinetic studies

All doses, concentrations, C_{max}, and AUC of the product below are expressed in terms of GRNX, the active ingredient.

<Summary of the submitted data>

Following the oral administration of GRNX to rats, dogs and monkeys, the pharmacokinetics were evaluated. Plasma GRNX concentrations in rats were measured by high performance liquid chromatography (HPLC) and those in dogs and monkeys by liquid chromatography/tandem mass spectrometry (LC/MS/MS). The radioactivity of ^{14}C-labeled GRNX was measured by liquid scintillation counter (LSC). Plasma GRNX concentrations in monkeys were calculated based on the existence ratio of GRNX after analysis by bioimage analyzer following separation by thin layer chromatography (TLC).

(1) Absorption

The bioavailabilities calculated based on AUCs observed following single intravenous doses (10, 15, and 5 mg/kg, respectively) and single oral doses (10, 8, and 5 mg/kg, respectively) of GRNX to rats,

dogs, and monkeys were 78.7, 66.7, and 76.7%, respectively. Following a single oral dose of GRNX 10 mg/kg to rats, plasma GRNX C_{max} was decreased to 33% and AUC to 43% in the fed state compared with the fasting state, showing food effects.

After single oral doses of GRNX 25-200 mg/kg to rats, the plasma GRNX C_{max} was decreased to 45-54% and AUC to 23-33% in females compared to males, whereas there were no gender differences in plasma GRNX C_{max} or AUC in dogs (8-75 mg/kg) and monkeys (25-100 mg/kg). In these studies, although plasma GRNX C_{max} and AUC0-∞ were increased in a dose-dependent manner, there were no major differences in $t_{1/2}$ between the different doses, and the $t_{1/2}$ was 1.60-3.73 hr for rats, 5.26-7.81 hr for dogs, and 4.05-6.46 hr for monkeys.

(2) Distribution

Following a single oral dose of ^{14}C-labeled GRNX 5 mg/kg to rats under the fasting condition, the radioactivity levels in the stomach, small intestine, liver, esophagus, and kidneys at 15 minutes post-dose were 3.6-16 times higher than that in plasma and the radioactivity levels in the cerebrum and spinal cord at 15 minutes post-dose were 0.02-0.04 times that in plasma. The radioactivity distribution in blood cells was 26.8-36.0% at 15 minutes to 24 hours post-dose. Following the oral administration of ^{14}C-labeled GRNX 5 mg/kg to monkeys, tissue distribution of radioactivity was investigated. As a result, at 1 hour post-dose, radioactivity was extensively distributed to systemic tissues, excluding the cerebrum, spinal cord, vitreous body, etc. The radioactivity distribution in blood cells was 6.6-13.3% at 30 minutes to 24 hours post-dose. Following the oral administration of ^{14}C-labeled GRNX 5 mg/kg to rats during organogenesis (day 13 of gestation) and during late pregnancy (day 19 of gestation), radioactivity passed the placenta and was transferred to the fetus.

(3) Metabolism

^{14}C-labeled GRNX was given to rats, dogs, and monkeys by single oral administration (rats and monkeys), intravenous administration (dogs), and intraduodenal administration (monkeys). As a result, GRNX ($\geq$70%) was predominantly present in plasma and urine followed by its sulfate conjugate (M1, $\leq$30%). In bile, M1 ($\geq$40%) and a glucuronide conjugate (M6, $\geq$40%) were mainly present in rats and M1 ($\geq$80%) was predominantly present in monkeys. The effects of GRNX on the metabolic activity of different CYP isoforms in human liver microsomes were investigated. As a result, GRNX at 1000 μmol/L (426 μg/mL) decreased the activity of CYP2A6, 2C19, 2D6, and 2E1 to 75.1, 83.8, 77.1, and 82.4%, respectively, showing an inhibitory effect, while inhibitory effects on other isoforms were weak. GRNX did not induce CYP isoforms and *in vitro* metabolic reactions of GRNX itself were also negligible.

(4) Excretion

Following a single oral dose of ^{14}C-labeled GRNX 5 mg/kg to male rats under the fasting condition, 63.6, 15.0, and 6.95% of the administered radioactivity was excreted in bile, urine, and feces, respectively, within 24 hours post-dose. The excretion of radioactivity after a single oral dose of

^{14}C-labeled GRNX 5 mg/kg was measured up to 96 hours post-dose in the rats and up to 168 hours post-dose in the monkeys. As a result, within the measuring period, 97.8% of the administered radioactivity in the rats was excreted (84.8% in feces, 13.0% in urine) and 99.6% of the administered radioactivity in the monkeys was excreted (60.7% in feces, 38.9% in urine). An investigation of the mechanism of GRNX urinary excretion in the rat suggested the following possibility: Tubular secretion via transporter is involved in the urinary excretion of GRNX and the cumulative urinary excretion rate is decreased with an increase in dose partly because CLr is reduced due to saturation of tubular secretion.

(5) Pharmacokinetic drug interactions

In vitro protein binding of GRNX was 66.7-71.9% in mice, 86.5-89.0% in rats, 64.5-67.6% in dogs, 71.2-74.5% in monkeys, and 78.3-84.0% in humans. Human *ex vivo* serum protein binding was 78.9% at 3 hours post-dose and 79.8% at 12 hours post-dose, which were almost constant. The major binding protein was albumin and binding to the binding site I was suggested. Thus, the potential for interaction with warfarin, which binds to the binding site I, was evaluated. As a result, GRNX and warfarin did not affect the protein binding of each other. The inhibitory effect of GRNX on theophylline metabolism was investigated using human liver microsomes. As a result, the inhibition constant (Ki value) for theophylline metabolism (3-demethylation and 8-hydroxylation) was 4.06 and 9.15 mmol/L, respectively, which were similar to those of GFLX (4.46 and 18.06 mmol/L, respectively).

<Outline of the review by the PMDA>

The PMDA asked for the applicant's view on the necessity of advising caution about possible interactions between GRNX and drugs inhibiting tubular secretion and the concomitant use of these drugs, on the basis that tubular secretion seems involved in the urinary excretion of GRNX and the possibility of saturation of tubular secretion with increasing dose has been suggested in rats.

The applicant responded as follows.

It has been estimated that the proportion of CLr in CL/F (CL) after oral administration of GRNX is about 48% and the proportion of CLnr in CL/F (CL) is about 52%. AUCs calculated by simulating plasma concentrations in the case of no renal clearance (assuming that renal excretion is completely inhibited by the concomitant use with drugs inhibiting tubular secretion) and in the case of a decrease in renal clearance to 1/2 (assuming that renal excretion is reduced to 1/2 by the concomitant use with drugs inhibiting tubular secretion), using data from Study 61001, and AUCs calculated based on population pharmacokinetic analysis involving Japanese patients with normal renal function ($CL_{Cr} \geq 80$) to moderate renal impairment ($50 > CL_{Cr} \geq 20$) seem within a range where the safety has been confirmed, in view of AUC and C_{max} (165.5 μg·hr/mL and 12.34 μg/mL, respectively) after a single oral dose of GRNX 600 mg to healthy Japanese subjects (Study 61001). Moreover, according to the results of population pharmacokinetic analysis assessing the effects of concomitant renal transporter inhibitors on the pharmacokinetics of GRNX, it has been inferred that such inhibitors do

not affect the kinetics of GRNX (Antimicrob Agents Chemother. 2004; 48 (12): 4766). Based on the above, GRNX is eliminated from the body via both renal and nonrenal routes and even if renal excretion is inhibited by drugs inhibiting tubular secretion, there should be no clinically significant changes in the kinetics of GRNX. Also, since a finding that GRNX alters the kinetics of drugs that are excreted by tubular secretion has not been obtained so far, we think that it is unnecessary to advise caution about the concomitant use of such drugs and GRNX. However, we plan to conduct a study for identifying transporters involved in the renal excretion of GRNX and assessing their affinity so that further information can be provided after marketing.

The PMDA accepted the applicant's response that advising caution regarding the concomitant use of GRNX and tubular secretion inhibitors is unnecessary at present. However, Study AI464047 showed that the AUC in patients with renal impairment not requiring dialysis (CL_{Cr} <30 mL/min) was 51% higher than that in subjects with normal renal function, and interaction between GRNX and tubular secretion inhibitors in patients with severe renal impairment who were not included in the population pharmacokinetic analysis should be unknown at present.

(iii) Summary of toxicology studies

All doses and concentrations of the product below are expressed in terms of GRNX, the active ingredient.

<Summary of the submitted data>

(1) Single-dose toxicity

Single dose toxicity was evaluated in mice by oral (0, 1000, 1500, and 2000 mg/kg, males and females) and intravenous (0, 100, 150, 200, and 250 mg/kg for males and females, 300 mg/kg for females only) routes, in rats by oral (0, 1000, 1500, and 2000 mg/kg, males and females) and intravenous (0, 100, 150, 200, 250, and 300 mg/kg, males and females) routes, and in dogs by oral (1000 and 2000 mg/kg, males only) and intravenous (200 and 300 mg/kg, males only) routes. The approximate oral lethal dose has been determined to be at least 2000 mg/kg in all animal species studied and the approximate intravenous lethal dose has been determined to be between 200 and 300 mg/kg for all animal species studied.

(2) Repeated-dose toxicity

Repeated-dose toxicity was evaluated in rats, dogs, and monkeys by oral and intravenous routes. Studies of 1 month duration (oral administration: 0, 25, 50, 100, 200, 400, and 800 mg/kg/day; the 800 mg/kg/day group contained females only; intravenous administration: 0, 10, 30, and 100 mg/kg/day) and of 3 months duration (oral administration: 0, 50, 100, 200, 400, and 800 mg/kg/day; the 50 mg/kg/day group contained males only, whereas the 800 mg/kg/day group contained females only; intravenous administration: 0, 10, 30, and 100 mg/kg/day) were conducted in rats. Studies of 1 month duration (oral administration: 0, 8, 25, and 75 mg/kg/day; intravenous administration: 0, 5, 15, and 50 mg/kg/day) and of 6 months duration (oral administration: 0, 8, 20, and 50 mg/kg/day) were

conducted in dogs. Studies of 1 month duration (oral administration: 0, 25, 50, and 100 mg/kg/day; intravenous administration: 0, 12, 30, and 75 mg/kg/day) and of 3 months duration (oral administration: 0, 10, 30, and 100 mg/kg/day; intravenous administration: 0, 8, 20, and 50 mg/kg/day) were conducted in monkeys. Animals that died/were killed in extremis associated with GRNX were noted in the 100 mg/kg/day group of the 3-month intravenous administration study in rats (1/16, male) and in the 75 mg/kg/day group of the 1-month intravenous administration study in monkeys (1/7, female). There was a gender difference in the exposure (AUC) in an oral administration study in rats, and the exposure was 3 to 4 times higher in males than in females.

Observed toxic changes associated with repeated administration of GRNX are as listed below.

The effects on the central nervous system were mydriasis and salivation after intravenous administration to rats, vomiting and salivation after oral and intravenous administration to dogs, and vomiting and salivation after oral administration to monkeys (it was suggested that vomiting and salivation observed in dogs and monkeys were also associated with gastrointestinal tract irritation). The findings observed in rats occurred at about 9- to 10-fold the C_{max} at the proposed human clinical dose. The findings observed in dogs occurred at about 1- to 4-fold the C_{max} at the proposed human clinical dose. The findings observed in monkeys occurred at about 3- to 5-fold the C_{max} at the proposed human clinical dose.

The effects on the cardiovascular system were QTc interval prolongation in the 75 mg/kg/day group of the 1-month intravenous administration study in monkeys, and a negative p-wave in ECG in the 75 mg/kg/day group of the 1-month oral administration study in dogs and in the 50 mg/kg/day group of the 1-month intravenous administration study in dogs.

The effects on the gastrointestinal tract were as follows:
Loose stools considered attributable to the antibacterial action of GRNX were seen in rats and monkeys. In the 3-month, oral administration study in monkeys, atrophy of the fundic gland was noted in the 100 mg/kg/day group, which was a reversible change and it has been inferred that this finding was caused by direct irritation associated with a high dose of GRNX administered over a long period of time.

The effects on the joints were as follows:
Articular cartilage disorder occurred in the dogs in the 75 mg/kg/day group of the 1-month oral administration study and in the 50 mg/kg/day group of the 1-month intravenous administration study. In rats, articular cartilage disorder occurred at doses $\geq$400 mg/kg/day in the 1-month and 3-month oral administration studies and in the 100 mg/kg/day group of the 3-month intravenous administration study.

The effects on the liver were as follows:

Lipid droplet deposit in hepatocytes was observed in male rats in the 400 mg/kg/day group of the 1-month oral administration study and in male rats treated with ≥100 mg/kg/day and female rats in the 800 mg/kg/day group of the 3-month oral administration study. In dogs, increased ALT at doses ≥25 mg/kg/day and infiltration of inflammatory cells in the vicinity of the hepatic central vein in the 75 mg/kg/day group were observed in the 1-month oral administration study. These changes in the liver occurred at an exposure level almost equivalent to the human AUC at the proposed clinical dose. However, lipid droplet deposit in the rats was not associated with changes in liver function test values such as AST and ALT, and as to increased ALT and infiltration of inflammatory cells in dogs, similar changes did not occur in the 1-month intravenous administration study or a longer study, i.e. the 6-month oral administration study. Therefore, it has been inferred that GRNX has no strong liver damaging effect.

In all animal species tested in repeated dose toxicity studies, reddish violet or violet coloration of the organs/tissues including oral mucosa, palpebral conjunctiva, skin, and stomach was observed in a dose- and treatment duration-dependent manner (The lowest dose where this effect was observed was 8 mg/kg/day in the 6-month repeated oral administration study in dogs). The cause of coloration has been inferred to be the deposit of metabolites of GRNX, and there were no functional decline or histopathologic changes considered attributable to coloration and these findings were reversible. Therefore, it has been concluded that these are changes of little toxicological significance. Based on the results from clinical studies, it has been inferred that coloration is unlikely to occur in humans at usual doses and with an usual duration of treatment. Although coloration is reversible, it takes a relatively long time to recover. Thus, in order to assess its genotoxicity, a skin micronucleus test using hairless mice, a comet assay using canine colored skin, and a bacterial reverse mutation test of the presumed causative substance were performed, which all produced negative results. In repeated dose toxicity studies in dogs and monkeys, dark brown discoloration or violet coloration of the thyroid gland was observed, which has also been inferred to be caused by the deposit of metabolites of GRNX, and there were no histological/functional abnormalities.

Although ocular toxicity and pancreatic toxicity are known to be associated with existing quinolones, there have been no changes suggestive of ocular or pancreatic toxicity with GRNX and it has been inferred that GRNX is unlikely to induce such toxicities.

No observed adverse effect levels (NOAEL) in different repeated dose toxicity studies have been determined as follows.

Animal species	Route of administration	Duration of treatment	NOAEL (mg/kg/day)
Rat	Oral	1 month	200 (male) 400 (female)
		3 months	50 (male) 200 (female)
	Intravenous	1 month	30
		3 months	30
Dog	Oral	1 month	8
		6 months	20
	Intravenous	1 month	15
Monkey	Oral	1 month	50
		3 months	30
	Intravenous	1 month	30
		3 months	50

The exposure to GRNX (AUC, C_{max}) at NOAELs obtained from these repeated dose toxicity studies was almost equivalent to or less than the human exposure at the proposed clinical dose and the possibility that toxic changes observed at a dose close to the NOAEL such as central nervous toxicity (vomiting, etc.) and hepatic toxicity may occur in humans can not be excluded. Moreover, although there is a certain safety margin, it is also necessary to pay attention to the effects on ECG which could lead to fatal changes (QT/QTc interval prolongation, etc.).

(3) Genotoxicity

Genotoxicity studies performed include a bacterial reverse mutation test, a gene mutation assay using cultured mammalian cells, a chromosomal aberration assay using cultured mammalian cells, a mouse micronucleus test, and *in vivo*/*in vitro* rat hepatocyte unscheduled DNA synthesis assay. Although the chromosomal aberration assay using cultured mammalian cells showed that GRNX was clastogenic to the mammalian cells treated at high concentrations ($\geq$250 μg/mL and $\geq$350 μg/mL in the absence and presence of metabolic activation [6-hour treatment], $\geq$100 μg/mL in the absence of metabolic activation [24-hour treatment]), a mouse micronucleus test was negative (500 mg/kg, intraperitoneal administration) and other tests also produced negative results. Therefore, it has been inferred that GRNX is unlikely to induce genotoxicity in the living body.

(4) Carcinogenicity

No carcinogenicity study of GRNX has been performed because its expected clinical use is basically for a short period of time and GRNX is unlikely to have a carcinogenic potential.

(5) Reproductive and developmental toxicity

Reproductive and developmental toxicity was investigated in rats and rabbits. In a rat study of fertility and early embryonic development to implantation (oral administration: 0, 25, 100, and 400 mg/kg/day for males; 0, 60, 250, and 1000 mg/kg/day for females), there were changes such as a reduction in body weight gain in male rats treated with $\geq$100 mg/kg/day and female rats in the 1000 mg/kg/day group, while neither the reproductive competence of adult male and female animals nor the early embryonic development was affected. The NOAEL was determined to be 25 mg/kg/day for paternal

general toxicity and 250 mg/kg/day for maternal general toxicity, and it has been concluded that there are no problems up to the highest dose tested for the reproductive competence of adult male and female animals and early embryonic development. In a rat study for effects on embryo-fetal development (oral administration: 0, 60, 250, and 1000 mg/kg/day), decreased food consumption and a reduction in body weight gain were noted in maternal animals in the 1000 mg/kg/day group while there were no effects on the reproductive competence or the fetus. The NOAEL was determined to be 250 mg/kg/day for maternal general toxicity and 1000 mg/kg/day for both maternal reproductive function and embryo/fetus. In a rabbit study for effects on embryo-fetal development (intravenous administration: 0, 6.25, 12.5, and 25 mg/kg/day), decreased food consumption and a reduction in body weight gain were observed in maternal animals in all GRNX groups. Abortions/premature births likely associated with these findings were also found sporadically in each group and 1 maternal animal in the 12.5 mg/kg/day group died after abortion. For fetuses, a trend towards a fetal bodyweight reduction and an increased number of fetuses with a thymic remnant in the neck were noted in the 25 mg/kg/day group, which were considered to be changes that reflect fetal growth retardation associated with decreased food consumption in maternal animals. It has been concluded that GRNX has no teratogenicity and the no NOAEL has been determined to be less than 6.25 mg/kg/day for both maternal general toxicity and reproductive competence and 12.5 mg/kg/day for embryo/fetus. In a rat study for effects on pre- and postnatal development, including maternal function (oral administration: 0, 60, 250, and 1000 mg/kg/day), decreased food consumption and a reduction in body weight gain were observed in maternal animals during pregnancy at $\geq$250 mg/kg/day while there were no effects on maternal reproductive competence or F_1 and F_2 offspring and the NOAEL has been determined to be 60 mg/kg/day for maternal general toxicity and 1000 mg/kg/day for maternal reproductive competence and F_1 and F_2 offspring.

(6) Antigenicity

Antigenicity studies performed include an active systemic anaphylaxis (ASA) test and a homologous passive cutaneous anaphylaxis (PCA) test in guinea pigs, and a test for assessing the potential for IgE antibody production in mice, which all produced negative results.

(7) Other toxicity studies

A phototoxicity study using hairless mice and a phototoxicity study in guinea pigs were conducted and both of which produced negative results.

The photo-Ames test using bacteria to assess the photogenotoxicity was performed, which produced a negative result. On the other hand, the photo-chromosome aberration test in cultured mammalian cells showed that the clastogenic effect was enhanced by ultraviolet irradiation, but it has been determined that such effect of GRNX is weaker than those of LFLX and CPFX.

For joint toxicity, a 1-week repeated oral dose study and a 1-week repeated intravenous dose study in juvenile dogs (3 months old) were performed and it has been determined that the joint toxicity of

GRNX is weaker than those of CPFX and NFLX.

<Outline of the review by the PMDA>

The PMDA asked the applicant to reconsider the potential for coloration in humans, taking account of the following conditions:

Concerning tissue coloration observed in repeated dose studies, the applicant has concluded that such coloration is unlikely to occur in humans based on the results of clinical studies. However, AUC at which coloration occurred in the 1-month oral administration study in dogs was almost equivalent to the AUC at the proposed human clinical dose, and furthermore, GRNX has an affinity for melanin. Therefore, drug concentrations in the skin are predicted to be higher in nonwhite races.

The applicant responded as follows.

Tissue coloration seems related to cumulative AUC and coloration occurred at a mean cumulative AUC of 2850-6272 μg･hr/mL in dogs and at a mean cumulative AUC of 6500-13671 μg･hr/mL in monkeys. In a Japanese phase I clinical study, the mean cumulative AUC following repeated oral administration of 400 mg once daily for 14 days was 1552.6 μg･hr/mL, which was about 1/2 of the minimum cumulative AUC at which coloration occurred in dogs. It has also been suggested that a compound that is presumed to be the coloring substance, is localized to the regions where collagen fibers and elastic fibers are distributed, and the coloring substance is unlikely to be localized to epidermal tissues containing melanin. Thus, when the usual clinical dose (400 mg) is administered for 14 days, tissue coloration is unlikely to occur in humans. However, if cumulative AUC is increased following chronic administration, the possibility of coloration can not be excluded.

The PMDA accepts the applicant's response, but considers that it is necessary to pay an adequate attention to possible tissue coloration in humans following chronic administration because the maximum individual cumulative AUC following repeated oral dose of 400 mg once daily for 14 days in humans was 1736 μg･hr/mL and the minimum individual cumulative AUC at which coloration occurred in dogs was 2475.2 μg･hr/mL, indicating that the ratio of the exposure at which coloration occurred in animals to the exposure after 14-day administration in humans was as small as less than 1.5.

The PMDA has concluded that GRNX may be used, based on the results of non-clinical safety studies, but considers that it is necessary to pay an adequate attention to central nervous toxicity (vomiting etc.), hepatic toxicity, cardiac toxicity (QTc interval prolongation etc.), and tissue coloration etc. in clinical use.

4. Clinical data

(i) Summary of results of clinical pharmacokinetic and pharmacodynamic studies

All doses of the product below are expressed in terms of GRNX, the active ingredient.

<Summary of the submitted data>

For filing this application, in order to assess the pharmacokinetics, safety, and tolerability of GRNX, a single oral dose study at doses from 50 mg to 800 mg (Study AI464001) and a 14-day, multiple oral dose study at doses from 100 mg to 1200 mg (Study AI464002) in healthy non-Japanese subjects were conducted overseas. In Japan, a single oral dose study at doses from 100 mg to 600 mg (Study 61001), and a 7-day multiple oral dose study at 200 mg and a 14-day, multiple oral dose study at 400 mg (Study 61002), in healthy Japanese male subjects, were conducted. In addition, a study to assess the absolute bioavailability of oral GRNX (Study AI464032), ^{14}C-GRNX distribution and excretion study (Study AI464031), and a study to assess the effects of a high-fat meal on the pharmacokinetics in healthy non-Japanese subjects (Study AI464007) and a study to assess the effects of a normal meal on the pharmacokinetics in healthy Japanese subjects (Study 61004) were conducted. With respect to the potential for drug-drug interaction with GRNX, a total of 5 foreign studies using morphine (Study AI464038), digoxin (Study AI464050), an enteral nutrition product (Study AI464055), an antacid (Study AI464057) and omeprazole (Study AI464058) and 1 Japanese study using theophylline (Study 61013) were performed. Furthermore, for the pharmacokinetics of GRNX in special populations, a study using non-Japanese subjects with hepatic impairment (Study AI464052) and a study using non-Japanese subjects with renal impairment (Study AI464047) were performed. For the purpose of supporting the effectiveness of GRNX, tissue and fluid penetration was investigated. In foreign countries, investigations were made on penetration into lung tissues (Study AI464048), bronchial mucosa and alveolar macrophages (Study AI464049), human milk (Study AI464061), hypodermal tissues, nasal mucosa, bile, liver, small intestine, large intestine, etc. (Study AI464037). In Japan, sputum penetration (Study 61007) and tissue penetration in the otorhinolaryngology field (Study 61012) were studied. From a safety standpoint, a phototoxicity study (Study AI464006) and a 28-day multiple oral dose study (Study AI464008) at the proposed clinical dose of 400 mg were performed.

(1) Japanese studies

1) Single oral dose study [Study Number: Study 61001, Study Period: [redacted] 19[redacted] to [redacted] 19[redacted], Evaluation Data]

The pharmacokinetics of the GRNX capsule formulation following single doses of 100, 200, 400, and 600 mg was assessed in 24 healthy Japanese male adults. It was confirmed that the C_{max} and AUC are increased with increasing dose in a dose-dependent manner between 100 mg and 600 mg.

The mean cumulative urinary excretion rates over 0-72 hours at 100, 200, 400, and 600 mg were 52.86, 49.38, 47.31, and 39.92%, respectively.

Pharmacokinetic parameters of GRNX following a single oral dose to healthy Japanese subjects

Dose	C_{max} (μg/mL)	AUC (μg·hr/mL)	$T_{1/2}$ (hr)	CLr (mL/hr)
100 mg	2.09±0.47	21.5±6.3	14.46±3.54	2685.5±774.1
200 mg	4.89±1.53	48.9±15.3	12.65±1.96	2127.8±463.8
400 mg	7.43±1.42	100.7±16.4	12.36±2.21	1961.6±449.5
600 mg	12.34±2.08	165.5±26.3	12.39±1.36	1525.0±429.1

Each dose group contained 6 subjects. Arithmetic mean±SD

2) Multiple dose study [Study Number: Study 61002, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

The pharmacokinetics of the GRNX capsule formulation following 7-day multiple administration of 200 mg or 14-day multiple oral administration of 400 mg was assessed in 12 healthy Japanese male adults. The plasma GRNX concentration reached a steady-state by Day 7.

Pharmacokinetic parameters of the GRNX capsule formulation following multiple oral doses of 200 mg once daily for 7 days or 400 mg once daily for 14 days to healthy Japanese subjects

Dose	C_{max} (μg/mL)	AUC (μg·hr/mL)	$T_{1/2}$ (hr)	CLr (mL/hr)
200 mg (Day 1)	4.84±0.77	46.9±6.9	8.76±0.89	1950±476
200 mg (Day 4)	4.49±0.57	59.5±7.7	9.36±0.50	2250±552
200 mg (Day 7)	5.80±0.91	72.2±8.7	9.33±0.76	1750±205
400 mg (Day 1)	8.36±1.64	98.9±13.4	11.66±1.55	1900±456
400 mg (Day 7)	11.06±1.81	138.2±14.8	9.76±0.60	1950±474
400 mg (Day 14)	10.90±2.08	146.8±16.2	10.67±0.55	1640±487

The 200 mg group contained 5 subjects and the 400 mg group contained 6 subjects. Arithmetic mean±SD

3) Food effect study [Study Number: Study 61004, Study Period: [redacted] 20[redacted], Evaluation Data]

The pharmacokinetics of GRNX following a single oral dose of 400 mg in a fasting state or at 30 minutes after consuming a standard Japanese meal was assessed in 14 healthy Japanese male adults. The following results have shown that the consumption of food does not affect the C_{max} or AUC of GRNX.

The ratios of C_{max} and AUC of GRNX 400 mg administered in a fasting state versus after consuming a Japanese meal

Pharmacokinetic parameter	Fasting (N=14)	After meal (N=14)	Ratio (90% confidence interval)
C_{max} (μg/mL)	7.00	6.13	0.876 (0.807, 0.952)
AUC (μg·hr/mL)	88.2	81.6	0.925 (0.881, 1.04)

Geometric mean

4) Study of penetration into sputum [Study Number: Study 61007, Publication: None, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

The penetration of GRNX into sputum after GRNX 400 mg was administered once daily for 10 days was studied in patients with secondary infection of chronic respiratory disease (chronic bronchitis, diffuse panbronchiolitis, bronchiectasis, emphysema, pulmonary fibrosis, bronchial asthma, old

pulmonary tuberculosis, etc.) (1 male and 4 females). The ratio of GRNX in sputum relative to plasma at 3 hours post-dose when the sputum and plasma concentrations reach their peaks was 0.216-0.948. The ratio of GRNX in sputum relative to plasma in each patient was almost constant up to 24 hours post-dose and its time course was similar to the time course of plasma concentration.

5) Tissue penetration study in the otorhinolaryngology field [Study Number: Study 61012, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

Plasma and tissue GRNX concentrations after a single oral dose of 400 mg were measured in 10 male and 5 female patients with chronic sinusitis, chronic otitis media, chronic tonsillitis, or palate tonsil hypertrophy. The ratio of GRNX in tissue relative to plasma was 1.028±0.386 for paranasal sinus mucosa, 1.038±0.381 for middle ear mucosa, and 1.605±0.244 for palatine tonsil tissue.

6) Co-administration study with theophylline [Study Number: Study 61013, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

The effects of GRNX (400 mg, co-administered from Day 5 of treatment with theophylline) on the pharmacokinetics of steady-state theophylline (400 mg in two divided doses) were investigated in 9 healthy Japanese male adults. The plasma theophylline concentrations were 6.63-8.19 μg/mL on Day 4, 7.87-9.61μg/mL on Day 8, and 8.17-9.60 μg/mL on Day 11 and it was inferred that co-administration of GRNX increases the plasma concentration of theophylline by approximately 20%.

(2) Foreign studies

1) Single dose study [Study Number AI464001, Study Period: [redacted] 19[redacted] to [redacted] 19[redacted], Reference Data]

The pharmacokinetics of GRNX (a capsule formulation) following single oral doses of 50, 100, 200, 400, 600, and 800 mg was assessed in 36 healthy non-Japanese male adults. C_{max} was shown to be increased in an almost dose-dependant manner while AUC was slightly more than proportional to the dose.

Pharmacokinetic parameters of the GRNX capsule formulation following a single oral dose to healthy non-Japanese subjects

Dose	C_{max} (μg/mL)	AUC (μg·hr/mL)	$T_{1/2}$ (hr)	CLr (mL/min)
50 mg	0.60 (11.2%)	6.9 (6.8%)	10.5±2.4	66.8±9.7
100 mg	1.16 (9.2%)	14.3 (9.0%)	11.7±3.2	54.7±9.9
200 mg	2.81 (12.8%)	38.6 (14.3%)	15.4±2.2	42.5±7.7
400 mg	6.15 (32.9%)	83.5 (13.2%)	12.6±1.1	34.2±3.8
600 mg	6.95 (9.6%)	102.8 (16.7%)	13.4±2.7	43.0±8.0
800 mg	10.67 (23.0%)	149.1 (31.4%)	13.2±3.0	27.1±7.8

Each dose group contained 6 subjects. Geometric mean (coefficient of variation %) or arithmetic mean±SD

2) Multiple dose study [Study Number AI464002, Study Period: [redacted] 19[redacted] to [redacted] 19[redacted], Reference Data]

The pharmacokinetics of the GRNX capsule formulation following 14-day, once-daily multiple administration of 100, 200, 400, 800 or 1200 mg were assessed in 30 healthy non-Japanese adults. As a result, it was demonstrated that a steady state was reached by around Day 4 within the dose range up to 400 mg, whereas the mean plasma trough concentration following the administration of a dosage exceeding 400 mg, i.e., a dosage of 800 or 1200 mg, continues to rise over time also after Day 4.

3) Food effect study [Study Number AI464007, Study Period: [redacted] 19[redacted] to [redacted] 19[redacted], Reference Data]

The single oral dose pharmacokinetics of GRNX 400 mg administered in a fasting state as compared to 5 minutes after consuming a high-fat meal was evaluated in healthy non-Japanese adults (13 males, 1 female). The following results have demonstrated that the consumption of food does not affect the C_{max} or AUC of GRNX.

The ratios of C_{max} and AUC of GRNX 400 mg administered in a fasting state versus after consuming a high-fat meal

Pharmacokinetic parameter	Fasting (N=13) *	Immediately after meal (N=13) *	Ratio (90% confidence interval)
C_{max} (μg/mL)	5.76	4.69	0.81 (0.71, 0.94)
AUC (μg·hr/mL)	71.7	63.8	0.89 (0.85, 0.93)

Geometric mean. *Excluding 1 dropout case.

4) Study to assess the pharmacokinetics and metabolism of ^{14}C-labeled GRNX [Study Number AI464031, Study Period: [redacted] 20[redacted], Evaluation Data]

After ^{14}C-labelled GRNX 600 mg was orally administered to 8 healthy non-Japanese male adults, the pharmacokinetics of plasma GRNX and the radioactivity were investigated up to 168 hours post-dose. 41.8% of the administered radioactivity was excreted in the urine and 45.4% of the administered radioactivity was excreted in the feces. As urinary metabolites, a glucuronide conjugate of GRNX (M6) (3%) and a sulfate conjugate of GRNX (M1) (2%) were detected. M1 was also detected in plasma as a trace metabolite. In the feces, 34% was excreted as the unchanged drug and 55% was excreted as M1 (major metabolite). M5 (oxidative metabolite) was not detected in subjects administered ^{14}C-labelled GRNX. M2 and M3, which were detected in animals in non-clinical studies, were not detected in this study.

5) Pharmacokinetic study in subjects with hepatic impairment [Study Number AI464052, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

The pharmacokinetics of GRNX following a single oral dose of 600 mg was evaluated in 14 non-Japanese subjects with mild to severe hepatic impairment and 6 subjects with normal hepatic function (13 males, 7 females). C_{max} declined in the group of subjects with moderate or severe hepatic impairment, whereas there were no significant differences in AUC according to the severity of hepatic

impairment.

C_{max}, AUC, and $T_{1/2}$ following a single oral dose of GRNX 600 mg in subjects with hepatic impairment versus subjects with normal hepatic function

Pharmacokinetic parameter	Mild (n=5)*	Moderate (n=6)	Severe (n=2)	Normal hepatic function (n=6)
C_{max} (μg/mL)	9.8 (21.1%)	8.3 (17.5%)	7.0 (1.4%)	11.0 (29.0%)
AUC (μg·hr/mL)	113.9 (16.5%)	108.6 (14.1%)	113.9 (37.1%)	113.0 (25.8%)
$T_{1/2}$ (hr)	16.7±6.2	20.2±6.8	16.3±2.6	11.8±1.5

Geometric mean (coefficient of variation %) or arithmetic mean±SD. *Excluding 1 subject with an outlier.

6) Pharmacokinetic study in subjects with renal impairment [Study Number AI464047, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

The pharmacokinetics of GRNX following a single oral dose of 600 mg was evaluated in 20 non-Japanese subjects with renal impairment not requiring hemodialysis (CL_{cr} <30 mL/min), undergoing hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD) and 6 subjects with normal renal function (15 males, 11 females). In the subjects with renal impairment not requiring dialysis, C_{max} was lowered by approximately 20%, $T_{1/2}$ was prolonged from 14.4±3.3 hours to 26.5±6.9 hours, and AUC was increased by approximately 51%.

C_{max}, AUC, and $T_{1/2}$ following a single oral dose of GRNX 600 mg in subjects with renal impairment not requiring dialysis, subjects with renal impairment undergoing dialysis, and subjects with normal renal function

Pharmacokinetic parameter	Normal renal function CL_{Cr} > 80mL/min	Renal impairment CL_{Cr} < 30mL/min	3 hours before HD session	Immediately after HD session	CAPD
C_{max} (μg/mL)	12.6 (30.3%)	10.1 (37.0%)	6.0 (23.6%)	9.2 (24.0%)	7.1 (26.7%)
AUC (μg·hr/mL)	136.4 (20.1%)	205.4 (36.4%)	138.0 (37.4%)	156.5 (34.6%)	165.0 (27.7%)
$T_{1/2}$ (hr)	14.4±3.3	26.5±6.9	32.7±4.5	24.5±5.0	28.5±6.5

Geometric mean (coefficient of variation %) or arithmetic mean±SD.

7) Study of penetration into lung tissues [Study AI464048, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

Penetration of GRNX into lung parenchyma following a single oral dose of 600 mg was investigated in non-Japanese patients undergoing lung biopsy or lung tissue resection (16 males, 11 females). The GRNX concentration in lung parenchyma reached its peak at 4-6 hours post-dose (15.16 μg/g) and the ratio of GRNX in lung parenchyma relative to plasma (lung parenchyma concentration/plasma concentration) was 1.28 at 2-4 hours post-dose and 2.57 at 4-6 hours post-dose.

8) Study to assess the effects of a cation-containing product [Study Number AI464057, Study Period: [redacted] 20[redacted], Evaluation Data]

The effects of an aluminum hydroxide/magnesium hydroxide combination product on the absorption of GRNX were assessed in healthy non-Japanese adults (12 males, 8 females). After GRNX and an

aluminum hydroxide/magnesium hydroxide combination product were orally co-administered, the C_{max} and AUC of GRNX were decreased by 60.6% and 58%, respectively. The C_{max} and AUC of oral GRNX given 2 hours before the administration of an aluminum hydroxide/magnesium hydroxide combination product were reduced by 3.3% and 11.6%, respectively, as compared with the administration of GRNX alone. The AUC of oral GRNX given 2 or 4 hours after the administration of an aluminum hydroxide/magnesium hydroxide combination product was reduced by 22% and 15.5%, respectively.

9) Study to assess the absolute bioavailability [Study Number AI464032, Study Period: [redacted] 20[redacted], Evaluation Data]

The pharmacokinetics of GRNX following 1-hour continuous intravenous infusion of 600 mg compared with oral administration of 600 mg (the 200 mg tablet + the 400 mg tablet) was evaluated in healthy non-Japanese adults (7 males, 7 females). The absolute bioavailability of oral GRNX was approximately 92%.

(3) Others

1) Formulations used in Japan and overseas

The capsule formulations used in clinical studies were identical for both Japan and foreign countries (the same components/amounts, the same manufacturing process, the same manufacturing site). Meanwhile, for the tablet formulations, the components/amounts and the manufacturing process were the same, but the manufacturing sites were different. Therefore, after the dissolution behavior was confirmed, the tablet formulation was used for Japanese clinical studies. When the pharmacokinetic parameters were compared between a Japanese phase I study using the capsule (61001) and a foreign phase I study using the capsule (AI464001) and between a food effect study using the tablet conducted in Japan (61004) and a food effect study using the tablet conducted in a foreign country (AI464007), the C_{max} and AUC values were higher in Japanese subjects compared to non-Japanese subjects in both comparisons. However, it was confirmed that the C_{max} and AUC were similar when adjustments were made for body weight, and it was determined that the tablet formulations manufactured in Japan and overseas used in clinical studies are equivalent.

2) Switch from the capsule formulation to the tablet formulation

The capsule formulation was used in Japanese and foreign phase I studies (single dose and multiple dose studies) and the tablet formulation was used in clinical pharmacology studies and phase II or later studies. Thus, the pharmacokinetic parameters were compared between a phase I study (AI464001) and a food effect study using the tablet (AI464007) conducted in a foreign country and between a phase I study (61001) and a food effect study using the tablet (61004) conducted in Japan, which confirmed that the similarity of the pharmacokinetic
s between the capsule and the tablet. The results are presented below.

Single dose pharmacokinetic parameters of the capsule and the tablet in foreign studies

Pharmacokinetic parameter	Formulation and dosage	Geometric mean	Coefficient of variation
C_{max} (μg/mL)	Tablet 400 mg (200 mg×2)	5.76	25.4
	Capsule 400 mg (100 mg×4)	6.15	32.9
AUC (μg・hr/mL)	Tablet 400 mg (200 mg×2)	71.7	24.3
	Capsule 400 mg (100 mg×4)	83.5	13.2

The tablet group contained 13 subjects and the capsule group contained 6 subjects.

Single dose pharmacokinetic parameters of the capsule and the tablet in Japanese studies

Pharmacokinetic parameter	Formulation and dosage	Geometric mean	Ratio estimate	90% confidence interval for the ratio
C_{max} (μg/mL)	Tablet 400 mg (200 mg×2)	7.00	0.96	0.79～1.16
	Capsule 400 mg (100 mg×4)	7.31		
AUC (μg・hr/mL)	Tablet 400 mg (200 mg×2)	88.22	0.89	0.75～1.04
	Capsule 400 mg (100 mg×4)	99.54		

The tablet group contained 14 subjects and the capsule group contained 6 subjects.

Based on the above, since there were no major differences in bioavailability between the two formulations used in clinical studies and it was confirmed that the C_{max} and AUC following a single dose of GRNX were similar between Japanese and non-Japanese subjects when adjusted for body weight, the applicant has concluded that foreign clinical data can be used for regulatory submission in Japan. [See (ii) <Outline of the review by the PMDA> (1) “Submission data package”]

3) Population pharmacokinetic analysis

Based on Study 61001 (the number of subjects: 24, the number of samples: 382), Study 61002 (the number of subjects: 11, the number of samples: 502), and Study 61004 (the number of subjects: 14, the number of samples: 437), and a phase II study in patients with respiratory tract infections (61003; the number of patients: 55, the number of samples: 75) and a phase III study (61006; the number of subjects: 133, the number of samples: 346), which were conducted in Japan, the pharmacokinetics of GRNX in Japanese subjects were evaluated by population pharmacokinetic analysis. As a result, it was shown that CL/F was dependent on CL_{Cr} and body weight and that the volume of distribution (Vd) was dependent on body weight and gender. Although CL/F was decreased in a CL_{Cr}-dependent manner, and AUC and C_{max} were increased, when subjects were subgrouped by renal function and gender, it was considered that an increase in the exposure to GRNX associated with decreased renal function should be within a range where the safety has been confirmed as long as the severity of renal impairment is mild to moderate. Higher C_{max} values in women than in men were considered to be due to body weight differences between men and women, which affected the volume of distribution.

<Outline of the review by the PMDA>

With respect to the dosage for low-body-weight patients with severe renal impairment who are not undergoing dialysis etc., the PMDA asked for the applicant's view on the necessity of including a dose reduction rule instead of leaving it to the doctor's discretion, based on the findings that the pharmacokinetics of GRNX is affected by body weight, that AUC is increased by 51% in patients with severe renal impairment who are not undergoing dialysis (CL_{Cr}<30 mL/min) (Study AI464047), and that the efficacy of GRNX 200 mg has been confirmed in a Japanese phase II clinical study.

The applicant responded as follows.

The following investigation was conducted in order to determine the necessity of dose reduction in low-body-weight (<40 kg) patients with severe renal impairment who are not undergoing dialysis etc. (CL_{Cr}<30 mL/min).

a. Relationship between AUC and the occurrence of adverse events

In Study 61006 (PK/PD study in patients with secondary infection of chronic respiratory disease), the mean total AUC following the administration of GRNX 400 mg to 11 Japanese patients with low body weight was 145.0 μg・hr/mL (Range: 111-181 μg・hr/mL). Assuming that the mean total AUC in patients with low body weight (145.0 μg・hr/mL) is increased by 51% with the presence of severe renal impairment, it was estimated that the mean total AUC in low-body-weight patients with severe renal impairment reaches 219.0 μg・hr/mL. Thus, the occurrence of adverse events in Japanese patients with a total AUC exceeding 200 μg・hr/mL was surveyed. As a result, 5 out of 131 subjects in the PK analysis population had a total AUC exceeding 200 μg・hr/ml (201-232 μg・hr/mL) and adverse events occurred in 4 out of the 5 subjects. All of the adverse events reported were mild in severity and none of them were specific for these subjects.

b. Relationship between body weight and the occurrence of adverse events

Across all Japanese studies, 23 associated symptoms were reported in 11 patients in a subgroup with a body weight <40 kg (34 patients), but the incidence was not higher as compared with those with a body weight ≥40kg and there were no severe associated symptoms. Abnormal laboratory changes were reported by 17 patients (21 events), but the incidence of abnormal laboratory changes was not increased as compared with those with a body weight ≥40 kg and there were also no laboratory changes specific to low-body-weight patients.

c. Occurrence of adverse events by renal function test values

CL_{Cr} was calculated using the patient's body weight, age, and serum C_{Cr} and patients were classified into normal renal function (>80 mL/min), mild renal function abnormalities (50-80 mL/min), moderate renal function abnormalities (30-50 mL/min), and severe renal function abnormalities (≤30 mL/min). Then, the relationship between the renal function and adverse events was assessed. Logistic regression analysis was performed for the incidence of associated symptoms and the incidence of

abnormal laboratory changes by CL_{Cr} across all Japanese studies. As a result, creatinine clearance was not correlated with either incidence. Even when the 31 subjects treated with 200 mg in Study 61003 were excluded, the same results were obtained.

d. Dose reduction for low-body-weight patients with severe renal impairment who are not undergoing dialysis etc.

i) Based on Study 61001 data, the mean total AUC following multiple administration of GRNX 400 mg to Japanese low-body-weight patients with severe renal impairment was estimated at 219.0 μg・hr/mL. Five patients had a total AUC exceeding 200 μg・hr/mL and the associated symptoms and abnormal laboratory changes reported were all mild in severity, but the incidence was 60.0% (3/5) for both associated symptoms and abnormal laboratory changes, which was higher than those in low-body-weight patients or patients with a $CL_{Cr} \leq 30$ mL/min across all studies. The results are as shown below.

Incidence of adverse events in different patient subgroups

	Patients with total AUC >200 μg・hr/mL (Study 61006)	Low-body-weight patients (<40 kg) (All studies)	Patients with $CL_{Cr} \leq 30$ mL/min (All studies)
Incidence of associated symptoms	60.0% (3/5)	32.4% (11/34)	35.7% (5/14)
Incidence of abnormal laboratory changes	60.0% (3/5)	32.4% (11/34)	42.9% (6/14)

ii) Following multiple administration of GRNX 400 mg to low-body-weight patients (11 patients) in Study 61006, the lowest free AUC value reported was 28 μg・hr/mL (Case Number 603101), and the free AUC at a reduced dose of 200 mg was estimated at 14 μg・hr/mL. GRNX has been shown to produce an efficacy rate of at least 90% at a free AUC/MIC ratio of ≥30-50 and the MIC required to achieve it was calculated to be 0.20-0.39 μg/mL. Referring to this result, the MIC required to achieve a free AUC/MIC ratio of at least 50 when reducing the dose from 400 mg to 200 mg in low-body-weight patients with severe renal impairment was calculated. As a result, it was found that even at a reduced dose of 200 mg, 95.5% of the pathogens of respiratory tract infections can be covered and it was considered that a good efficacy rate can be expected.

"Precautions of Dosage and Administration" in the proposed package insert indicates that the dose may be reduced for low-body-weight patients with severe renal impairment who are not undergoing dialysis etc. at the doctor's discretion, because it was judged that a good efficacy rate can be expected even at 200 mg. However, although the mean total AUC was estimated at 219 μg・hr/mL in low-body-weight patients with severe renal impairment, and the adverse events reported by subjects with a total AUC ≥200 μg・hr/mL in Study 61006 were mild in severity and none of them were specific for these subjects, given that (a) the incidence of adverse events (4/5 subjects) tends to be higher compared with low-body-weight patients or patients with a $CL_{Cr} \leq 30$ mL/min across all studies and (b) according to AUC/MIC analysis, the same level of efficacy as 400 mg can be expected even at a reduced dose of 200 mg, it is considered that the dose of GRNX can be reduced to 200 mg for all

low-body-weight patients with severe renal impairment.

Based on the occurrence of adverse events in Study 61006, the PMDA accepted the applicant's view that the dose of GRNX can be reduced to 200 mg, which is expected to produce adequate efficacy, for all low-body-weight (<40kg) patients with severe renal impairment who are not undergoing dialysis etc. (CL_{Cr} <30 mL/min). Concerning the recommended dose reduction for all of these patients, it is necessary to provide information on dose adjustment by, for example, including the information in the package insert. [See (ii) <Outline of the review by the PMDA> (6) Dosage and administration]

The PMDA asked the applicant to investigate whether the background factors of a patient with an outlier who was excluded from the pharmacokinetic analysis (1 case, AI464052-1-5) in a pharmacokinetic study involving subjects with hepatic impairment (Study AI464052) are different from those of other patients in the same group and discuss its results.

The applicant responded as follows.
Study AI464052 is a foreign clinical study to assess the pharmacokinetics and safety of a single dose of GRNX in subjects with hepatic impairment. The subjects were divided into 4 groups according to their hepatic function (mild hepatic impairment, moderate hepatic impairment, severe hepatic impairment, and healthy subjects as a control group) and the effects of hepatic impairment on the pharmacokinetics of GRNX were assessed by comparing the pharmacokinetics following a single oral dose of 600 mg between patients with hepatic impairment and healthy subjects. In this study, AI464052-1-5 had mild hepatic impairment and the pharmacokinetic parameters of individual patients in this group are as shown below.

Pharmacokinetic parameters in patients with mild hepatic impairment

Patient No.	C_{max} (μg/mL)	AUC(INF) (μg・hr/mL)	t_{max} (hr)	$t_{1/2}$ (hr)	UR (%)	CLr (mL/min)
AI464052-1-1	10.8	123.2	0.75	15.3	31.6	25.8
AI464052-1-2	13.0	135.6	0.75	18.6	20.9	15.5
AI464052-1-3	7.5	85.9	2.00	12.7	22.1	25.8
AI464052-1-4	9.6	108.6	1.00	10.5	8.3	7.7
AI464052-1-5	10.7	267.0	1.33	21.1	11.9	4.5
AI464052-1-6	8.8	123.3	3.00	26.4	14.5	11.8
Mean (SD)	10.1 (1.9)	140.6 (64.2)	1.47 (0.88)	17.4 (5.8)	18.2 (8.4)	15.2 (9.0)

In order to consider why AI46052-1-5 had an AUC value far from the average of this group, the following points were evaluated.

a. Demographic factors

AI464052-1-5 had a baseline creatinine clearance (CL_{Cr}) of 48.5 mL/min, which was lower compared with other patients in this group (the mean±SD for patients with mild hepatic impairment was 75.0±21.9 mL/min).

b. Severity of hepatic impairment

AI464052-1-5 had a higher total bilirubin (1.6) relative to the normal range (0-1.3), but the albumin and prothrombin values were normal (4.1 and 10.3, respectively).

c. Liver and renal function test values

AI464052-1-5's baseline liver and renal function test values were normal except for total bilirubin.

d. Discussion

The pharmacokinetic parameters and CL_{Cr} in patients with moderate or severe hepatic impairment are presented below.

Pharmacokinetic parameters in patients with moderate or severe hepatic impairment

Severity	Patient No.	C_{max} (μg/mL)	AUC (INF) (μg・hr/mL)	%UR	CLr (mL/min)	CL_{Cr}* (mL/min)
Moderate	AI464052-7	7.3	96.0	14.5	15.3	110.2
	AI464052-8	7.1	98.3	27.7	28.5	98.0
	AI464052-9	8.6	105.0	32.7	31.2	105.8
	AI464052-10	9.7	120.9	24.1	20.1	58.2
	AI464052-11	7.3	101.5	32.4	32.1	125.2
	AI464052-12	10.7	135.2	8.1	6.1	72.4
	Mean	8.4 (1.5)	109.5 (15.4)	23.3 (10.0)	22.2 (10.3)	95.0 (25.0)
Severe	AI464052-13	7.0	149.0	24.8	16.8	103.0
	AI464052-14	7.1	87.0	15.0	17.3	99.8
	Mean	7.0 (0.1)	118.0 (43.8)	19.9 (6.9)	17.1 (0.4)	101.4 (2.3)

CL_{Cr}*: Values before the administration of the investigational drug.

Patients with mild, moderate, or severe hepatic impairment had similar AUC values regardless of the severity of hepatic impairment except for AI464052-1-5 with mild hepatic impairment. Patients with a CL_{Cr} >80 mL/min had an AUC of 85.9-149.0 μg・hr/mL, those with a CL_{Cr} >50 and ≤80 mL/min had an AUC of 123.2-135.6 μg・hr/mL, and those with a CL_{Cr} >30 and ≤50 mL/min had an AUC of 267.0 μg・hr/mL, showing that AUC was increased with a decrease in CL_{Cr}. It is known that the blood half life is prolonged and the AUC is increased by 51% in patients with severe renal impairment who have a CL_{Cr} <30 mL/min (Study AI464047), and in the case of AI464052-1-5, a low renal clearance (4.5 mL/min) in addition to mild hepatic impairment seems associated with increased AUC.

The PMDA accepted the applicant's response that dose adjustment is unnecessary when GRNX alone is administered to patients with hepatic impairment (mild to severe) or renal impairment (including severe renal impairment not requiring dialysis (CL_{Cr}<30mL/min)) (Study AI464052 and Study AI464047). However, based on the finding that a patient with a low creatinine clearance in addition to mild hepatic impairment (AI464052-1-5) had an AUC outside the variation range of the pharmacokinetics in healthy adults, it should be necessary to advise caution for patients with hepatic impairment and a low creatinine clearance, including dose adjustment, due to concerns about an increase in the exposure.

The PMDA asked the applicant to explain the effects of co-administration with theophylline on the efficacy of GRNX since there was a concern about decreases in C_{max} and AUC of GRNX after the co-administration of GRNX 400 mg and theophylline 400 mg compared to GRNX 400 mg alone.

The applicant responded as follows.
The capsule formulation (administered in a fasting state) was used in GRNX 400 mg multiple dose study (Study 61002) and the tablet formulation (administered after a meal) was used in a co-administration study with theophylline (Study 61013). Although it has been confirmed that the pharmacokinetic parameters are similar between Study 61001 using the capsule and Study 61004 using the tablet, the C_{max} and AUC of the tablet have been found to be slightly lower than those of the capsule. In addition, although Study 61004 has concluded that the pharmacokinetics of oral GRNX is not affected by food, fed C_{max} and AUC were decreased by about 12% and about 7%, respectively, compared with fasted C_{max} and AUC. Therefore, higher plasma GRNX concentrations over time in Study 61002 compared to Study 61013 were possibly associated with the different formulations and the food effect. AUC_{0-24} reflecting the efficacy of GRNX was not lowered on Day 11 in Study 61013 compared to that on Day 7 in Study 61002. Based on the above, differences in plasma GRNX concentrations over time between Study 61002 and Study 61013 should be the consequences of the different dosing conditions between the two studies and it is presumed that there are no effects of concomitant theophylline on the efficacy of GRNX.

The PMDA accepted the applicant's response, considering that the co-administration of GRNX and theophylline is unlikely to affect the efficacy of GRNX since the AUC considered correlated with the therapeutic effects of GRNX was similar with or without theophylline, regardless of the dosing condition.

(ii) Summary of clinical efficacy and safety
All doses of the product below are expressed in terms of GRNX, the active ingredient.

<Outline of the submitted data>
As efficacy and safety evaluation data, 13 Japanese studies (Phase I: 2 studies, clinical pharmacology: 4 studies, Phase II: 1 study, Phase III: 6 studies) and 25 foreign studies (Phase I/clinical pharmacology: 14 studies, Phase II: 4 studies, Phase III: 7 studies) were submitted. In addition, as efficacy and safety reference data, 22 foreign studies (Phase I/clinical pharmacology: 13 studies, Phase III: 9 studies) were submitted.

Among adverse events reported in Japanese and foreign clinical studies, those for which a causal relationship to GRNX could not be denied were classified as adverse drug reactions.

Also, among abnormal laboratory changes observed in Japanese clinical studies, those for which a

causal relationship to the drug could not be denied were classified as adverse drug reactions. Concerning abnormal laboratory changes reported in foreign clinical studies, causality assessment was not performed.

As the 47 foreign clinical studies (Evaluation Data: 25 studies, Reference Data: 22 studies) were used for safety assessment, the summary of individual studies mainly describes the safety. The incidence of laboratory abnormalities in foreign clinical studies was calculated, using a population with normal baseline values for each laboratory parameter.

(1) Japanese phase I studies

1) Single oral dose study [Study Number: Study 61001, Publication: None, Study Period: [redacted] 19[redacted] to [redacted] 19[redacted], Evaluation Data]

A randomized, double-blind, placebo-controlled study was conducted at a single study site in Japan in order to evaluate the pharmacokinetics, safety and tolerability of a single dose of GRNX in healthy Japanese male adults (6 subjects in each GRNX group, 2 subjects in each placebo group, 32 subjects in total). 100, 200, 400 or 600 mg of GRNX was administered once daily. [See "(i) Summary of results of clinical pharmacokinetic and pharmacodynamic studies" for the pharmacokinetics]

All of 32 treated subjects (24 subjects treated with GRNX, 8 subjects treated with placebo) were included in the safety analysis.

Eight adverse events were reported by 5/24 subjects treated with GRNX (20.8%): somnolence in 1 subject in the 100 mg group, 4 events of headache in 1 subject and nausea in 1 subject in the 400 mg group, and somnolence in 2 subjects in the 600 mg group. One event of postural dizziness was reported by 1/8 subjects treated with placebo (12.5%). One adverse drug reaction occurred in 1/24 subjects treated with GRNX (4.2%), which was 1 event of nausea in the GRNX 400 mg group. One abnormal laboratory change occurred in 1/24 subjects treated with GRNX (4.2%), which was "white blood cell count decreased" in the 100 mg group and was classified as an adverse drug reaction. There were no deaths, serious adverse events, other significant adverse events, or discontinuations of GRNX due to adverse events.

Regarding electrocardiography, QTc was assessed, using the Bazett's and Fridericia's correction formulae. By either correction formula, no subjects had QTc interval prolongations to values >450 msec after the administration of GRNX during the treatment period. Using the Bazett's formula, QTc interval increases from baseline >60 msec were noted in 1 subject each in the 100 mg, 200 mg, and 600 mg groups (100 mg group: 344 msec at baseline → 415 msec at 4 hours post-dose, 200 mg group: 369 msec at baseline → 431 msec at 12 hours post-dose, 600 mg group: 333 msec at baseline → 396 msec at 72 hours post-dose), and all of which occurred after 2 hours post-dose, which corresponds to t_{max}. Using the Fridericia's formula, no subjects had QTc interval increases from baseline >60 msec. By either correction formula, none of the subjects in the 400 mg group had

borderline values (31-60 msec). QTc interval increases from 1 hour pre-dose (Bazett's formula) were >60 msec post-dose in 1 subject each in the 100 mg, 200 mg, and 600 mg group. Although their QTc interval increases from 1 hour pre-dose were 71 msec, 62 msec, and 63 msec, respectively, their QTc intervals were 415 msec, 410 msec, and 396 msec, respectively, which were all within the normal range.

2) Multiple dose study [Study Number: Study 61002, Publication: None, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

A randomized, double-blind, placebo-controlled study in 16 healthy Japanese male adults was conducted at a single study site in Japan in order to evaluate the pharmacokinetics, safety and tolerability of multiple doses of GRNX (Step 1: 6 subjects in the GRNX group, 2 subjects in the placebo group, Step 2: 6 subjects in the GRNX group, 2 subjects in the placebo group). After subjects received multiple doses of GRNX 200 mg or placebo once daily for 7 days and the safety of GRNX 200 mg was confirmed in Step 1, multiple doses of GRNX 400 mg or placebo were to be administered once daily for 14 days in Step 2. Randomization was performed for each step. [See "(i) Summary of results of clinical pharmacokinetic and pharmacodynamic studies" for the pharmacokinetics]

Although all of 16 treated subjects (12 subjects treated with GRNX, 4 subjects treated with placebo) were included in the safety analysis, as 1 subject in the GRNX group for Step 1 requested to be withdrawn from the study before the 2nd day of treatment, GRNX was discontinued.

Four adverse events occurred in 1/6 subjects (16.7%) in the GRNX group for Step 1, including headache (2 events), nausea (1 event), and acute tonsillitis (1 event), and 2 adverse events occurred in 2/6 subjects (33.3%) in the GRNX group for Step 2 (headache in 1 subject, loose stools in 1 subject). In the placebo groups, 1/4 subjects (25.0%) experienced 1 adverse event of somnolence. Three adverse drug reactions occurred in 1/6 subjects (16.7%) in the GRNX group for Step 1 (headache and nausea), whereas there were no adverse drug reactions in the GRNX group for Step 2. Two abnormal laboratory changes were observed in 1/6 subjects (16.7%) in the GRNX group for Step 2 and both ALT increased and AST increased were classified as adverse drug reactions. The severity of ALT increased was rated as moderate. There were no deaths, serious adverse events, other significant adverse events, or discontinuations of GRNX due to adverse events.

Regarding electrocardiography, although 1 subject in the 200 mg group had a QTc interval prolongation to >450 msec (Bazett's formula) during the treatment period (413 msec at baseline → 453 msec at 6 hours post-dose on Day 0), which occurred after t_{max}. No subjects had QTc interval prolongations to >450 msec (Fridericia's formula). QTc interval increases from baseline >60 msec (Bazett's formula) were noted in 1 subject each in the 200 mg and 400 mg groups (200 mg group: 346 msec at baseline → 408 msec at 72 hours post-dose on Day 6, 400 mg group: 311 msec at baseline → 398 msec at 2 hours post-dose on Day 9, 375 msec at 6 hours post-dose on Day 13, 380 msec at 12 hours post-dose on Day 13, 378 msec at 48 hours post-dose on Day 13, 378 msec at 72 hours

post-dose on Day 13). QTc interval increases from baseline >60 msec (Fridericia's formula) were observed in 2 subjects who were the same subjects with QTcB interval increases from baseline >60 msec. These two subjects had no QTc prolongation from the start of treatment until Day 5 and developed prolongations after Day 6. One subject in the 400 mg group had borderline values with respect to change from baseline in QTc interval according to the Fridericia's formula, which were negative when the Bazett's formula was used.

Blood pressure was decreased by about 10-15 mmHg on the 2nd to the 4th days of treatment with GRNX, but tended to return to baseline levels thereafter. None of the subjects reported oral mucosal coloration.

(2) Japanese clinical pharmacology studies

1) Food effect study [Study Number: Study 61004, Publication: None, Study Period: [redacted] 20[redacted], Evaluation Data]

An open-label, randomized, crossover study in 14 healthy Japanese male adults was conducted at a single study site in Japan in order to assess the effects of food on the pharmacokinetics of GRNX and confirm the safety. This was a two-arm, two-period, crossover study and a single dose of GRNX 400 mg was to be administered in the fasting state and after a meal. A 6-day washout period was included between the crossover phases [See "(i) Summary of results of clinical pharmacokinetic and pharmacodynamic studies" for the pharmacokinetics]

All of 14 treated subjects were included in the safety analysis population.

Twenty nine adverse events were reported by 5/14 subjects (35.7%), of which the main events were headache, dizziness, cough, rhinorrhoea, abdominal discomfort, and abdominal tenderness (2 cases each, 14.3%). Twelve adverse drug reactions were reported by 3/14 subjects (21.4%) and the main events were dizziness, abdominal discomfort, and abdominal tenderness (2 cases each, 14.3%). Seventeen abnormal laboratory changes occurred in 9/14 subjects (64.3%), of which the main events were lymphocyte count decreased, neutrophil count increased, white blood cell count increased, and protein urine present (2 cases each, 14.3%).

The incidence of adverse events was 3/14 subjects (21.4%) with 18 events after a meal and 4/14 subjects (28.6%) with 11 events under a fasting state.

There were no deaths, serious adverse events, other significant adverse events, or discontinuations of GRNX due to adverse events.

2) Study of penetration into sputum [Study Number: Study 61007, Publication: None, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

An open-label, uncontrolled study in 5 patients with secondary infection of chronic respiratory disease

was conducted at 5 study sites in Japan in order to assess GRNX penetration into sputum after the administration of 400 mg once daily and the efficacy, safety, and bacteriological efficacy of 10-day administration of GRNX.

All of 5 subjects treated with GRNX were included in the Full Analysis Set (hereinafter referred to as FAS) and were included in the efficacy and safety analysis. Four subjects excluding 1 subject with no pathogen isolated were included in the assessment of bacteriological efficacy [See "(i) Summary of results of clinical pharmacokinetic and pharmacodynamic studies" for the pharmacokinetics].

A clinical response (efficacy rate) [assessed based on the criteria recommended by the Japanese Society of Chemotherapy "Clinical evaluation methods for new antimicrobial agents to treat respiratory tract infections (draft)"] was obtained in 3/5 subjects on the 3rd day of treatment, at the end of treatment, and 7 days after the end of treatment. Among the two ineffective cases, one case was a patient with diffuse panbronchiolitis and *P.aeruginosa* (MIC 0.78 μg/mL) was detected, but this patient had repeatedly developed secondary infection of diffuse panbronchiolitis before enrollment into this study. The other case was a patient with old pulmonary tuberculosis and no pathogen was isolated/fixed.

Regarding the safety, 2 abnormal laboratory changes were reported by 2/5 subjects (blood glucose decreased and ALT increased, one case each) and both of which were classified as adverse drug reactions. There were no deaths, serious adverse events, significant adverse events, or discontinuations of GRNX due to adverse events.

3) Tissue penetration study in the otorhinolaryngology field [Study Number: Study 61012, Publication: None, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

An open-label, uncontrolled study in 15 patients undergoing surgery (5 cases each for paranasal sinus mucosa, middle ear mucosa, and palatine tonsil tissue) was conducted at 3 study sites in Japan in order to assess the penetration into paranasal sinus mucosa, middle ear mucosa, and palatine tonsil tissue and the safety of GRNX following a single oral dose of 400 mg before surgery.

All of 15 subjects treated with GRNX were included in the safety analysis. [See "(i) Summary of results of clinical pharmacokinetic and pharmacodynamic studies" for the pharmacokinetics]

Two adverse events were reported by 2/15 subjects (13.3%) (headache and chest pain, one case each) and there were no adverse drug reactions. There were no deaths, serious adverse events, significant adverse events, or discontinuations of GRNX due to adverse events.

4) Co-administration study with theophylline [Study Number: Study 61013, Publication: None, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

An open-label, uncontrolled study in 9 healthy Japanese male adults was conducted at a single study

site in Japan in order to assess the safety of co-administration of GRNX with theophylline and its effects on theophylline concentrations.

Theophylline (200 mg twice daily) was to be orally administered from Day 1 to Day 4 and then theophylline and GRNX (400 mg once daily) were to be orally co-administered from Day 5 to Day 11.

All of 9 subjects treated with GRNX were included in the safety analysis. [See "(i) Summary of results of clinical pharmacokinetic and pharmacodynamic studies" for the pharmacokinetics]

Six adverse events occurred in 4/9 subjects, which include 3 events of headache, 1 event of abdominal pain, and 2 events of diarrhoea, and among which, abdominal pain and diarrhoea were classified as adverse drug reactions. One abnormal laboratory change observed was "blood bilirubin increased" in 1/9 subjects. There were no clinically relevant abnormal changes or abnormal findings in vital signs or ECGs. There were no serious adverse events or adverse drug reactions associated with co-administration of GRNX with theophylline. There were no deaths, serious adverse events, other significant adverse events, or discontinuations of GRNX due to adverse events.

(3) Japanese phase II and phase III studies

1) Japanese phase II study [Study Number: Study 61003, Publication: None, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

An open-label, uncontrolled study was conducted at 26 study sites in Japan in order to evaluate the safety and efficacy of GRNX in patients with mild to moderate pneumonia (including mycoplasmal pneumonia and chlamydial pneumonia) or secondary infection (or acute exacerbation) of chronic respiratory disease (chronic bronchitis, diffuse panbronchiolitis, bronchiectasis, emphysema, pulmonary fibrosis, bronchial asthma, old pulmonary tuberculosis, etc.) (Target number of cases: 30 cases for the 200 mg group, 30 cases for the 400 mg group, Total 60 cases).

The 200 mg group was orally administered GRNX 200 mg once daily and when there was no safety problem, the 400 mg group was to be orally administered GRNX 400 mg once daily. The duration of treatment was at least 7 days and up to 14 days.

All of 62 subjects treated with GRNX (31 subjects in the 200 mg group, 31 subjects in the 400 mg group) were included in the safety analysis. Fifty-nine subjects excluding 3 subjects with diseases other than the target diseases (30 subjects in the 200 mg group, 29 subjects in the 400 mg group) were included in the FAS, and 49 subjects after excluding 10 subjects with protocol violations as to the exclusion criteria or concomitant medications from the FAS (25 subjects in the 200 mg group, 24 subjects in the 400 mg group) were included in the Per Protocol Set (hereinafter referred to as PPS) and in the efficacy analysis. 26 subjects after excluding 23 subjects with no presumptive pathogen identified from the PPS (16 subjects in the 200 mg group, 10 subjects in the 400 mg group) were included in the assessment of bacteriological response.

The clinical response rate at the end of treatment (efficacy rate), which was the primary endpoint, [assessed based on the criteria recommended by the Japanese Society of Chemotherapy "Clinical evaluation methods for new antimicrobial agents to treat respiratory tract infections (draft)"] was 96.0% (24/25 subjects, 95% confidence interval: [79.6%, 99.9%]) in the 200 mg group and 87.5% (21/24 subjects, 95% confidence interval: [67.6%, 97.3%]) in the 400 mg group. The efficacy rate 7 days after the end of treatment among 40 subjects excluding 5 subjects with missing data on the clinical response rate 7 days after the end of treatment was 100% (19/19 subjects, 95% confidence interval: [82.4%, 100%]) in the 200 mg group and 94.7% (18/19 subjects, 95% confidence interval: [74.0%, 99.9%]) in the 400 mg group.

Efficacy rate (at the end of treatment)

Diagnosis	Dose (mg)	No. of cases	Clinical response		Efficacy rate (%)	95% confidence interval
			Effective cases	Ineffective cases		
Respiratory tract infection	200	25	24	1	96.0	79.6, 99.9%
	400	24	21	3	87.5	67.6, 97.3%
	Total	49	45	4	91.8	80.4, 97.7%
Pneumonia	200	16	15	1	93.8	69.8, 99.8%
	400	12	10	2	83.3	51.6, 97.9%
	Total	28	25	3	89.3	71.8, 97.7%
Secondary infection of chronic respiratory disease	200	9	9	0	100.0	66.4, 100.0%
	400	12	11	1	91.7	61.5, 99.8%
	Total	21	20	1	95.2	76.2, 99.9%

The bacteriological response was as shown below. Only 1 subject in the 400 mg group was infected with two pathogens and the remaining subjects were all infected with a single pathogen. The detected pathogens were 10 strains of Gram positive bacteria, 16 strains of Gram negative bacteria, and 1 strain of mycoplasma, for a total of 27 strains. The bacterial outcome by pathogen and eradication rate at the end of treatment were 100% (16/16 strains) in the 200 mg group and 72.7% (8/11 strains) in the 400 mg group. The bacteriological response by pathogen at the end of treatment is shown in the following table.

Bacteriological response (Bacterial eradication rate at the end of treatment)

Pathogen	Dose (mg)	Eradication	Persistence	Unknown	Eradication rate (%)
S. aureus	200	1	0	0	[1/1]
	400	0	0	0	
MSSA	200	1	0	0	[1/1]
	400	0	0	0	
S. pneumoniae	200	3	0	0	[3/3]
	400	0	0	0	
PISP	200	1	0	0	[1/1]
	400	0	0	0	
PSSP	200	2	0	0	[2/2]
	400	0	0	0	
S. intermedius	200	0	0	0	
	400	1	0	0	[1/1]
S. constellatus	200	1	0	0	[1/1]
	400	0	0	0	
Total	200	9	0	0	100.0
	400	1	0	0	[1/1]
K. pneumoniae	200	0	0	0	
	400	1	0	0	[1/1]
K. oxytoca	200	1	0	0	[1/1]
	400	0	1	0	[0/1]
P. aeruginosa	200	0	0	0	
	400	1	1	0	[1/2]
H. influenzae	200	3	0	0	[3/3]
	400	4	1	0	[4/5]
BLNAR	200	2	0	0	[2/2]
	400	0	0	0	
M. (*B*) *catarrhalis*	200	0	0	0	
	400	1	0	0	[1/1]
Total	200	6	0	0	100.0
	400	7	3	0	70.0
Mycoplasma	200	1	0	0	[1/1]
	400	0	0	0	
Chlamydia	200	0	0	0	
	400	0	0	0	
Others	200	0	0	0	
	400	0	0	0	
Total	200	16	0	0	100.0
	400	8	3	0	72.7

Eradication rate (%)=Eradicated strains／(Eradicated strains＋Persistent strains)×100
Others: Bacteria and fungi excluding Gram positive and Gram negative bacteria, Mycoplasma, and Chlamydia

With regard to the safety, 19 adverse events occurred in 10/31 subjects (32.3%) in the 200 mg group and adverse events with an incidence of 5% or greater were headache (2/31 subjects, 6.5%) and diarrhoea (2/31 subjects, 6.5%). In the 400 mg group, 17 adverse events occurred in 12/31 subjects (38.7%) and adverse events with an incidence of 5% or greater were bradycardia (2/31 subjects, 6.5%), constipation (2/31 subjects, 6.5%), and diarrhoea (4/31 subjects, 12.9%). Seven adverse drug reactions were reported by 3/31 subjects (9.7%) in the 200 mg group (headache, eye pain, ocular hyperaemia, eyelid oedema, eye pruritus, nasal congestion, and rash, one case each) and 3 adverse drug reactions were reported by 2/31 subjects (6.5%) in the 400 mg group (bradycardia, diarrhoea, and vomiting, one case each). Twenty-two abnormal laboratory changes were observed in 13/30 subjects (43.3%) in the

200 mg group (blood ALP increased (3/30 subjects, 10.0%), eosinophil count increased (2/27 subjects, 7.4%), platelet count increased (2/29 subjects, 6.9%), ALT increased (4/30 subjects, 13.3%), and AST increased (3/30 subjects, 10.0%)). In the 400 mg group, 20 abnormal laboratory changes were observed in 8/31 subjects (25.8%) and adverse events with an incidence of 5% or greater were platelet count increased (2/31 subjects, 6.5%), ALT increased (3/31 subjects, 9.7%), AST increased (2/31 subjects, 6.5%), and γ-GTP increased (3/31 subjects, 9.7%). Eleven abnormal laboratory changes classified as adverse drug reactions were observed in 8/30 subjects (26.7%) in the 200 mg group and those with an incidence of 5% or greater were blood ALP increased (3/30 subjects, 10.0%), ALT increased (3/30 subjects, 10.0%), and AST increased (3/30 subjects, 10.0%). In the 400 mg group, 16 abnormal laboratory changes classified as adverse drug reactions were seen in 6/31 subjects (19.4%) and those with an incidence of 5% or greater were ALT increased (3/31 subjects, 9.7%), AST increased (2/31 subjects, 6.5%), and γ-GTP increased (3/31 subjects, 9.7%).

Serious adverse events reported were pneumonia aggravated in 1 subject and pulmonary tuberculosis aggravated in 1 subject in the 200 mg group, and pneumonia aggravated in 1 subject in the 400 mg group and all of these adverse events were assessed as "unrelated to the drug." Other significant adverse events excluding serious adverse events occurred in 2 subjects (6 events) in the 200 mg group, including ALT increased (unlikely related to the drug), eyelid oedema, eye itching, ocular hyperaemia, nasal congestion, and eye pain (all assessed as probably related to the drug) which led to the discontinuation of GRNX. In the 400 mg group, 8 significant adverse events were reported by 2 subjects, which include increases in AST, ALT, γ-GTP, ALP, total bilirubin, direct bilirubin, and CRP. A prolongation of electrocardiogram QTc interval was reported by 1 subject (assessed as probably related to the drug). There were no deaths.

2) Japanese phase III studies

a. Double-blind study in patients with bacterial pneumonia [Study Number: Study 61005, Publication: None, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

A randomized, double-blind, levofloxacin (LVFX)-controlled study was conducted at 100 study sites in Japan in order to evaluate the efficacy and safety of GRNX in patients with bacterial pneumonia (target number of cases: 130 cases per group, total 260 cases).

GRNX 400 mg was to be orally administered once daily for 10 days in the GRNX group and LVFX 100 mg was to be orally administered three times daily for 10 days in the LVFX group.

All of 253 treated subjects (GRNX group: 135 subjects, LVFX group: 118 subjects) were included in the safety analysis, 232 subjects excluding 21 subjects with diseases other than the target diseases (GRNX group: 123 subjects, LVFX group: 109 subjects) were included in the FAS, and 199 subjects after excluding 33 subjects with protocol violations as to concomitant medications etc. from the FAS (GRNX group: 112 subjects, LVFX group: 87 subjects) were included in the PPS and in the efficacy analysis.

With respect to the background factors, the proportion of subjects without concomitant medications was higher in the GRNX group than in the LVFX group for the PPS (GRNX group: 18.8%, LVFX group: 4.6%, *p*=0.003, Fisher's exact test). Also, the proportion of dyspnoea "－" was lower in the GRNX group than in the LVFX group (GRNX group: 65.2%, LVFX group: 74.7%, *p*=0.123, Wilcoxon test), and the proportion of chest pain "－" was higher in the GRNX group than in the LVFX group (GRNX group: 64.3%, LVFX group: 54.0%, *p*=0.149, Fisher's exact test).

The number of subjects with the presumptive pathogen identified was 59 in the GRNX group and 40 in the LVFX group and of which, 3 subjects each in the GRNX and LVFX groups were infected with multiple pathogens. The most common pathogen isolated among subjects infected with a single pathogen was *S. pneumoniae* in 43 subjects (GRNX group: 24 subjects, LVFX group: 19 subjects) followed by *H. influenzae* in 34 subjects (GRNX group: 25 subjects, LVFX: 9 subjects). Among *S. pneumoniae*, PSSP was most frequently isolated both in the GRNX and LVFX groups and among *H. influenzae* in the GRNX group, BLNAS was most frequently isolated.

The clinical response rate at the end of treatment (efficacy rate), which was the primary endpoint, [assessed based on the criteria recommended by the Japanese Society of Chemotherapy "Clinical evaluation methods for new antimicrobial agents to treat respiratory tract infections (draft)"] was 99.1% (111/112 subjects) in the GRNX group and 94.3% (82/87 subjects) in the LVFX group and the difference between the treatment groups was 4.9% (95% confidence interval: [-0.3%, 10.0%]). Since the lower limit of the 95% confidence interval showed a better value than -10% predefined as the non-inferiority margin, the non-inferiority was confirmed.

The bacteriological response rate at the end of treatment (bacterial eradication rate) was 100% in both groups (GRNX group: 59/59 subjects, LVFX group: 40/40 subjects) and the bacteriological response rate at 7 days after the end of treatment was 100% (50/50 subjects) in the GRNX group and 86.8% (33/38 subjects) in the LVFX group.

Regarding the safety, 93 adverse events occurred in 60/135 subjects (44.4%) in the GRNX group and 97 adverse events in 51/118 subjects (43.2%) in the LVFX group. Adverse events with an incidence of 3% or greater in either group were insomnia (GRNX group: 4/135 subjects <3.0%>, LVFX group: 9/118 subjects <7.6%>), dizziness (4/135 subjects <3.0%> and 4/118 subjects <3.4%>, respectively), headache (5/135 subjects <3.7%> and 9/118 subjects <7.6%>, respectively), pharyngolaryngeal pain (5/135 subjects <3.7%> and 3/118 subjects <2.5%>, respectively), constipation (4/135 subjects <3.0%> and 6/118 subjects <5.1%>, respectively), and diarrhoea (6/135 subjects <4.4%> and 8/118 subjects <6.8%>, respectively). Thirty adverse drug reactions were observed in 21/135 subjects (15.6%) in the GRNX group and 14 adverse drug reactions in 10/118 subjects (8.5%) in the LVFX group and adverse drug reactions with an incidence of 3% or greater in both group were diarrhoea (4/135 subjects <3.0%> and 4/118 subjects <3.4%>, respectively).

One-hundred six abnormal laboratory changes were reported by 56/134 subjects (41.8%) in the GRNX group and 107 abnormal laboratory changes were reported by 57/117 subjects (48.7%) in the LVFX group. Abnormal laboratory changes with an incidence of 3% or greater in either group were blood CK increased (5/129 subjects <3.9%> and 5/114 subjects <4.4%>, respectively), blood LDH increased (4/132 subjects <3.0%> and 1/115 subjects <0.9%>, respectively), blood ALP increased (5/132 subjects <3.8%> and 6/114 subjects <5.3%>, respectively), blood amylase increased (10/133 subjects <7.5%> and 4/114 subjects <3.5%>, respectively), eosinophil count increased (5/131 subjects <3.8%> and 9/115 subjects <7.8%>, respectively), ALT increased (21/132 subjects <15.9%> and 17/115 subjects <14.8%>, respectively), AST increased (18/132 subjects <13.6%> and 13/115 subjects <11.3%>, respectively), blood glucose increased (9/131 subjects <6.9%> and 13/115 subjects <11.3%>, respectively), blood potassium increased (6/131 subjects <4.6%> and 2/115 subjects <1.7%>, respectively), γ-GTP increased (2/132 subjects <1.5%> and 4/115 subjects <3.5%>, respectively), and blood urea increased (1/132 subjects <0.8%> and 4/115 subjects <3.5%>). Fifty-seven abnormal laboratory changes classified as adverse drug reactions were reported in 33/134 subjects (24.6%) in the GRNX group and 39 abnormal laboratory changes classified as adverse drug reactions were reported in 23/117 subjects (19.7%) in the LVFX group. Those with an incidence of 3% or greater were blood amylase increased (8/133 subjects <6.0%> and 2/114 subjects <1.8%>, respectively), ALT increased (14/132 subjects <10.6%> and 10/115 subjects <8.7%>, respectively), AST increased (12/132 subjects <9.1%> and 6/115 subjects <5.2%>, respectively), blood potassium increased (4/131 subjects <3.1%> and 0/115 subjects <0.0%>, respectively), ALP increased (2/132 subjects <1.5%> and 4/114 subjects <3.5%>, respectively), and blood glucose increased (2/131 subjects <1.5%> and 4/115 subjects <3.5%>, respectively).

Adverse events (including abnormal laboratory changes) with an incidence ≥2% higher in the GRNX group than in the LVFX group were haemoptysis, loose stools, blood LDH increased, blood amylase increased, neutrophil count decreased, AST increased, and blood potassium increased and of which, blood amylase increased, neutrophil count decreased, AST increased, and blood potassium increased were classified as adverse drug reactions.

There were two deaths each in the GRNX and LVFX groups. In the GRNX group, 1 subject had acute myocardial infarction (died 9 days after the start of treatment) and 1 subject had lung neoplasm malignant (died about 4 months after the start of treatment). In the LVFX group, 1 subject had obstructive airways disorder (died on Day 10 of treatment) and 1 subject had lung neoplasm malignant (died about 2 months after the start of treatment). All of these deaths were assessed as “unrelated to GRNX or LVFX.”

b. PK/PD study in patients with secondary infection of chronic respiratory disease [Study Number: Study 61006, Publication: None, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

An open-label, uncontrolled study was conducted at 72 study sites in Japan in order to evaluate the

efficacy and safety of GRNX, estimate the AUC of GRNX by PPK analysis, and assess the similarity to foreign clinical data for the AUC/MIC distribution and its relationship with the efficacy rate in patients with secondary infection of chronic respiratory disease (chronic bronchitis, diffuse panbronchiolitis, bronchiectasis, emphysema, pulmonary fibrosis, bronchial asthma, old pulmonary tuberculosis, etc.) (target number of cases of 135).

GRNX 400 mg was to be orally administered once daily and the duration of treatment was 10 days.

The primary endpoint chosen was the clinical response 7 days after the end of treatment (efficacy rate), which was used as the primary endpoint for a foreign clinical study, so as to assess the similarity to foreign clinical data. The secondary endpoints were the efficacy rates on the 3rd day of treatment, at the end of treatment, and 7 days after the end of treatment based on the assessment criteria recommended by the Japanese Society of Chemotherapy.

All of 136 subjects treated with GRNX were included in the safety analysis, 135 subjects excluding 1 subject with a disease other than the target diseases were included in the FAS, and 125 subjects after excluding 2 subjects with protocol violations as to the exclusion criteria, 3 subjects with protocol violations as to concomitant medications/therapies, 3 subjects who failed to complete the treatment period, and 2 subjects who were unevaluable for the primary endpoint from the FAS were included in the PPS and in the efficacy analysis. Seventy subjects after excluding 55 subjects with no pathogen identified from the PPS were included in the assessment of bacteriological response, and 66 subjects excluding 4 subjects for whom susceptibility data was unavailable were included in the PK/PD analysis.

The efficacy rate 7 days after the end of treatment based on the overseas assessment criteria, which was the primary endpoint, was 84.0% (105/125 subjects, 95% confidence interval: [76.4, 89.9%]) and the efficacy rates on the 3rd day of treatment, at the end of treatment, and 7 days after the end of treatment based on the assessment criteria recommended by the Japanese Society of Chemotherapy (the secondary endpoints) were 57.3% (71/124 subjects), 87.8% (108/123 subjects), and 83.7% (103/123 subjects), respectively. The efficacy rate 7 days after the end of treatment based on the overseas assessment criteria by disease was 70.0% (21/30 subjects) for bronchiectasis, 71.4% (10/14 subjects) for old pulmonary tuberculosis, 85.7% (6/7 subjects) for pulmonary fibrosis, 88.9% (16/18 subjects) for bronchial asthma, and 90% or higher for other diseases (chronic bronchitis, diffuse panbronchiolitis, emphysema).

The bacteriological response rate at the end of treatment and 7 days after the end of treatment (bacterial eradication rate) was 90.1% (64/71 strains, 95% confidence interval: [80.7, 95.9%]) and 85.9% (61/71 strains, 95% confidence interval: [75.6, 93.0%]), respectively.

Bacteriological response (bacterial eradication rate at the end of treatment)

Pathogen	No. of strains	Bacterial outcome			Bacterial eradication rate (%)	95% confidence interval
		Eradicated	Persistent	Unknown		
S. aureus (MSSA)	8	7	1	0	87.5	47.3, 99.7%
S. pyogenes	1	1	0	0	[1/1]	
S. pneumoniae (PSSP)	6	5	0	1	[5/5]	
S. pneumoniae (PISP)	5	5	0	0	[5/5]	
S. pneumoniae (PRSP)	3	3	0	0	[3/3]	
Subtotal	23	21	1	1	95.5	77.2, 99.9%
M.(B) catarrhalis	8	8	0	0	100.0	63.1, 100.0%
K. pneumoniae	5	3	1	1	[3/4]	
H. influenzae (BLP)	1	1	0	0	[1/1]	
H. influenzae (BLNAS)	9	9	0	0	100.0	66.4, 100.0%
H. influenzae (BLNAR)	18	16	0	2	100.0	79.4, 100.0%
H. influenzae (Resistance unknown)	2	2	0	0	[2/2]	
H. parainfluenzae	2	2	0	0	[2/2]	
P. aeruginosa	6	1	5	0	16.7	0.4, 64.1%
S. maltophilia	1	1	0	0	[1/1]	
Subtotal	52	43	6	3	87.8	75.2, 95.4%
Total	75	64	7	4	90.1	80.7, 95.9%

Bacterial eradication rate (%)＝Eradicated strains／Eradicated and persistent strains×100

Bacteriological response (Bacterial eradication rate 7 days after the end of treatment)

Pathogen	No. of strains	Bacterial outcome			Bacterial eradication rate (%)	95% confidence interval
		Eradicated	Persistent	Unknown		
S. aureus (MSSA)	8	6	2	0	75.0	34.9, 96.8%
S. pyogenes	1	1	0	0	[1/1]	
S. pneumoniae (PSSP)	6	5	0	1	[5/5]	
S. pneumoniae (PISP)	5	5	0	0	[5/5]	
S. pneumoniae (PRSP)	3	3	0	0	[3/3]	
Subtotal	23	20	2	1	90.9	70.8, 98.9%
M.(B) catarrhalis	8	7	0	1	100.0	59.0, 100.0%
K. pneumoniae	5	3	2	0	[3/5]	
H. influenzae (BLP)	1	1	0	0	[1/1]	
H. influenzae (BLNAS)	9	8	1	0	88.9	51.8, 99.7%
H. influenzae (BLNAR)	18	16	0	2	100.0	79.4, 100.0%
H. influenzae (resistance unknown)	2	2	0	0	[2/2]	
H. parainfluenzae	2	2	0	0	[2/2]	
P. aeruginosa	6	1	5	0	16.7	0.4, 64.1%
S. maltophilia	1	1	0	0	[1/1]	
Subtotal	52	41	8	3	83.7	70.3, 92.7%
Total	75	61	10	4	85.9	75.6, 93.0%

Bacterial eradication rate (%)＝Eradicated strains／Eradicated and persistent strains×100

Eighty-seven adverse events occurred in 47/136 subjects (34.6%) and adverse events with an incidence of 3% or greater were headache (7/136 subjects, 5.1%) and constipation (5/136 subjects, 3.7%). Twenty-six adverse drug reactions were reported by 19/136 subjects (14.0%).

One-hundred eleven abnormal laboratory changes were reported by 60/135 subjects (44.4%) and

abnormal laboratory changes with an incidence of 3% or greater were blood amylase increased (7/130 subjects, 5.4%), eosinophil count increased (8/133 subjects, 6.0%), ALT increased (19/135 subjects, 14.1%), AST increased (20/135 subjects, 14.8%), γ-GTP increased (4/133 subjects, 3.0%), blood glucose increased (13/133 subjects, 9.8%), blood Cr increased (6/133 subjects, 4.5%), and blood potassium increased (4/133 subjects, 3.0%). Forty-nine abnormal laboratory changes classified as adverse drug reactions were reported in 26/135 subjects (19.3%), and those with an incidence of 3% or greater were blood amylase increased (5/130 subjects, 3.8%), ALT increased (13/135 subjects, 9.6%), AST increased (14/135 subjects, 10.4%), and γ-GTP increased (4/133 subjects, 3.0%).

Serious adverse events reported were actinomycosis, CO_2 narcosis, pneumothorax, pulmonary fibrosis, atrial fibrillation, blood pressure decreased, anxiety, and acute cardiac failure in one subject each. As to the causality with GRNX, actinomycosis, CO_2 narcosis, pulmonary fibrosis, atrial fibrillation, anxiety, and acute cardiac failure were assessed as "unrelated" and pneumothorax and blood pressure decreased were assessed as "unlikely to be related."

Two deaths occurred (acute cardiac failure and acute myocardial infarction). Both deaths were assessed as "unrelated to GRNX."

c. Open-label clinical study in patients with lower respiratory tract infections including mycoplasmal pneumonia, chlamydial pneumonia, and acute bronchitis [Study Number: Study 61008, Publication: None, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

An open-label, uncontrolled study was conducted at 51 study sites in Japan in order to evaluate the efficacy and safety of GRNX in patients with lower respiratory tract infections including mycoplasmal pneumonia, chlamydial pneumonia, and acute bronchitis.

GRNX 400 mg was to be orally administered once daily and the duration of treatment was 7-10 days.

All of 144 subjects treated with GRNX (community-acquired pneumonia: 105 subjects, acute bronchitis: 19 subjects, diseases other than the target diseases: 20 subjects) were included in the safety analysis, 124 subjects excluding 20 subjects with diseases other than the target diseases (community-acquired pneumonia: 105 subjects, acute bronchitis: 19 subjects) were included in the FAS, and 102 subjects after excluding 22 subjects with protocol violations as to the inclusion criteria etc. from the FAS (community-acquired pneumonia: 89 subjects, acute bronchitis: 13 subjects) were included in the PPS and in the efficacy analysis. Forty-two subjects after excluding 60 subjects with no pathogen identified by a bacteriological test before treatment from the PPS (community-acquired pneumonia: 37 subjects, acute bronchitis: 5 subjects) were included in the assessment of bacteriological response.

The clinical response rate at the end of treatment (the efficacy rate), which was the primary endpoint, [assessed based on the criteria recommended by the Japanese Society of Chemotherapy "Clinical

evaluation methods for new antimicrobial agents to treat respiratory tract infections (draft)"] was 99.0% (101/102 subjects, 95% confidence interval: [94.7%, 100%]). The efficacy rate was 63.0% (63/100 subjects, 95% confidence interval: [52.8%, 72.4%]) on the 3rd day of treatment and 98.0% (97/99 subjects, 95% confidence interval: [92.9%, 99.8%]) 7 days after the end of treatment. The efficacy rate at the end of treatment by target disease and the bacteriological response at the end of treatment and 7 days after the end of treatment by pathogen are presented below.

Efficacy rate by target disease (at the end of treatment)

Target disease			No. of cases	Clinical response		Efficacy rate (%)	95% confidence interval
				Effective	Ineffective		
Total			102	101	1	99.0	94.7,100.0%
Community-acquired pneumonia			89	88	1	98.9	93.9, 100.0%
	Mycoplasmal pneumonia (including mixed infection)		20	20	0	100.0	83.2, 100.0%
		Mycoplasmal pneumonia	16	16	0	100.0	79.4, 100.0%
		Bacterial pneumonia＋Mycoplasmal pneumonia	1	1	0	[1/1]	
		Mycoplasmal pneumonia＋Chlamydial pneumonia [a)]	3	3	0	[3/3]	
	Chlamydial pneumonia (including mixed infection)		16	15	1	93.8	69.8, 99.8%
		Chlamydial pneumonia	11	10	1	90.9	58.7, 99.8%
		Bacterial pneumonia＋Chlamydial pneumonia	2	2	0	[2/2]	
		Mycoplasmal pneumonia＋Chlamydial pneumonia [a)]	3	3	0	[3/3]	
	Bacterial pneumonia		56	56	0	100.0	93.6, 100.0%
Acute bronchitis			13	13	0	100.0	75.3, 100.0%
	Chlamydial acute bronchitis (including mixed infection)		1	1	0	[1/1]	
		Chlamydial acute bronchitis	1	1	0	[1/1]	
	Bacterial acute bronchitis		12	12	0	100.0	73.5, 100.0%

a): "Mycoplasmal pneumonia＋Chlamydial pneumonia"under "Mycoplasmal pneumonia (including mixed infection)" and "Chlamydial pneumonia (including mixed infection)" was counted as Mycoplasmal pneumonia.

Bacteriological response (bacterial eradication rate at the end of treatment)

Target disease			No. of cases	Bacteriological response					Eradication rate (%)	95% confidence interval
				Eradicated	Decreased	Partially eradicated	Persistent	Unevaluable		
Total			42	32	0	6	0	4	84.2	68.7, 94.0%
Community-acquired pneumonia			37	27	0	6	0	4	81.8	64.5, 93.0%
	Mycoplasmal pneumonia (including mixed infection)		11	6	0	3	0	2	66.7	29.9, 92.5%
		Mycoplasmal pneumonia	7	6	0	0	0	1	100.0	54.1, 100.0%
		Bacterial pneumonia＋Mycoplasmal pneumonia	1	0	0	1	0	0	[0/1]	－
		Mycoplasmal pneumonia ＋ Chlamydial pneumonia*	3	0	0	2	0	1	[0/2]	－
	Chlamydial pneumonia (including mixed infection)		6	0	0	4	0	2	[0/4]	－
		Chlamydial pneumonia	1	0	0	0	0	1	－	－
		Bacterial pneumonia ＋ Chlamydial pneumonia	2	0	0	2	0	0	[0/2]	－
		Mycoplasmal pneumonia ＋ Chlamydial pneumonia*	3	0	0	2	0	1	[0/2]	－
	Bacterial pneumonia		23	21	0	1	0	1	95.5	77.2, 99.9%
Acute bronchitis			5	5	0	0	0	0	[5/5]	－
	Bacterial acute bronchitis		5	5	0	0	0	0	[5/5]	－

Bacterial eradication rate (%)＝ Cases of eradication (presumed eradication)/cases of eradication, decrease, partial eradication, and persistence×100

*: ”Mycoplasmal pneumonia＋Chlamydial pneumonia” under “Mycoplasmal pneumonia (including mixed infection)” and “Chlamydial pneumonia (including mixed infection)” was counted more than once.

Bacteriological response (bacterial eradication rate 7 days after the end of treatment)

Target disease			No. of cases	Bacteriological response					Eradication rate (%)	95% confidence interval
				Eradicated	Decreased	Partially eradicated	Persistent	unevaluable		
Total			42	31	0	5	1	5	83.8	68.0, 93.8%
Community-acquired pneumonia			37	26	0	5	1	5	81.3	63.6, 92.8%
	Mycoplasmal pneumonia (including mixed infection)		11	6	0	3	0	2	66.7	29.9, 92.5%
		Mycoplasmal pneumonia	7	6	0	0	0	1	100.0	54.1, 100.0%
		Bacterial pneumonia + Mycoplasmal pneumonia	1	0	0	1	0	0	[0/1]	－
		Mycoplasmal pneumonia + Chlamydial pneumonia*	3	0	0	2	0	1	[0/2]	－
	Chlamydial pneumonia (including mixed infection)		6	0	0	4	0	2	[0/4]	－
		Chlamydial pneumonia	1	0	0	0	0	1	－	－
		Bacterial pneumonia＋Chlamydial pneumonia	2	0	0	2	0	0	[0/2]	－
		Mycoplasmal pneumonia + Chlamydial pneumonia*	3	0	0	2	0	1	[0/2]	－
	Bacterial pneumonia		23	20	0	0	1	2	95.2	76.2, 99.9%
Acute bronchitis			5	5	0	0	0	0	[5/5]	－
	Bacterial acute bronchitis		5	5	0	0	0	0	[5/5]	－

Bacterial eradication rate (%)＝ Cases of eradication (presumed eradication)/cases of eradication, decrease, partial eradication, and persistence×100

*: "Mycoplasmal pneumonia＋Chlamydial pneumonia" under "Mycoplasmal pneumonia (including mixed infection)" and "Chlamydial pneumonia (including mixed infection)" was counted more than once.

Ninety-two adverse events occurred in 49/144 subjects (34.0%) and adverse events with an incidence of 3% or greater were headache (8/144 subjects, 5.6%) and diarrhoea (11/144 subjects, 7.6%). Twenty-seven adverse drug reactions were observed in 18/144 subjects (12.5%) and adverse drug reactions with an incidence of 3% or greater were diarrhoea (5/144 subjects, 3.5%).

One-hundred forty-one abnormal laboratory changes were reported by 73/143 subjects (51.0%) and abnormal laboratory changes with an incidence of 3% or greater were blood CPK increased (6/140 subjects, 4.3%), blood ALP increased (6/143 subjects, 4.2%), blood amylase increased (6/142 subjects, 4.2%), eosinophil count increased (8/143 subjects, 5.6%), ALT increased (19/143 subjects, 13.3%), AST increased (13/143 subjects, 9.1%), γ-GTP increased (9/142 subjects, 6.3%), blood glucose increased (13/140 subjects, 9.3%), Cr urine increased (7/143 subjects, 4.9%), protein urine present (8/143 subjects, 5.6%), and blood potassium increased (5/142 subjects, 3.5%). Seventy-six abnormal laboratory changes classified as adverse drug reactions were seen in 42/143 subjects (29.4%) and those with an incidence of 3% or greater were blood amylase increased (6/142 subjects, 4.2%), eosinophil count increased (5/143 subjects, 3.5%), ALT increased (15/143 subjects, 10.5%), AST increased (8/143 subjects, 5.6%), γ-GTP increased (7/142 subjects, 4.9%), and protein urine present (5/143 subjects, 3.5%).

Serious adverse events reported were cardiac failure, pneumonia, pulmonary tuberculosis, rash, hepatic mass, and hospitalization (although there was a trend towards improvement in terms of antipyresis and X-ray, the patient was admitted to another hospital due to the patient's strong request) in one subject each. The rash was moderate in severity and was assessed as "possibly related to the drug." Hospitalization was rated as moderate and was assessed as "unrelated to the drug." The remaining events were all severe and were assessed as "unrelated to the drug." Other significant adverse events observed were treatment discontinuation due to adverse events in 2 subjects, hypoglycaemia in 1 subject, and blood pressure decreased in 1 subject. The two discontinued cases were "treatment discontinuation due to influenza" and "treatment discontinuation due to AST (GOT) increased, ALT (GPT) increased, γ-GTP increased, ALP increased, and urine glucose present." One event of γ-GTP increased was severe, and the other events were moderate or mild.

As abnormal changes in ECG, electrocardiogram QT prolonged was reported by 1 subject and was assessed as "unlikely related to the drug." In addition, hypoglycaemia was reported by 1 subject and was assessed as "unrelated to the drug."

d. Open-label clinical study in patients with sinusitis, laryngopharyngitis, or tonsillitis [Study Number: Study 61009, Publication: None, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]
An open-label, uncontrolled study was conducted at 13 study sites in Japan in order to evaluate the efficacy and safety of GRNX in patients with sinusitis, pharyngitis/laryngitis or tonsillitis (peritonsillitis, peritonsillar abscess) (target number of cases: 25 cases for sinusitis, 42 cases for laryngopharyngitis/tonsillitis/peritonsillitis, total 67 cases).

GRNX 400 mg was to be orally administered once daily and the duration of treatment was 10 days.

All of 71 subjects treated with GRNX were included in the safety analysis and in the FAS. Sixty-six subjects after excluding 2 subjects with protocol violations as to concomitant medications/therapies and 3 subjects with incomplete observations in terms of the items or timing/duration (unevaluable for the primary endpoint) from the FAS (25 subjects with sinusitis, 20 subjects with laryngopharyngitis, 21 subjects with tonsillitis) were included in the PPS and in the efficacy analysis. Fifty-eight subjects after excluding 8 subjects with no pathogen identified from the PPS (20 subjects with sinusitis, 19 subjects with laryngopharyngitis, 19 subjects with tonsillitis) were included in the assessment of bacteriological response.

The clinical response at the end of treatment (efficacy rate) by disease, which was the primary endpoint, was 92.0% for sinusitis (23/25 subjects, 95% confidence interval: [74.0, 99.0%]), 85.0% for laryngopharyngitis (17/20 subjects, 95% confidence interval: [62.1, 96.8%]), and 95.2% for tonsillitis (20/21 subjects, 95% confidence interval: [76.2, 99.9%]). The efficacy rate on the 3rd day of treatment was 60.0% for sinusitis (15/25 subjects, 95% confidence interval: [38.7, 78.9%]), 45.0% for

laryngopharyngitis (9/20 subjects, 95% confidence interval: [23.1, 68.5%]), and 57.1% for tonsillitis (12/21 subjects, 95% confidence interval: [34.0, 78.2%]). The efficacy rate 7 days after the end of treatment was 91.3% for sinusitis (21/23 subjects, 95% confidence interval: [72.0, 98.9%]), 89.5% for laryngopharyngitis (17/19 subjects, 95% confidence interval: [66.9, 98.7%]), and 95.0% for tonsillitis (19/20 subjects, 95% confidence interval: [75.1, 99.9%]). Among the 58 subjects included in the assessment of bacteriological response, all of 57 subjects excluding 1 subject with tonsillitis who was unevaluable at the end of treatment, showed eradication of the microorganism (presumed eradication).

Regarding the safety, 14 adverse events occurred in 12/71 subjects (16.9%) and 5 adverse drug reactions were observed in 4/71 subjects (5.6%). These 5 adverse drug reactions were 2 events of loose stools, gastrointestinal upset in 1 subject, stomach discomfort in 1 subject, and rash in 1 subject.

Forty-six abnormal laboratory changes were observed in 36/69 subjects (52.2%) and abnormal laboratory changes with an incidence of 3% or greater were white blood cell count decreased (2/67 subjects, 3%), AST increased (2/67 subjects, 3%), bilirubin conjugated increased (3/67 subjects, 4.5%), blood bilirubin increased (3/67 subjects, 4.5%), γ-GTP increased (5/67 subjects, 7.5%), blood glucose decreased (5/67 subjects, 7.5%), blood glucose increased (6/67 subjects, 9.0%), blood Cr increased (2/67 subjects, 3.0%), blood BUN increased (2/67 subjects, 3.0%), protein urine present (2/67 subjects, 3.0%), blood chloride decreased (2/67 subjects, 3.0%), and blood potassium increased (3/67 subjects, 4.5%). Thirteen abnormal laboratory changes classified as adverse drug reactions were reported in 10/69 subjects (14.5%) and those with an incidence of 3% or greater were protein urine present (2/67 subjects, 3.0%).

As a serious adverse event, blood CK increased was reported by 1 subject, but this was assessed as "unlikely to be related," and resolved later. There were no deaths.

e. Open-label, uncontrolled study in patients with respiratory tract infections caused by Penicillin-resistant *Streptococcus pneumoniae* [Study Number: Study 61010, Publication: None, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

An open-label, uncontrolled study was conducted at 57 study sites in Japan in order to evaluate the efficacy and safety of GRNX in patients with respiratory tract infections caused by penicillin-resistant *Streptococcus pneumoniae* (PRSP).

GRNX 400 mg was to be orally administered once daily for 7-10 days.

All of the 99 subjects treated with GRNX (community-acquired pneumonia: 68 subjects, secondary infection of chronic respiratory disease: 19 subjects, acute bronchitis: 12 subjects) were included in the safety analysis and the FAS; and 83 subjects, after excluding 16 subjects with protocol violations as to the inclusion criteria, etc., from the FAS, (community-acquired pneumonia: 56 subjects, secondary infection of chronic respiratory disease: 18 subjects, acute bronchitis: 9 subjects) were included in the

PPS. Sixty-six subjects after excluding 17 subjects in total, i.e. 16 subjects with no pathogen isolated and 1 subject not tested, from the PPS (community-acquired pneumonia: 44 subjects, secondary infection of chronic respiratory disease: 15 subjects, acute bronchitis: 7 subjects) were included in the bacteriological analysis. Fifty-one subjects, after excluding 15 subjects without *Streptococcus pneumoniae* identified as a pathogen from the bacteriological analysis population (community-acquired pneumonia: 33 subjects, secondary infection of chronic respiratory disease: 14 subjects, acute bronchitis: 4 subjects) were included in the *Streptococcus pneumoniae* analysis and in the efficacy analysis.

The efficacy rate by pathogen is shown below.

Efficacy rate by pathogen (at the end of treatment)

Pathogen	Cases included in analysis	Clinical response		Efficacy rate (%)	95% confidence interval
		Effective	Ineffective		
S. pneumoniae	51	49	2	96.1	86.5, 99.5%
PRSP	9	8	1	88.9	51.8, 99.7%
PISP	16	15	1	93.8	69.8, 99.8%
PSSP	22	22	0	100.0	84.6, 100.0%
Resistance unknown	4	4	0	[4/4]	―

Efficacy rate (%)＝Effective cases／Cases included in analysis×100

One subject with PRSP isolated who did not respond to treatment, had mild pneumonia caused by multi-drug resistant PRSP, which is resistant to cephems and macrolides [multi-drug resistant PRSP: *Streptococcus pneumoniae* resistant to any two or more of quinolones, cephems, and macrolides]. Although the bacteria were eradicated on Day 3 of treatment and the symptoms were improving, the subject discontinued treatment due to moderately severe increases in liver function tests on Day 3. The subject received panipenem/betamiprom (5 days) and azithromycin (AZM) (3 days) after the discontinuation of GRNX, resulting in the improvement of symptoms. Another subject with PISP isolated who did not respond to treatment had severe pneumonia caused by macrolide-resistant PISP and the bacteria were eradicated on Day 4 of treatment, but the subject discontinued treatment on Day 4 due to worsening of symptoms. The subject received imipenem/cilastatin (8 days), clarithromycin (CAM) (5 days), and AZM (3 days) after the discontinuation of GRNX, resulting in the improvement of symptoms. Other subjects with multi-drug resistant *Streptococcus pneumoniae* insolated (14 subjects) were all effective cases.

Concerning the safety, 60 adverse events were reported by 38/99 subjects (38.4%) and adverse events with an incidence of 3% or greater were nasopharyngitis (3/99 subjects, 3.0%), dysgeusia (3/99 subjects, 3.0%), headache (3/99 subjects, 3.0%), diarrhoea (3/99 subjects, 3.0%), stomatitis (4/99 subjects, 4.0%), and back pain (5/99 subjects, 5.1%). Twenty-eight adverse drug reactions were observed in 17/99 subjects (17.2%) and adverse drug reactions with an incidence of 3% or greater were dysgeusia (3/99 subjects, 3%).

One-hundred seven abnormal laboratory changes were observed in 56/99 subjects (56.6%) and abnormal laboratory changes with an incidence of 3% or greater were blood pressure decreased (5/99 subjects, 5.1%), blood CK increased (3/99 subjects, 3.0%), blood LDH increased (3/99 subjects, 3.0%), blood ALP increased (3/99 subjects, 3.0%), blood amylase increased (5/98 subjects, 5.1%), eosinophil count increased (3/99 subjects, 3.0%), ALT increased (16/99 subjects, 16.2%), AST increased (12/99 subjects, 12.1%), blood bilirubin increased (4/99 subjects, 4.0%), γ-GTP increased (3/99 subjects, 3.0%), blood glucose increased (7/98 subjects, 7.1%), red blood cells urine positive (2/66 subjects, 3.0%), white blood cells urine positive (2/66 subjects, 3.0%), protein urine present (6/97 subjects, 6.2%), blood chloride decreased (3/99 subjects, 3.0%), and blood potassium increased (3/99 subjects, 3.0%). Fifty-two abnormal laboratory changes classified as adverse drug reactions were observed in 30/99 subjects (30.3%) and those with an incidence of 3% or greater were blood ALP increased (3/99 subjects, 3.0%), blood amylase increased (4/98 subjects, 4.1%), ALT increased (13/99 subjects, 13.1%), AST increased (7/99 subjects, 7.1%), and γ-GTP increased (3/99 subjects, 3.0%).

Serious adverse events reported were clostridium colitis, enterocolitis viral, hemiparesis, and CRP increased in one subject each. With respect to the causality to GRNX, clostridium colitis was assessed as “probably related” and resolved 7 days after the discontinuation of treatment. The other cases were assessed as “unrelated.” Severe adverse events reported were blood pressure increased, neutrophil count decreased, and blood glucose increased in one subject each. Other significant adverse events reported were electrocardiogram QTc interval prolonged in 1 subject, blood pressure increased in 1 subject, AST increased, ALT increased, blood ALP increased, and γ-GTP increased in 1 subject, and neutrophil count decreased and white blood cell count decreased in 1 subject. Although 4 subjects had QTc interval increases from baseline >60 msec (7 events), it was determined that these changes were not clinically relevant at the ECG review committee (the Bazett’s correction formula). There were no deaths.

f. Open-label, uncontrolled study in patients with acute otitis media or acute exacerbation of chronic otitis media [Study Number: Study 61011, Publication: None, Study Period: [redacted] 20[redacted] to [redacted] 20[redacted], Evaluation Data]

An open-label, uncontrolled study was conducted at 17 study sites in Japan in order to evaluate the efficacy and safety of GRNX in patients with acute otitis media or acute exacerbation of chronic otitis media.

GRNX 400 mg was to be orally administered once daily and the duration of treatment was 7 days.

All of the 50 subjects treated with GRNX (acute otitis media: 35 subjects, acute exacerbation of chronic otitis media: 15 subjects) were included in the safety analysis and the FAS. Forty-seven subjects, after excluding 1 subject who failed to complete the treatment period and 2 subjects with protocol violations as to concomitant medications/therapies from the FAS, were included in the PPS

and in the efficacy analysis. Forty-four subjects, after excluding 3 subjects with no pathogen isolated from the PPS, were included in the assessment of bacteriological response.

The clinical response rate at the end of treatment (the efficacy rate), which was the primary endpoint, was 87.2% (41/47 subjects, 95% confidence interval: [74.3, 95.2%]). The efficacy rate was 42.6% (20/47 subjects, 95% confidence interval: [28.3, 57.8%]) on the 3rd day of treatment and 81.8% (36/44 subjects, 95% confidence interval: [67.3, 91.8%]) 7 days after the end of treatment. The bacterial eradication rate was 93.2% (41/44 subjects, 95% confidence interval: [81.3, 98.6%]) at the end of treatment and 92.7% (38/41 subjects, 95% confidence interval:[80.1, 98.5%]) at 7 days after the end of treatment.

Regarding the safety, 30 adverse events occurred in 16/50 subjects (32.0%) and adverse events with an incidence of 3% or greater were nasopharyngitis (2/50 subjects, 4.0%), otitis externa (3/50 subjects, 6.0%), diarrhoea (2/50 subjects, 4.0%), abdominal pain (2/50 subjects, 4.0%), loose stools (2/50 subjects, 4.0%), vomiting (2/50 subjects, 4.0%), and rash (2/50 subjects, 4.0%). Eight adverse drug reactions were observed in 5/50 subjects (10.0%) and adverse drug reactions with an incidence of 3% or greater were loose stools (2/50 subjects, 4.0%).

Forty-two abnormal laboratory changes were reported by 25/50 subjects (50.0%) and abnormal laboratory changes with an incidence of 3% or greater were blood CPK increased (3/50 subjects, 6.0%), blood glucose decreased (3/50 subjects, 6.0%), blood glucose increased (9/50 subjects, 18.0%), white blood cells urine positive (3/50 subjects, 6.0%), and protein urine present (6/50 subjects, 12.0%) and 4 abnormal laboratory changes classified as adverse drug reactions were observed in 2/50 subjects (4.0%).

There were no deaths or serious adverse events.

(4) Foreign clinical studies

1) Phase I/Clinical pharmacology studies

a. Photosensitivity study (Study AI464006, Evaluation Data)

A randomized, double-blind, placebo-controlled study in healthy adults was conducted to assess the photosensitivity of GRNX. Eleven subjects and 10 subjects were randomized into the GRNX groups (multiple oral administration of 400 mg or 800 mg once daily for 6 days), respectively. At 400 mg, no evident photosensitivity was observed under UVA (320-400 nm), UVB (290-320 nm), visible (400-700 nm) or continuous spectrum (200-700 nm) irradiation.

Thirty-nine adverse events were reported by 16/21 subjects (76%) in the GRNX groups and the main adverse events were headache (6/21 subjects, 29%), rash (4/21 subjects, 19%), and abdominal pain (3/21 subjects, 14%). In the placebo group, 11 adverse events were reported by 5/10 subjects (50%) and the main adverse events were laboratory abnormalities (ALT increased, AST increased) (3/10

subjects, 30%), headache (2/10 subjects, 20%), and γ-GTP increased (2/10 subjects, 20%). Fifteen adverse drug reactions were reported by 10/21 subjects (48%) in the GRNX groups and the main adverse drug reactions were rash (3/21 subjects, 14%) and conjunctivitis (2/21 subjects, 10%).

Abnormal laboratory changes were reported by 2/21 subjects (10%) in the GRNX groups; both subjects had blood bicarbonate decreased.

b. 28-day, multiple dose study (Study AI464008, Evaluation Data)

A randomized, double-blind, placebo-controlled study in healthy adults was conducted to evaluate the safety and tolerability of 28-day multiple administration of GRNX. Thirty-two subjects were randomized into the GRNX group (400 mg was orally administered once daily for 28 days).

Fifty-seven adverse events were reported by 22/32 subjects (69%) in the GRNX group and the main adverse events were rash (8/32 subjects, 25%), pruritus (5/32 subjects, 16%), headache (4/32 subjects, 13%), nausea (4/32 subjects, 13%), laboratory abnormalities (ALT increased, amylase increased) (4/32 subjects, 13%), and dizziness (4/32 subjects, 13%). In the placebo group, 5/13 subjects (39%) experienced 17 adverse events, and the main adverse events were headache (4/13 subjects, 31%), constipation (2/13 subjects, 15%), CK increased (2/13 subjects, 15%), and pruritus (2/13 subjects, 15%). Forty-four adverse drug reactions were observed in 19/32 subjects (59%) in the GRNX group and the main adverse drug reactions were rash (6/32 subjects, 19%), headache (4/32 subjects, 13%), nausea (4/32 subjects, 13%), dizziness (4/32 subjects, 13%), and pruritus (4/32 subjects, 13%).

Abnormal laboratory changes were observed in 30/32 subjects (94%) in the GRNX group and the main abnormal laboratory findings were albumin decreased (17/32 subjects, 53%), neutrophil count decreased (13/32 subjects, 41%), CK increased (2/7 subjects, 29%), ALT increased (9/32 subjects, 28%), and blood potassium increased (9/32 subjects, 28%). In the placebo group, abnormal laboratory changes were observed in 12/13 subjects (92%) and the main abnormal laboratory findings were lipase increased (1/2 subjects, 50%), albumin decreased (6/13 subjects, 46%), and blood potassium increased (3/13 subjects, 23%).

c. Pharmacokinetic study (Study AI464031, Evaluation Data)

An open-label, uncontrolled study in 8 healthy male adults was conducted to assess the pharmacokinetics and safety after a single oral dose of 600 mg of ^{14}C-labeled GRNX.

As an adverse event, a headache (moderate) was reported by 1 subject. There were no adverse drug reactions.

d. Bioavailability (BA) study (Study AI464032, Evaluation Data)

A 2×2 crossover study in 14 healthy adults was conducted to assess the bioavailability of the oral formulation (GRNX 600 mg, a single oral dose) relative to the intravenous infusion formulation (GRNX 600 mg, a single intravenous dose).

Eleven adverse events occurred in 9/14 subjects (64%) in the intravenous infusion group and 3 adverse events occurred in 3/14 subjects (21%) in the oral administration group, and injection site reaction was commonly reported in the intravenous infusion group (9/14 subjects, 64%). In the oral administration group, a headache and dizziness (one case each) were reported, which were classified as adverse drug reactions.

Abnormal laboratory changes observed in the intravenous infusion group were platelet count decreased, blood potassium increased, and γ-GTP increased (one case each) and those in the oral administration group were ALP increased and γ-GTP increased (one case each).

e. Study of penetration into lung tissues (Study AI464048, Evaluation Data)

An open-label, uncontrolled study in 27 subjects undergoing lung biopsy or resection was conducted to assess the ratio of GRNX in lung parenchyma tissue relative to plasma after a single oral dose of 600 mg.

Forty-three adverse events were reported by 26/27 subjects (96%) and the main adverse events were pain (26/27 subjects, 96%), nausea (4/27 subjects, 15%), itch (3/27 subjects, 11%), and hypotension (2/27 subjects, 7%). There were no adverse drug reactions.

f. Study of penetration into alveolar macrophage etc. (Study AI464049, Evaluation Data)

An open-label, uncontrolled study in 24 healthy adults was conducted to assess GRNX concentrations in bronchial mucosa, alveolar epithelial lining fluid, alveolar macrophage, and plasma.

Fourteen adverse events were reported by 8/24 subjects (33%) and the main adverse events were pyrexia (2/24 subjects, 8%), pharyngitis (5/24 subjects, 21%), and cough (3/24 subjects, 13%). There were no adverse drug reactions.

g. Study on excretion in human milk (Study AI464061, Evaluation Data)

An open-label, uncontrolled study in 6 nursing mothers was performed to assess GRNX excretion in human milk.

Six adverse events were reported by 4/6 subjects (67%): 2 cases of taste disturbance, and 1 case each of face oedema, nasal dryness, nausea, and itch. Among these adverse events, nausea, nasal dryness, and taste disturbance were classified as adverse drug reactions.

h. Drug interaction study with morphine (Study AI464038, Evaluation Data)

A 4×4 crossover study in 24 healthy adults was conducted to assess the possible effects of intravenous morphine on the pharmacokinetics of GRNX.

Seventeen adverse events were reported by 8/22 subjects (36%) in the GRNX alone group, 64 adverse events were reported by 17/23 subjects (74%) in the morphine alone group, 59 adverse events were reported by 18/22 subjects (82%) in the group of subjects who received morphine followed by GRNX, and 85 adverse events were reported by 18/21 subjects (86%) in the group of subjects who received GRNX followed by morphine. One-hundred five adverse drug reactions were observed in 22/22 subjects (100%) and the main adverse drug reactions were pruritus (14/22 subjects, 64%), nausea (9/22 subjects, 41%), injection site reaction (8/22 subjects, 36%), and dizziness (7/32 subjects, 32%).

i. Drug interaction study with digoxin (Study AI464050, Evaluation Data)

An open-label, uncontrolled study in 16 healthy adults was conducted to assess the possible effects of GRNX on the steady-state pharmacokinetics of digoxin.

Five adverse events were reported by 3/15 subjects (20%) in the GRNX alone group, 11 adverse events were reported by 8/16 subjects (50%) in the digoxin alone group, and 19 adverse events were reported by 7/16 subjects (44%) in the GRNX+digoxin group. Ten adverse reactions to GRNX were observed in 6/16 subjects (38%) and the main adverse drug reactions were nausea (3/16 subjects, 19%), A-V block (2/16 subjects, 13%), and dizziness (2/16 subjects, 13%).

j. Drug interaction study with dried aluminum hydroxide gel/magnesium hydroxide (Study AI464057, Evaluation Data)

A randomized, open-label study in 20 healthy adults was conducted to assess the possible effects of dried aluminum hydroxide gel/magnesium hydroxide on the pharmacokinetics of GRNX.

Four adverse events occurred in 2/9 subjects (22%) (pain, abdominal pain, nausea, and rectal haemorrhage) in the GRNX+ dried aluminum hydroxide gel/magnesium hydroxide coadministration group and among these adverse events, abdominal pain, nausea, and rectal haemorrhage were classified as adverse drug reactions.

k. Drug interaction study with omeprazole (Study AI464058, Evaluation Data)

An open-label, uncontrolled study in 14 healthy adults was conducted to assess the possible effects of omeprazole on the bioavailability of GRNX.

Adverse events occurred in 3/14 subjects (21%) in the GRNX alone group, 18 adverse events occurred in 6/14 subjects (43%) in the omeprazole alone group, and 9 adverse events occurred in 5/12 subjects (25%) in the GRNX+ omeprazole group. Eleven adverse reactions to GRNX were observed in 5/14

subjects (36%) and the main adverse reactions were headache (3/14 subjects, 21%) and nausea (2/14 subjects, 14%).

l. Single dose study in subjects with renal impairment (Study AI464047, Evaluation Data)

An open-label, uncontrolled study in 26 subjects (including subjects without renal impairment as controls) was conducted to investigate the pharmacokinetics of GRNX after a single oral dose of 600 mg.

Thirty-four adverse events were reported by 12/25 subjects (48%) and the main adverse events were headache (3/25 subjects, 12%) and dizziness (3/25 subjects, 12%). Five adverse drug reactions were observed in 5/25 subjects (19%). Abnormal laboratory changes reported were prothrombin time prolonged (1/1 subject, 100%) and urine protein increased (1/16 subjects, 6%) of which prothrombin time prolonged was classified as an adverse drug reaction.

m. Single dose study in subjects with hepatic impairment (Study AI464052, Evaluation Data）

An open-label, uncontrolled study in 20 subjects (including subjects without hepatic impairment as controls) was conducted to investigate the pharmacokinetics of GRNX after a single oral dose of 600 mg.

Four adverse events were reported by 3/20 subjects (15%) (hypersensitivity, ventricular bigeminy, diarrhoea, and laboratory abnormalities <blood glucose increased and blood glucose decreased>). Of which, 2 events were classified as adverse drug reactions (1/20 subjects (5%), hypersensitivity and diarrhoea).

2) Phase II/Phase III studies

a. Phase II study in patients with acute exacerbation of chronic bronchitis (Study AI464003, Evaluation Data)

A randomized, double-blind, multi-center, comparative study in patients with acute exacerbation of chronic bronchitis was conducted to evaluate the efficacy and safety of GRNX 400 mg orally administered once daily for 5 days and 10 days.

In the 5-day treatment group, 75/147 subjects (51%) experienced adverse events and the main adverse events were dyspnoea (10%) and sputum increased (10%). Among those subjects, 30/147 subjects (20%) had adverse drug reactions. In the 10-day treatment group, 65/147 subjects (44%) experienced adverse events, of whom 24/147 subjects (16%) had adverse drug reactions. The main abnormal laboratory findings in the 5-day treatment group were blood glucose increased (9/36 subjects, 25%) and blood bicarbonate increased (21/105 subjects, 20%) and those in the 10-day-treatment group were blood glucose increased (10/40 subjects, 25%) and blood bicarbonate increased (20/109 subjects, 18%).

b. Phase II study in patients with community-acquired pneumonia (Study AI464004, Evaluation Data)

An open-label, uncontrolled, multi-center study in patients with community-acquired pneumonia was conducted to evaluate the efficacy and safety of GRNX 400mg orally administered once daily for 10 days.

Adverse events occurred in 131/208 subjects (63%) and the main adverse event was respiration abnormal. Of whom, 53/208 subjects (25%) had adverse drug reactions. The main abnormal laboratory findings were AST increased (19/178 subjects, 11%), ALT increased (22/177 subjects, 12%), blood glucose increased (8/31 subjects, 26%), and blood bicarbonate increased (25/157 subjects, 16%).

As a serious adverse drug reaction, moderate abdominal pain was observed in 1 subject. One death (83 year-old, Caucasian woman) occurred. This patient was admitted to the intensive care unit due to acute respiratory failure on Day 7 of study treatment and died of bilateral pneumonia 2 days later. A causal relationship to GRNX was denied.

c. Phase II study in patients with acute bacterial sinusitis (Study AI464005, Evaluation Data)

An open-label, uncontrolled, multi-center study in patients with acute bacterial sinusitis was conducted to evaluate the efficacy and safety of GRNX 400mg orally administered once daily for 5 days and 10 days.

Adverse events were reported by 73/262 subjects (28%) in the 5-day treatment group and by 117/281 subjects (42%) in the 10-day treatment group. Adverse drug reactions were observed in 33/262 subjects (13%) and in 59/281 subjects (21%), respectively. The main abnormal laboratory findings in the 5-day treatment group were haemoglobin decreased (23/234 subjects, 10%), white blood cell count decreased (27/245 subjects, 11%), neutrophil count decreased (29/245 subjects, 12%), ALT increased (22/229 subjects, 10%), blood glucose increased (9/81 subjects, 11%), and blood bicarbonate decreased (49/232 subjects, 21%), and those in the 10-day treatment group were white blood cell count decreased (30/252 subjects, 12%), neutrophil count decreased (26/254 subjects, 10%), ALT increased (24/237 subjects, 10%), and blood bicarbonate decreased (43/224 subjects, 19%). Serious adverse drug reactions reported were chest pressure and dyspnoea in one subject in the 10-day treatment group.

d. Phase III study in patients with mild to moderate community-acquired pneumonia (Study AI464017, Evaluation Data)

A randomized, double-blind, multi-center, CAM-controlled study in patients with mild to moderate community-acquired pneumonia was conducted to evaluate the efficacy and safety of GRNX upon orally administering 400mg orally once daily for 5 days.

In the GRNX group, adverse events occurred in 115/154 subjects (75%) and the main adverse events

were headache (15/154 subjects, 10%), diarrhoea (21/154 subjects, 14%), respiration abnormal (20/154 subjects, 13%), cough (15/154 subjects, 10%), and sputum increased (16/154 subjects, 10%). Adverse drug reactions were observed in 60/154 subjects (39%), and the main adverse drug reaction was diarrhoea (20/154 subjects, 13%). In the CAM group, adverse events occurred in 122/156 subjects (78%) and the main adverse events were headache (26/156 subjects, 17%), dysgeusia (26/156 subjects, 17%), diarrhoea (25/156 subjects, 16%), respiration abnormal (23/156 subjects, 15%), and cough (20/156 subjects, 13%). Adverse drug reactions were observed in 68/156 subjects (44%) and the main adverse drug reaction was dysgeusia (26/156 subjects, 17%). The main abnormal laboratory changes from normal baseline values in the GRNX group were AST increased (20/123 subjects, 16%), ALT increased (20/122 subjects, 16%), blood amylase increased (14/143 subjects, 10%), blood glucose decreased (2/16 subjects, 13%), and blood bicarbonate decreased (14/125 subjects, 11%), and those in the CAM group were AST increased (24/131 subjects, 18%), ALT increased (20/128 subjects, 16%), blood glucose increased (3/21 subjects, 14%), and neutrophil count decreased (17/145 subjects, 12%).

e. Phase III study in patients with mild to moderate community-acquired pneumonia (Study AI464018, Evaluation Data)

A randomized, double-blind, multi-center, AMPC/CVA-controlled study in patients with mild to moderate community-acquired pneumonia was conducted to evaluate the efficacy and safety of GRNX upon orally administering 400 mg once daily for 5 days.

In the GRNX group, 77/186 subjects (41%) experienced adverse events and 25/186 subjects (13%) had adverse drug reactions. In the AMPC/CVA group, 89/174 subjects (51%) experienced adverse events and 36/174 subjects (21%) had adverse drug reactions. The main abnormal laboratory findings in the GRNX group were ALT increased (33/143 subjects, 23%), blood bicarbonate increased (35/151 subjects, 23%), AST increased (27/146 subjects, 18%), haemoglobin decreased (22/146 subjects, 15%), blood glucose increased (4/26 subjects, 15%), neutropenia (24/169 subjects, 14%), blood amylase increased (23/170 subjects, 14%), blood potassium increased (20/153 subjects, 13%), blood bicarbonate decreased (18/151 subjects, 12%), and eosinophil count increased (17/166 subjects, 10%).

f. Phase III study in patients with community-acquired pneumonia (Study AI464019, Evaluation Data)

A randomized, double-blind, multi-center, LVFX-controlled study in patients with community-acquired pneumonia was conducted to evaluate the efficacy and safety of GRNX 400mg orally administered once daily for 7-10 days.

In the GRNX group, adverse events occurred in 64/136 subjects (47%) and the main adverse event was headache (13/136 subjects, 10%). Adverse drug reactions were observed in 24/136 subjects (18%). In the LVFX group, adverse events occurred in 52/134 subjects (39%) and adverse drug reactions were observed in 16/134 subjects (12%). The main abnormal laboratory findings observed in the GRNX group were blood glucose increased (9/17 subjects, 53%), ALT increased (22/102 subjects,

22%), neutrophil count decreased (16/118 subjects, 14%), blood potassium increased (16/117 subjects, 14%), blood bicarbonate increased (14/107 subjects, 13%), eosinophil count increased (13/112 subjects, 12%), AST increased (13/105 subjects, 12%), blood creatinine increased (13/121 subjects, 11%), and blood sodium increased (12/109 subjects, 11%).

g. Phase III study in patients with acute exacerbation of chronic bronchitis (Study AI464022, Evaluation Data)

A randomized, double-blind, multi-center, AZM-controlled study in patients with acute exacerbation of chronic bronchitis was conducted to evaluate the efficacy and safety of GRNX 400 mg orally administered once daily for 5 days.

In the GRNX group, adverse events occurred in 220/400 subjects (55%) and the main adverse events were cough (48/400 subjects, 12%) and sputum increased (40/400 subjects, 10%). Adverse drug reactions were observed in 61/400 subjects (15%). In the AZM group, 192/386 subjects (50%) experienced adverse events, of whom 70/386 subjects (18%) had adverse drug reactions. The main abnormal laboratory findings in the GRNX group were blood glucose increased (7/35 subjects, 20%) and blood glucose decreased (5/35 subjects, 14%).

h. Phase III study in patients with acute exacerbation of chronic bronchitis (Study AI464023, Evaluation Data)

A randomized, double-blind, multi-center, AMPC/CVA-controlled study in patients with acute exacerbation of chronic bronchitis was conducted to evaluate the efficacy and safety of GRNX 400 mg orally administered once daily for 5 days.

In the GRNX group, 70/227 subjects (31%) experienced adverse events, of whom 18/227 subjects (8%) had adverse drug reactions. In the AMPC/CVA group, 86/218 subjects (39%) experienced adverse events, of whom 24/218 subjects (11%) had adverse drug reactions. The main abnormal laboratory findings in the GRNX group were blood glucose increased (10/43 subjects, 23%), blood bicarbonate increased (31/158 subjects, 20%), blood potassium increased (22/185 subjects, 12%), blood amylase increased (22/193 subjects, 11%), and ALT increased (19/181 subjects, 10%).

Serious adverse drug reactions observed in the GRNX group were moderate vomiting in one subject and moderate diarrhoea, abdominal pain, and gastrointestinal haemorrhage in one subject. These events resolved following the discontinuation of GRNX.

i. Phase III study in patients with acute sinusitis (Study AI464024, Evaluation Data)

A randomized, double-blind, multi-center, AMPC/CVA-controlled study in patients with acute sinusitis was conducted to evaluate the efficacy and safety of GRNX 400 mg orally administered once daily for 5 days or 10 days.

Adverse events were reported by 113/245 subjects (46%) in the GRNX 5-day treatment group and the main adverse events were diarrhoea (24/245 subjects, 10%) and rhinitis (29/245 subjects, 12%). Adverse drug reactions occurred in 69/245 subjects (28%). In the 10-day treatment group, 108/240 subjects (45%) experienced adverse events and the main adverse event was rhinitis (30/240 subjects, 13%). Adverse drug reactions were reported by 49/240 subjects (20%). In the AMPC/CVA group, 134/237 subjects (57%) experienced adverse events and the main adverse events were diarrhoea (52/237 subjects, 22%), headache (30/237 subjects, 13%), and rhinitis (28/237 subjects, 12%). Adverse drug reactions were reported by 81/237 subjects (34%). The main abnormal laboratory findings in the GRNX 5-day treatment group were blood bicarbonate decreased (28/205 subjects, 14%) etc., those in the GRNX 10-day treatment group were blood glucose increased (5/29 subjects (17%), blood bicarbonate decreased (33/199 subjects, 17%), AST increased (20/207 subjects, 10%), and ALT increased (19/192 subjects, 10%) etc., and those in the AMPC/CVA group were blood glucose increased (6/30 subjects, 20%), blood bicarbonate decreased (37/198 subjects, 19%), and ALT increased (25/208 subjects, 12%) etc.

Serious adverse events reported were 1 case of hospitalization due to alcohol dependence, 1 case of hospitalization due to severe vaginal haemorrhage, and 1 case of hospitalization due to sick sinus syndrome in the GRNX 5-day treatment group, 1 case of hospitalization due to right upper lobar pneumonia in the GRNX 10-day treatment group, and 1 case of hospitalization due to severe chest pain and upper abdominal pain and 1 case of overnight hospital stay due to uterine haemorrhage in the AMPC/CVA group.

j. Phase III study in patients with community-acquired pneumonia (Study AI464029, Evaluation Data)

A randomized, double-blind, multi-center, CAM-controlled study in patients with community-acquired pneumonia was conducted to evaluate the efficacy and safety of GRNX 400 mg orally administered once daily for 7-10 days.

In the GRNX group, 112/159 subjects (70%) experienced adverse events and the main adverse events were respiration abnormal (22/159 subjects, 14%), headache (20/159 subjects, 13%), dyspnoea (19/159 subjects, 12%), and cough (18/159 subjects, 11%). Of whom, 39/159 subjects (25%) had adverse drug reactions. In the CAM group, 123/156 subjects (79%) experienced adverse events and the main adverse events were respiration abnormal (26/156 subjects, 17%), cough (19/156 subjects, 12%), sputum increased (19/156 subjects, 12%), and headache (17/156 subjects, 11%). Of whom, 51/156 subjects (33%) had adverse drug reactions. The main abnormal laboratory findings in the GRNX group were blood glucose increased (1/7 subjects, 14%), ALT increased (15/132 subjects, 11%), AST increased (13/128 subjects, 10%), and blood bicarbonate decreased (12/125 subjects, 10%).

(5) Other foreign clinical studies

1) Phase I/Clinical pharmacology studies (Study Numbers: Study AI464001, Study AI464002, Study AI464007, Study AI464036, Study AI464037, Study AI464053, Study AI464055, Study AI464059, Study AI464069, Study AI464051, Study AI464010, Study AI464092, Study AI464011, Study AI464064, Reference Data)

Adverse events with an incidence of 5% or greater in any of 14 foreign phase I/clinical pharmacology studies were rash, headache, pain, diarrhoea, nausea, abdominal pain, vomiting, secretion discharge, dizziness, somnolence, pharyngitis, rhinitis, erythema, dysgeusia, constipation, dry skin, pruritus, pyrexia, infection, pleural effusion, pneumonia, dyspepsia, flatulence, depersonalisation, illusion, cough, lung disorder, eruption, hyperhidrosis, menstrual irregularity, eye irritation, asthenia, injection site pain, pharynx strangled sensation of, hypotension, palpitations, vasodilatation, albumin abnormal, ALT abnormal, calcium abnormal, γ-GTP abnormal, abnormal blood glucose level, sodium abnormal, neutrophils abnormal, lymphocyte abnormal, pollakiuria, anxiety, burning sensation, tachycardia, potassium abnormal, bilirubin abnormal, bicarbonate abnormal, phosphorus abnormal, and uric acid abnormal.

Adverse drug reactions with an incidence of 5% or greater were headache, diarrhoea, queasy, abdominal pain, vomiting, secretion discharge, dizziness, somnolence, pharyngitis, rhinitis, rash, dysgeusia, constipation, dry skin, pruritus, dyspepsia, flatulence, depersonalisation, asthenia, injection site pain, pharynx strangled sensation of, orthostatic hypotension, illusion, vasodilatation, palpitations, rash maculo-papular, and keratoconjunctivitis sicca.

2) Phase II/Phase III studies (Study Numbers: Study AI464009, Study AI464081, Study AI464015, Study AI464026, Study AI464073, Study AI464020, Study AI464021, Study AI464025, Study AI464027, Study AI464028, Reference Data)

Adverse events with an incidence of 5% or greater in any of 10 foreign phase II/phase III studies were chest pain, abdominal pain, respiration abnormal, headache, pain, nausea, diarrhoea, post procedural drainage, erythema, percussion test abnormal, pyrexia, infection, hypotension, constipation, hypocalcaemia, asthma, cough, sputum increased, insomnia, vasodilatation, erythema, pruritus, rash, asthenia, vomiting, oedema peripheral, constipation, insomnia, respiration abnormal, dyspnoea, lung disorder, respiratory disorder, abdominal distension, confusional state, dyspnoea, pleural effusion, haemoglobin abnormal, neutrophils abnormal, AST abnormal, ALT abnormal, creatinine abnormal, amylase abnormal, BUN/urea abnormal, white blood cell count abnormal, platelets abnormal, bilirubin total abnormal, alkaline phosphatase abnormal, pneumonia, anxiety, cellulitis, eosinophils abnormal, abnromal blood glucose level, potassium abnormal, sodium abnormal, bicarbonate abnormal, and chloride abnormal.

Adverse drug reactions with an incidence of 5% or greater were headache, diarrhoea, and queasy.

<Outline of the review by the PMDA>

(1) Submission data package

The PMDA asked the applicant to explain the necessity of the use of foreign clinical studies and the ability to extrapolate foreign clinical data to the Japanese population.

The applicant responded as follows.

It is considered that the efficacy and a certain extent of safety of GRNX could be confirmed by 13 Japanese clinical studies. However, early in the development program, we intended to use foreign clinical data by generating bridging data and assessed intrinsic factors, such as comparative PK between Japanese and non-Japanese subjects, and extrinsic factors, such as the frequency of isolation/susceptibility of pathogens, in order to confirm that foreign clinical data can be extrapolated to Japan. As a result, the AUC and C_{max} in the Japanese population were 1.2-1.8 times higher than those in non-Japanese subjects, which was inferred to be due to body weight differences, and it was concluded that GRNX is insensitive to the intrinsic and extrinsic factors. Based on this result, 2 Japanese studies (Study 61005, Study 61006) were conducted as bridging studies.

As the target diseases were partially different between the Japanese study 61005 in patients with bacterial pneumonia and the foreign study AI464019 in patients with community-acquired pneumonia, the study was conducted after harmonizing various criteria by, for example, excluding atypical pneumonia from Study AI464019. Although there were differences in the patient background such as the severity of infections and body weight between Japan and the foreign countries, as the target disease was bacterial pneumonia for both studies, it was considered that the data from Study AI464019 can be used as efficacy information for the case where GRNX is used widely. It was considered that the safety data can also be used in terms of evaluating safety information extensively since it was a study of the oral formulation in patients with community-acquired pneumonia.

With regard to the Japanese Study 61006, although the target diseases were different from the foreign Study AI464003, as the target disease in the foreign study were included as part of the target diseases in the Japanese study, it was judged that the foreign efficacy information can be used. Therefore, Study AI464003 data was used for microorganisms that could not be collected or was insufficient in Japan, and since none of the adverse events reported by patients with chronic bronchitis, emphysema, or bronchial asthma in Study AI464003 was specific in its nature or incidence compared to other diseases in Study 61006, and their incidence or the incidence of severe/serious events is not correlated with the AUC or body weight, it was considered that safety information can also be used. With respect to some of the proposed microorganisms of which no strains could be collected in Japan i.e. *Escherichia coli* and *Legionella pneumophila*, and a sufficient number of strains could not be collected in Japan, i.e. *Streptococcus* spp., *Klebsiella* spp., *Enterobacter* spp., *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*, foreign clinical data can be used because (a) the susceptibility of these species does not differ significantly between Japan and foreign countries, and

(b) as the AUC in Japanese subjects was 1.4 times higher than in non-Japanese subjects, these microorganisms are susceptible to GRNX based on MIC_{90}, and free AUC/MIC of at least 50 can be achieved. Moreover, the use of foreign clinical data enables comparison to be made with other drugs also for class effects as well, such as QTc interval prolongation, blood sugar abnormalities, effects on the hepatic function/central nervous system, photosensitivity, and joint toxicity, which can also be used for safety assessment.

The PMDA asked the applicant to explain the basis for concluding that body weight differences do not affect the use of foreign clinical data despite the fact that non-Japanese subjects weighed 1.3 to 1.5 times heavier than Japanese subjects, resulting in higher AUC values in Japanese subjects.

The applicant responded as follows.
In the Japanese study 61006 and foreign study AI464003, which were PK/PD studies, the body weight of Japanese and non-Japanese subjects (mean±SD) was 52.8±13.0 kg and 80.0±22.8 kg, respectively, and the mean body weight of non-Japanese subjects was 1.5 times that of Japanese subjects. Meanwhile, the AUC (mean±SD) was 122.2±34.2 μg・hr/mL and 82.9±23.4 μg・hr/mL, respectively, and the mean AUC in Japanese subjects was about 1.5 times that in non-Japanese subjects, and this difference seemed to reflect body weight differences.

However, (a) The C_{max} and AUC are proportional to the dose in both Japanese and non-Japanese subjects and the pharmacokinetics, such as accumulation following multiple doses and plasma and urinary metabolites, are similar. Thus, GRNX is considered to be insensitive to intrinsic factors; (b) AUC/MIC ratio is considered as a measure of efficacy and higher efficacy is expected in Japanese patients as compared with non-Japanese patients at the same 400 mg dose; (c) with regard to the safety, a higher AUC in Japanese subjects resulted in an increased incidence of associated symptoms due to gastrointestinal disorders and a trend towards more reports of AST increased in terms of laboratory abnormalities. However, when the adverse events were assessed according to body weight in both Japan and overseas, there was no trend towards an increase in adverse events in low-body-weight patients and the effects of body weight differences are considered as being insignificant. Therefore, there should be no problem with using foreign clinical data.

The PMDA considers as follows: It is not appropriate to conclude that differences in the pharmacokinetics between Japanese and non-Japanese subjects are attributable to body weight differences only because both the body weight and AUC showed about a 1.5-fold difference between Japanese and non-Japanese subjects. Furthermore, as the dosage and administration of LVFX, which was used as a comparator in the foreign clinical study, are different between Japan and the foreign country (Study 61005: 100 mg three times daily, Study AI464019: 500 mg once daily), it is also difficult to infer the relationship between GRNX and LVFX in Japan by analogy, using this data. Consequently, the PMDA has decided to evaluate the efficacy and safety of GRNX by focusing on

Japanese clinical data.

(2) Efficacy

1) Microorganisms that could not be collected in Japanese clinical studies

From among the proposed microorganisms, the PMDA made considerations for *Escherichia coli*, *Legionella pneumophila, Streptococcus* spp., *Klebsiella* spp., *Enterobacter*. spp., and *Mycoplasma pneumoniae*, for which a sufficient amount of clinical isolates could not be collected in Japanese clinical studies, in terms of pharmacokinetics and drug susceptibility. Bacterial strains collected in Japanese and foreign clinical studies and *in vitro* antibacterial activity are presented below.

Bacterial strains collected in Japanese and foreign clinical studies and *in vitro* antibacterial activity

[Prepared by the PMDA]

	Source	No. of strains	MIC range (μg/mL)	MIC_{90} (μg/mL)	Efficacy rate (%)
Escherichia coli	Foreign clinical study	45	≦0.06-0.25[a)]	≦0.06	84.4 (38/45)[b)]
Legionella spp. *L. pneumophila*	Foreign clinical study	—	—	—	75.0 (6/8)[e)]
	Japanese non-clinical study	21	0.002-0.0078	0.0039	—
Streptococcus spp.	Japanese clinical study	21	≦0.025-0.10[c)] (≦0.06~0.12)[a)]	0.10 (0.12)	90.5 (19/21)[d)]
	Foreign clinical study	95	≦0.06-0.25	0.12	88.4 (84/95)[b)]
Klebsiella spp. *K. pneumoniae* *K. oxytoca*	Japanese clinical study	10 3	0.05-0.39[c)] (≦0.06~0.12)[a)]	—	100.0 (13/13)[d)]
K. pneumoniae *K. oxytoca* *K. ozenae* *K. terrigena*	Foreign clinical study	53 11 1 2	≦0.06-1[a)]	0.25	89.6 (60/67)[b)]
Enterobacter spp. *E. cloacae* *E. aerogenes*	Japanese clinical study	1 1	0.05, 0.78[c)] (≦0.06,1)[a)]	—	2/2[d)]
E .cloacae *E. aerogenes* *E. sakazakii* *E.agglomerans*	Foreign clinical study	26 8 2 1	≦0.06-4[a)]	0.5	94.6 (35/37)[b)]
Mycoplasma spp. *M. pneumoniae*	Japanese clinical study	25	0.008-0.03	0.03	100.0 (25/25)[d), e)]
	Japanese non-clinical study	50	0.0156-0.0625	0.0313	—
	Foreign clinical study	54	—	—	98.1 (53/54)[e)]
	Foreign (US) non-clinical study	42	0.015-0.06[a)]	0.03	—

a) MIC by NCCLS method b) Efficacy rate at 7 days after the end of treatment
c) MIC by the method recommended by the Japanese Society of Chemotherapy
d) Efficacy rate at the end of treatment
e) Confirmed cases

Based on the above, since (a) MIC_{90} values tend to be lower in Japan than in foreign countries although there are slight differences in bacterial susceptibility between Japan and foreign countries, , (b) AUC and C_{max} values are higher in Japanese subjects than in non-Japanese subjects, and (c)

AUC/MIC ratio is correlated with the therapeutic efficacy of GRNX, and from the pharmacokinetics data and from the point of view of PK/PD using GRNX susceptibility of recent Japanese clinical isolates etc., GRNX is expected to exceed the target value even against microorganisms that could not be collected in Japanese clinical studies , and the efficacy in Japanese patients is unlikely to fall below the efficacy in non-Japanese patients. Consequently, the PMDA has considered that GRNX may be indicated for infections caused by these microorganisms on the premise that cases of such infections will actively be collected in post-marketing surveillance.

This conclusion by the PMDA will be finalized, taking the comments from the Expert Discussion into account.

2) Efficacy against resistant bacteria

The PMDA asked the applicant to explain the usefulness of GRNX against various resistant bacteria.

The applicant responded as follows.

Three strains of MRSA were isolated in Japanese studies and among which, 2 strains were eradicated by GRNX. In foreign studies, 16 strains were isolated and GRNX was effective against 14 of them. GRNX achieved eradication rates of 100% forpenicillin-resistant *Streptococcus pneumoniae* (27 cases of PRSP and 34 cases of PISP) and an eradication rate of 100% for 83 strains of multi-drug resistant *Streptococcus pneumoniae* as well. Foreign studies also showed that GRNX had eradication rates of 85.7% (12/14) for PRSP and 96.3% (77/80) for PISP. In Japan, 32 strains of *Moraxella (Branhamella) catarrhalis* were isolated and there were 29 cases of β-lactamase producing strains, for which the eradication rate was 100% (29/29). Also in foreign countries, the eradication rate was high, i.e. 93.3% (125/134) for β-lactamase producing strains. In Japanese studies, 117 strains of *Haemophilus influenzae* were isolated and BLNAR accounted for 43.6% (51/117). BLNAR was eradicated by GRNX in all cases. In this way, GRNX was considered to have a high eradicating activity against various resistant bacteria as well.

The PMDA considers as follows.

The applicant also mentions various resistant bacteria separately in the proposed indications for GRNX, e.g. “Garenoxacin-susceptible strains of *Staphylococcus* sp. (including garenoxacin-susceptible MRSA).” However, if a study intended to evaluate the usefulness of GRNX against resistant species of bacteria has not been performed, such species of bacteria should be represented by the wording “Garenoxacin-susceptible”, instead of separately mentioning the infecting bacteria of the same species (for example, *Staphylococcus aureus*, MRSA).

(3) Safety

Serious adverse events including QT interval prolongation, blood sugar abnormalities, abnormal hepatic function, central nervous system disorders, and photosensitivity, which are peculiar to fluoroquinolone antibacterial agents, have been reported. Thus, an investigation has been conducted

for these adverse drug reactions known as the class effects and adverse reactions characteristic of GRNX.
The details of the results are described below for each event.

1) Decreased blood pressure
The PMDA asked the applicant to explain decreased blood pressure, which is a risk associated with GRNX.

The applicant responded as follows.
In Japanese phase II and phase III clinical studies, 10 out of the 699 subjects (1.4%) having blood pressure measured in the GRNX group experienced decreased blood pressure although no subjective symptoms were noted. The incidence of decreased blood pressure was higher in subjects with cardiac disorder, coronary disorder, hypotension, or hypertension compared to those without such conditions. In a LVFX-controlled study where blood pressure monitoring was strictly performed from early beginning (Study 61005), decreased blood pressure was not reported [Note by the PMDA: For LVFX, decreased blood pressure were reported at 1.7% (2/118 subjects).]. However, since adverse events relevant to hypotension occurred at a rate of 0.4% (14/3456 subjects) in foreign clinical studies of the oral formulation and adverse events relevant to hypotension occurred at a rate of 7.1% (70/987 subjects) in foreign clinical studies of the injectable, patients with a systolic blood pressure of $\leq$90 mmHg were excluded from enrollment during a Japanese phase III clinical study. Under such a situation, as the safety has not been confirmed in these patients and caution needs to be exercised for possible changes in blood pressure in patients with a systolic blood pressure $\leq$90 mmHg, those patients will be included in the Careful Administration section of the package insert and an adequate surveillance will be conducted also after marketing.

The PMDA asked the applicant to explain the reason for setting up the review committee on blood pressure/pulse rate/respiratory rate in Study 61008 involving patients with respiratory tract infections.

The applicant responded as follows.
Considering that a causal relationship between GRNX and the occurrence of hypotension needs to be assessed, we commissioned the clinical trial committee of the Japanese Society of Chemotherapy, consisting of specialists not involved in the development of GRNX (the meeting held in [redacted] 20[redacted]), to perform such an assessment, with the intention of having a third party conduct the assessment. Referring to its results, the medical expert and coordinating investigators for the development of GRNX discussed the appropriateness of continuing the study ([redacted] 20[redacted]) and concluded that "at the present stage, the clinical study should be progressed with, by thoroughly issuing an alert." Based on these results, it was decided to ask a cardiologist to perform safety assessment on blood pressure changes etc. and a [redacted] with a safety assessment specialist was concluded as of [redacted] 11, 20[redacted]. Adverse events were to be closely examined by this review committee on blood pressure/pulse rate/respiratory rate, and a record of its review was to be reported to "a case review meeting" after the

completion of the study. As the outcome of this review consisted solely of the results of a review by a cardiologist, this outcome was considered as not affecting the results of assessment by the principal investigator, and was positioned as reference data for the "case review meeting."

The PMDA considers as follows.
Adequate caution is needed because (a) although direct comparison is difficult, the incidence of decreased blood pressure is higher in Japanese clinical studies compared to foreign clinical studies of the oral formulation, (b) Japanese patients compared to non-Japanese patients have higher exposure and are likely to be at higher risk for decreased blood pressure also from a pharmacokinetic point of view as well. It is important that patients themselves are fully informed of the risk for decreased blood pressure/the early detection etc., not to mention patients with a systolic blood pressure of $\leq$90 mmHg, cardiac disorder, coronary disorder, hypotension or hypertension and those receiving anti-hypertensives. Since the mechanism of the development of hypotension has not been clarified, an investigation to elucidate the mechanism should also be continued.

2) Blood sugar abnormalities
The PMDA asked the applicant to explain about blood sugar abnormalities associated with GRNX.

The applicant responded as follows.
One subject experienced symptomatic blood sugar abnormalities as a non-serious adverse event in a Japanese clinical study. This subject had sweating and coldness at around 22:00 on the night of the 6th day after the end of treatment with GRNX, visited an emergency outpatient clinic and was found to have a blood glucose level of 66 mg/dL suggestive of hypoglycaemia. However, the principal investigator commented that the event seemed associated with dehydration after having a bath and self-adjustment of insulin dose and denied its causal relationship to GRNX. In clinical studies, adverse events of blood sugar decreased and blood sugar increased were reported by 2.8% (19/682 subjects) and 8.4% (57/682 subjects), respectively, and among which, those classified as adverse drug reactions were reported by 1.3% (9/682 subjects) and 1.8% (12/682 subjects), respectively. These laboratory abnormalities were mostly mild or moderate in severity. Although there were 2 severe cases, as both of them had concurrent diabetes, blood glucose changes were determined to be due to the primary disease and a causal relationship to GRNX was denied. In Study 61006, laboratory abnormalities and AUC or C_{max} were evaluated. As a result, blood sugar increased was not correlated with either parameter. In foreign clinical studies of oral GRNX, the incidences of adverse events such as hypoglycaemia and hyperglycaemia with GRNX were similar to those with the comparators, i.e. AZM, CAM, AMPC/CVA, LVFX, and CPFX+MNZ. The incidence of laboratory abnormalities of blood sugar decreased among diabetic patients was 1% (3/301 subjects). The incidence of blood sugar increased was similar to those with the comparators. As described above, although it is necessary to pay attention to possible hyperglycaemia in diabetic patients, the incidence of serious hypoglycaemia as reported with GFLX, a drug of the same class, should be low.

The PMDA considers as follows.
In clinical studies of GFLX, a drug of the same class, conducted for regulatory submission, the incidence of abnormal changes in blood sugar related to GFLX was 0.1% (1/882 subjects) and the incidence of abnormal changes in blood sugar regardless of relationship to GFLX was merely 1.9% (21/1079 subjects: blood sugar decreased in 6 subjects, blood sugar increased in 15 subjects) (NIHS Notification No. 2045 dated 15 January 2002, Gatifloxacin Review Report). However, in post-marketing surveillance, 75 cases of serious hypoglycaemia and 14 cases of serious hyperglycaemia were reported, leading to the issuance of an alert about serious hypoglycaemia and hyperglycaemia (the estimated number of patients exposed to GFLX: 4.2 million, "Dear Dr. Letter" hypoglycaemia and hyperglycaemia associated with Gatiflo Tablets 100 mg, March 2003). The effects on insulin secretion were investigated with GFLX, whereas there have been no reports on the effects of GRNX on insulin secretion and, at the present stage the reported incidence of blood sugar abnormalities associated with GRNX can never be underestimated. Therefore, the PMDA believes that it is necessary to collect information properly after marketing and provide information promptly.

3) QTc interval prolongation
The PMDA asked the applicant to explain the effects of GRNX on QTc interval.

The applicant responded as follows.
In Japanese phase II and phase III clinical studies, there were no adverse events relevant to ECG abnormalities. Electrocardiography was performed in 483 subjects on the 3rd day of treatment and in 250 subjects on the 9 day of treatment. As a result, all of 3 subjects with QTc interval increase from baseline >60 msec and absolute QTc interval prolongation according to the Bazett's formula had an underlying cardiac disorder. All subjects including these subjects with QTc interval prolongations, showed no abnormal ECG findings. In foreign phase II and phase III clinical studies, the incidence of adverse events relevant to ECG abnormalities such as ventricular tachycardia, ventricular fibrillation, and ventricular flutter in the GRNX group was similar to those in the control groups. QTc interval prolongation following the administration of GRNX was not noted and there were no concentration-dependent QTc interval prolongations in common with other drugs of the same class. Based on these study data, GRNX is unlikely to cause QTc interval prolongation. Meanwhile, as QTc interval prolongation associated with hERG channel inhibition was observed at a high dose in a non-clinical study, it should be necessary to advise caution as described below so that GRNX is administered carefully to patients with QT interval prolongation. Specifically, patients will be advised to check subjective symptoms such as syncope and dizziness and medical institutions will be advised to check QTc changes and ventricular fibrillation and ventricular flutter by ECG. A study on QT interval prolongation is also planned for post-marketing surveillance.

Although the following 3 subjects received GRNX and died from acute myocardial infarction or acute cardiac failure within 30 day after the end of treatment with GRNX in Japan, a causal relationship to GRNX was denied by the principal investigator for all cases.

Case Number	Study Number	Age (years)	Sex	Cause of death	Duration of treatment (days)	No. of days from the end of treatment to death
510002	61005	72	Male	Acute myocardial infarction	10	9
600206	61006	78	Female	Acute cardiac failure	3	2
607403	61006	75	Male	Acute myocardial infarction	6	21

With respect to a patient with QTc interval prolongation (the Bazett's formula) in Study 61008, the principal investigator commented, "as the patient had not been going to a medical institution in the past, it was revealed after hospitalization that the patient had hypertension and diabetes left untreated for many years and it appears that a considerable burden has been placed on the heart for a long time." In addition, at an ECG review meeting held on [redacted] 7, 20[redacted], the ECG reader commented, "Chronic respiratory disease and myocardial disorder are suspected based on high P wave, widened QRS width, a negative P wave in V1, and ST-T change, and the patient has pre-existing secondary cardiac stress and myocardial disorder and is not eligible for enrollment into the study. The patient has hypertenstive cardiomyopathy." As to this comment, the case review committee instructed the ECG reader to reassess a causal relationship of cardiac failure and QTc interval prolongation with the investigational product. The ECG reader expressed his opinion as follows: "widened QRS width in ECG obtained from this patient was a finding that coincided with cardiac failure symptom occurring during the clinical study and I can not make a firm judgment on a relationship of the investigational product with the progression of cardiac failure and QTc. However, if organic myocardial disorder is present, serious respiratory failure would often result in the manifestation or exacerbation of cardiac failure and I think that the result of assessment by the patient's doctor (assessed as unrelated to the drug) is acceptable." The PMDA has judged that this opinion of the ECG reader is justified.

At the present stage, the PMDA has judged that such applicant's view on alerting patients and healthcare professionals appropriately and then continuing to monitor QT interval prolongation even after marketing, is appropriate. [See "(ii) <Outline of the review by the PMDA> (8) Post-marketing surveillance"]

4) Pigmentation

With respect to pigmentation specific to GRNX, as discussed in "Summary of toxicology studies" and "Outline of the review by the PMDA," the possibility of tissue coloration during a long-term treatment with GRNX can not be excluded and observation of oral mucosa alone as performed in clinical studies can not cover pigmentation in other organs. Therefore, the PMDA considers that the effects on the human body are unclear with the submitted data at the time of regulatory review. It should be necessary to continue to investigate pigmentation associated with GRNX for its mechanism of development, the identification of a causative substance and the effects of tissue pigmentation on

the function of pigmented organs, etc.

5) Photosensitivity

The PMDA asked the applicant to explain the potential of GRNX for causing photosensitivity.

The applicant responded as follows.

(a) Non-clinical studies including a 2-week oral administration phototoxicity study in hairless mice and a single intravenous administration phototoxicity study in guinea pigs demonstrated no phototoxicity of GRNX, (b) there were no photosensitive reactions in Japanese clinical studies, (c) a foreign clinical pharmacology study in healthy adults showed that the photosensitivity of GRNX was weaker than those of CPFX and LFLX, (d) in phase II and phase III clinical studies, photosensitive reactions, sunburn, and rash occurred less frequently with GRNX compared with LVFX, CPFX+MNZ, and AMPC/CVA, (e) photosensitive reactions and sunburn observed were mild, which were different from severe cases as reported with SPFX and LFLX. Based on the above, there should be no major problems.

The PMDA accepted the above response on the premise that post-marketing adverse drug reaction information will be examined carefully, although it was difficult to assess the photosensitivity adequately with the number of cases collected from Japanese and foreign clinical studies.

6) Hepatic dysfunction

The PMDA asked the applicant to explain about hepatic function abnormalities associated with GRNX.

The applicant responded as follows.

In a phase III study, there were abnormalities of aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), γ-glutamyl transpeptidase (γ-GTP), and blood bilirubin and conjugated bilirubin, but the incidence of these abnormalities with GRNX was similar to that with LVFX as the comparator. Among subjects with serious abnormalities in liver function test values, 1 subject simultaneously had eosinophil count abnormal, which was a transient change, unlike serious acute hepatitis as reported with trovafloxacin. Moreover, 0.1% of the subjects (1/690 subjects) simultaneously had an increase in ALT $\geq$3 times the upper limit of normal and an increase in blood bilirubin $\geq$2 times the upper limit of normal, which are considered as significant liver disorder. This subject had concurrent acute cardiac failure and ALT increased was considered the consequence of cardiac failure. The occurrence of hepatic function abnormalities was not correlated with AUC or C_{max} nor with body weight or age. Therefore, the occurrence of hepatic disorders with GRNX was similar to those with AZM, CAM, LVFX, and AMPC/CVA etc. and severe hepatitis involving allergy as reported with trovafloxacin, did not occur.

The PMDA confirmed that the incidence of hepatic dysfunction with GRNX was similar between

Japan and foreign countries and to those with the comparators based on the results of pooled analysis from clinical studies submitted this time (the tables below). However, following the administration of GRNX 400 mg, abnormal laboratory changes with an incidence higher in Japan than in foreign countries were ALT and AST only and Japanese patients have higher exposure than in non-Japanese patients. Thus, further information collection is needed also after marketing.

Incidence of adverse events (associated symptoms) by organ system (pooled analysis of foreign clinical studies)

Adverse events by organ system (associated symptoms)	GRNX (N=2792)	β-lactams (N=629)	Quinolones (N=134)	Macrolides (n=698)
ALT increased	7(0.3%)	3(0.5%)	0(0.0%)	1(0.1%)
AST increased	5(0.2%)	2(0.3%)	0(0.0%)	2(0.3%)
Liver function tests abnormal	5(0.2%)	0(0.0%)	2(1.5%)	3(0.4%)
Blood ALP increased	2(0.1%)	0(0.0%)	0(0.0%)	0(0.0%)
Blood ALP abnormal	0(0.0%)	0(0.0%)	0(0.0%)	1(0.1%)
Hepatic enzyme increased	1(0.0%)	0(0.0%)	1(0.7%)	4(0.6%)

Incidence of abnormal laboratory changes (pooled analysis of Japanese and foreign clinical studies)

Laboratory parameter, grade		GRNX group		Control group (Overseas)			
		Japan	Overseas	Total	Quinolones	Macrolides	β-lactams
ALP	Overall	20/690(2.9%)	101/2680(3.8%)	77/1403(5.5%)	16/130(12.3%)	16/678(2.4%)	45/595(7.6%)
	grade3-4	0/690(0.0%)	0/2680(0.0%)	0/1403(0.0%)	0/130(0.0%)	0/678(0.0%)	0/595(0.0%)
ALT	Overall	86/692(12.4%)	279/2665(10.5%)	185/1392(13.3%)	29/130(22.3%)	66/666(9.9%)	90/596(15.1%)
	grade3-4	2/692(0.3%)	13/2665(0.5%)	9/1392(0.6%)	2/130(1.5%)	2/666(0.3%)	5/596(0.8%)
AST	Overall	71/692(10.3%)	253/2675(9.5%)	168/1402(12.0%)	18/130(13.8%)	84/676(12.4%)	66/596(11.1%)
	grade3-4	1/692(0.1%)	13/2675(0.5%)	10/1402(0.7%)	3/130(2.3%)	4/676(5.9%)	3/596(0.5%)
TB	Overall	14/690(2.0%)	98/2661(3.7%)	44/1388(3.2%)	4/130(3.1%)	19/667(2.8%)	21/591(3.6%)
	grade3-4	0/690(0.0%)	2/2661(0.1%)	0/1388(0.0%)	0/130(0.0%)	0/667(0.0%)	0/591(0.0%)

7) Central nervous system disorders

The PMDA asked the applicant to explain the effects of GRNX on the central nervous system.

The applicant responded as follows.

With respect to central nervous system disorders, in Japanese clinical pharmacology studies, mental disorder did not occur, but nervous system disorders including headache (12.2%, 9/74 subjects), somnolence (4.1%, 3/74 subjects), and dizziness (2.7%, 2/74 subjects) were observed. In Japanese clinical studies, as adverse events classified as mental disorders, insomnia occurred (1.9%, 13/702 subjects) and among which, those events for which a causal relationship to GRNX could not be denied were reported by 0.6% (4/702 subjects). The main adverse events classified as nervous system disorders were headache (3.7%, 26/702 subjects) and dizziness (1.4%, 10/702 subjects) and among which, those events for which a causal relationship to GRNX could not be denied were reported by 1.7% (12/702 subjects) and 0.9% (6/702 subjects), respectively. The occurrence of nervous system disorders was not correlated with AUC or C_{max}. In foreign clinical studies, combination therapy with nonsteroidal antiinflammatory drugs such as ibuprofen, naproxen, and diclofenac sodium was

performed, and there were no drug interactions, such as clinically significant adverse reactions and convulsion did not occur, either.

The PMDA considers as follows.
As with other drugs of the same class, dizziness occurred with GRNX and the incidence of dizziness with fleroxacin whose incidence is highest among drugs of the same class is 0.76% (Hori, Seiji et al.: Separate volume, Syndrome Series 27, Nervous syndrome II (Suwa, Yasuo ed.), Nihon-Rinsyo, 1999 p.552－557). Although direct comparison between this data and the above study data is difficult, as GRNX may have a higher incidence of dizziness compared with the existing drugs of the same class, it is necessary to advise caution about dizziness adequately and then collect further information also after marketing. The submitted study data shows no major problems with other adverse reactions affecting the central nervous system and the PMDA accepted the applicant's explanation that a caution will be included in the package insert etc.

(4) The clinical positioning of GRNX
The PMDA considered the clinical positioning of GRNX based on the applicant's response as follows.

1) Respiratory tract infections
The Infectious Diseases Society of America (IDSA)'s Practice Guidelines for the Management of Community-Acquired Pneumonia in Adults (Bartlet JG, et al. *Clin. Infect. Dis*. 2000; 31: 347-382) also recommends fluoroquinolones as a first-choice therapy for elderly patients and patients with underlying disease. In light of this fact, as the applicant claims, the PMDA considers that GRNX is positioned as a first-choice drug for empiric therapy for patients with suspected secondary infection of chronic respiratory disease who have mild or moderate pneumonia and can take food orally, patients with suspected bacterial pneumonia who have received antibiotics recently or are allergic to penicillin, and patients with suspected atypical pneumonia who are aged 65 years or older or have underlying chronic heart or lung disease. According to the frequency of isolation of common resistant bacteria from Japanese clinical studies (see the table below), the frequency of isolation of resistant bacteria is increasing and GRNX with activity against PRSP, PISP, and BLNAR seems useful compared with other fluoroquinolones. On the other hand, based on the fact that the safety of the aforementioned tissue pigmentation is unclear, the PMDA believes that if other fluoroquinolones can be used, the use of GRNX before them is not recommended.

Frequency of isolation of common resistant bacteria from Japanese clinical studies

Resistant bacteria	Frequency of isolation (%)
S.aureus	
MRSA	6.0 (3/50 strains)
S.pneumoniae	
PRSP	20.8 (27/130 strains)
PISP	26.2 (34/130 strains)
Quinolone-resistant *S.pneumoniae*	2.8 (3/106 strains)
Multi-drug resistant *S.pneumoniae*	78.3 (83/106 strains)
M.catarrhalis	
β-lactamase-producing *M.catarrhalis*	90.6 (29/32 strains)
H.influenzae	
BLNAR	43.3 (52/120 strains)

Concerning nosocomial pneumonia, the applicant responded that the major pathogens are *S. aureus*, *P. aeruginosa*, *K. pneumoniae*, *E. cloacae*, *X. maltophilia*, *S. marcescens*, *H. influenzae*, *S. pneumoniae*, *A. calcoaceticus*, *and E. coli* and GRNX can be used for GRNX-susceptible microorganisms regardless of community-acquired pneumonia or nosocomial pneumonia. However, since patients with nosocomial pneumonia are more likely to have underlying conditions/previous illnesses and are more likely to have received antibiotics or immunosuppressive drugs and have undergone operation, compared to those with community-acquired pneumonia, the PMDA considers that those patients with nosocomial pneumonia are likely to become candidates to receive injectables.

Regarding the development of GRNX injectable in Japan, although a phase I single intravenous administration study (Study 70001) was conducted in 20[redacted], the development of the oral formulation (the product submitted for registration) took precedence and a study of GRNX injectable has not been performed since then. As retrospective analysis of foreign clinical studies of GRNX injectable showed that the incidence of decreased blood pressure was higher with GRNX than with the comparator, there is also a concern about a possible increase in the incidence of decreased blood pressure when developing the injectable in Japan. Thus, the applicant has explained that it would consider developing the injectable after taking also account of the post-marketing safety of oral GRNX.

For secondary infection of chronic respiratory disease, the applicant has explained that high doses of the existing fluoroquinolones or penicillin antibiotics are used in view of anti-resistance measures and the penetration into the lesion. The applicant responded that GRNX, compared with other fluoroquinolones, achieves high tissue concentrations as a reflection of high plasma concentrations and has a high AUC/MIC ratio and potent activity against multi-drug resistant bacteria, and a low MPC. Therefore, it should be possible to treat the disease while suppressing the production of resistant bacteria except for a population of patients with persistent infections caused by *Pseudomonas aeruginosa*.

The PMDA considers that it is necessary to judge which drug should be used, taking also account of safety factors such as tissue pigmentation, although high tissue concentrations and a low MPC can be an advantage of GRNX.

2) Otorhinologic infections

The applicant has described the necessity of GRNX for the treatment of otorhinologic infections as follows.

As the pathogens causing sinusitis, *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* etc. are important and caution needs to be exercised when choosing antibiotics against MRSA, highly β-lactamase producing *S. aureus*, *M. catarrhalis*, multi-drug resistant *S. pneumoniae* (MDRSP), and BLNAR etc., and reliable eradication of bacteria is recommended. In the present Japanese clinical study [Note by the PMDA: Study 61009], 1 strain each of PISP and PRSP, 5 strains of *M. catarrhalis* and 5 strains of BLNAR were isolated as pathogens from 25 subjects with sinusitis, and GRNX should be needed also for the reliable effectiveness and the prevention of the emergence of new resistant bacteria. *S. pneumoniae* and *H. influenzae* are the major pathogens of otitis media and *M. catarrhalis* and *S. aureus*, and group A beta-hemolytic streptococci are important as well. Also in the present Japanese clinical study, resistant bacteria including 2 strains of MRSA, 1 strain of PISP, 4 strains of PRSP, 5 strains of *M.catarrhalis*, and 3 strains of BLNAR were isolated from 47 subjects with otitis media, suggesting the necessity of GRNX.

The PMDA considers that the applicant's claim that GRNX is also effective against bacteria resistant to β-lactams etc. can be acceptable.

3) Choice between GRNX and other fluoroquinolones

The PMDA asked the applicant to explain the choice between GRNX and the applicant's products including tosufloxacin (hereinafter referred to as TFLX) and pazufloxacin (hereinafter referred to as PZFX).

The applicant responded as follows.

TFLX is an oral medicine, which is characterized by a potent antibacterial activity and a broad antibacterial spectrum. Both TFLX and GRNX are oral medicines and their indications overlap (respiratory tract infections and otorhinolaryngologic infections). We will recommend GRNX for pneumonia, otitis media, and sinusitis and TFLX, which has high sensitivity and potent antibacterial activity, for the pathogens of urinary tract infections and intestinal infections etc. PZFX is an injectable, characterized by higher C_{max} and faster elimination compared with the existing injectable fluoroquinolones, and is highly safe. The use of GRNX is recommended, among patients with severe pneumonia requiring hospitalization who received PZFX and then finished treatment with injectables, for those with pneumonia caused by GRNX-susceptible pathogens.

The PMDA considers that the usage of GRNX as described by the applicant is understandable from an efficacy point of view, given that the indication range of GRNX are narrower than those of TFLX and the oral formulation only was submitted for registration this time.

(5) Drug interactions

With regard to an investigation of the effects of drugs commonly used with GRNX on the incidence of adverse events, 380 subjects used concomitant antitussive/expectorant and 336 subjects used concomitant NSAID in Japanese clinical studies of GRNX, which did not result in an increased incidence of adverse events or an increased incidence of severe or serious adverse events. Thus, it was concluded that there are no interactions of GRNX with these drugs. As to NSAIDs which were commonly used with GRNX in foreign clinical studies of oral GRNX, the incidence of adverse events was not altered by concomitant ibuprofen or naproxen. Although the incidences of all adverse events affecting the central nervous system were elevated in subjects who received concomitant diclofenac sodium, the number of cases of such co-administration was limited and a relationship was unclear. There were no adverse events possibly relevant to GABA receptor inhibition, such as convulsion. A relationship between hypotension and the concomitant use of a diuretic drug (furosemide, etc.) as an antihypertensive, could not be analyzed rigorously due to a limited number of cases with hypotension, but its concomitant use with oral GRNX did not markedly alter the incidence of hypotension. There were no interactions with hypoglycemic drugs or insulin.

The PMDA considers as follows.

In non-clinical studies, GRNX has been determined to have less interactions with NSAID compared to other fluoroquinolones. However, based on the finding that the incidence of adverse events was increased with the concomitant use of diclofenac sodium although its relationship was unclear, it is necessary to exercise caution when using NSAID concomitantly. It is also necessary to be cautious about the concomitant use of GRNX with antihypertensives including diuretics or hypoglycemic drugs, as there are concerns of hypotension and hypoglycaemia. It is required to advise caution about the above two points in the package insert etc.

(6) Dosage and administration

The proposed dosage and administration is “The usual adult dosage for oral use is 400 mg of garenoxacin once daily.” The PRECAUTIONS section reads, “As a general rule, the duration of administration of this drug should be limited to the minimum period required for the treatment of the patient’s condition, after susceptibility of the microorganism to the drug has been confirmed, in order to prevent the emergence of drug-resistant microorganisms.” and “When the drug is used in low-body-weight (<40 kg) patients with severe renal impairment (Ccr <30 mL/min) who are not undergoing dialysis etc., a lower dose (200 mg) may be given at the discretion of the doctor.”

The PMDA asked the applicant to explain its view based on available clinical data (in terms of risk-benefit balance), concerning the reason for choosing 400 mg, instead of 200 mg, as the proposed dose.

The applicant responded as follows.

A phase II clinical study (Study 61003) investigated the safety and efficacy of 200 mg and 400 mg of

GRNX in patients with respiratory tract infections in an exploratory manner. As a result, the efficacy rate was 96.0% (24/25 subjects) at 200 mg and 87.5% (21/24 subjects) at 400 mg and there were no differences in the safety. The efficacy rate was slightly lower at 400 mg because more subjects with relatively severe conditions were assigned to the 400 mg group. The estimated efficacy rate at doses ≥200 mg was 100% for *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, i.e. the major pathogens of respiratory tract infections, while the estimated efficacy rate for *K. pneumoniae* was 80% at 200 mg and 87% at 400 mg. The MPC of GRNX was reported to be 0.031-1 μg/mL against strains of *S. pneumoniae* with MIC of 0.008-2 μg/mL and the trough value following the oral administration of 200 mg (0.8939±0.4169 μg/mL) falls below the MPC value, suggesting that 200 mg may be inadequate for preventing the development of bacterial resistance. Based on these findings, 400 mg, which is expected to produce a high efficacy rate from a AUC/MIC standpoint, was chosen as the recommended clinical dose.

A study investigating the efficacy, safety, and PK/PD parameters of GRNX in patients with secondary infection of chronic respiratory disease (Study 61006) was carried out. As a result, 400 mg of GRNX demonstrated adequate efficacy and there were no clinically relevant adverse events also from a safety point of view, justifying the clinical dose of 400 mg. Furthermore, a phase III, LVFX-controlled clinical study in patients with bacterial pneumonia (Study 61005) confirmed the non-inferiority of GRNX 400 mg over LVFX for the efficacy rate at the end of treatment. GRNX also achieved a high bacteriological response rate. In Japanese clinical studies, 31 subjects treated with 200 mg were compared with 671 subjects treated with 400 mg. As a result, since no negative results about the choice of 400 mg were obtained, it was decided to choose a dose of 400 mg.

The PMDA considers as follows.
Since the mean AUC in Japanese subjects was about 1.5 time that in non-Japanese subjects, there is a concern about a higher safety risk in Japanese patients than in non-Japanese patients. Meanwhile, in light of the fact that the dose used in a Japanese clinical study which successfully confirmed the non-inferiority of GRNX over LVFX (Study 61005) was 400 mg, it is unavoidable to choose 400 mg as the recommended clinical dose, which is expected to produce high efficacy from a PK/PD standpoint and suppress the emergence of resistant bacteria.

The above conclusion by the PMDA will be finalized, taking the comments from the Expert Discussion into account.

(7) Pediatric use

In the field of pediatric infections, it has been reported that the frequency of isolation of β-lactam-resistant *Streptococcus pneumoniae*, i.e. PISP and PRSP, and β-lactamase-nonproducing ampicillin resistant *Haemophilus influenzae* (BLNAR) tends to be increasing year by year these days. Therefore, the PMDA asked for the applicant's view on the development of GRNX to which PISP, PRSP, and BLNAR are susceptible for pediatric infections.

The applicant responded as follows.
GRNX has potent activity against the major pathogens of respiratory tract and otorhinolaryngologic infections and the development of GRNX for use in children has also been kept in mind since GRNX was selected as a compound for development. Based on non-clinical data etc., the development of GRNX for pediatrics should be undertaken as early as possible. However, according to the guideline for the clinical evaluation of antimicrobial agents, the confirmation of safety in an adult population should come before pediatric clinical trials for fluoroquinolones. Accordingly, we will consider the timing of development after confirming the post-marketing safety of GRNX to some extent.

The PMDA accepted the applicant's response.

(8) Post-marketing surveillance
For post-marketing surveillance, a Drug Use Investigation, the following Specified Drug Use Investigation to confirm the efficacy and safety of GRNX in the treatment of Legionella pneumonia, and Early Post-marketing Phase Vigilance have been planned.

In a Drug Use Investigation, a large number of Japanese patients exposed to GRNX will be collected and the occurrence of adverse drug reactions under routine drug uses will be identified. The sample size is 3000, which provides a 95% probability of detecting one case of adverse drug reactions with an incidence of 0.1% in the elderly patients including low-body-weight patients. The cardiovascular safety, such as hypotension in patients receiving concomitant nitroglycerin or isosorbide mononitrate etc. and its factors will be studied as the priority items.

A Specified Drug Use Investigation on Legionella pneumonia will be conducted to confirm the efficacy and safety of GRNX in the treatment of Legionella pneumonia because no patients with Legionella pneumonia could be collected during the development in Japan.

As described in (2) - 1) "Microorganisms that could not be collected in Japanese clinical studies," the PMDA considers that after marketing, it is necessary to actively collect cases of infections caused by not only Legionella but also other appropriate microorganisms for which a sufficient number of subjects could not be collected in Japanese clinical studies.

Since adequate safety information concerning the effects of GRNX on blood pressure and ECG QT interval was not available at present, the PMDA asked the applicant to explain about concrete measures such as post-marketing monitoring and alerting.

The applicant responded as follows.
The package insert of GRNX which is under regulatory review in the US [Note by the PMDA: The new drug application has been withdrawn] advises caution regarding the use of the injectable in

patients at risk of hypotension. Moreover, patients with a systolic blood pressure ≤90 mmHg were excluded from enrollment during a Japanese phase III clinical study and only a limited number of hypotensive patients have so far received GRNX. Therefore, also in the clinical use of oral GRNX in Japan, we will advise careful administration in patients with a systolic blood pressure ≤90 mmHg and intend to collect information on "the status of use in patients with a systolic blood pressure ≤90 mmHg and the occurrence of adverse reactions of decreased blood pressure" from early post-marketing phase. In addition, as to QT interval prolongation which was also observed with GRNX and has become a problem with other antibiotics of the same class, we are considering collecting information on "the status of use in patients with QT interval prolongation and the occurrence of adverse reactions of QT interval prolongation." However, after marketing, blood pressure or ECG is not taken in most cases, which makes it difficult to detect adverse reactions of hypotension or QT interval prolongation. Therefore, we will adequately educate MRs (medical representatives) based on internal training materials before the launch of the product and implement adverse drug reaction monitoring through these MRs. In this way, the status of use of GRNX in "patients with a systolic blood pressure ≤90 mmHg," "patients on vasopressors," "patients on nitroglycerin or isosorbide mononitrate" or "patients with QT interval prolongation," and "patients on class I antiarrhythmic drugs, patients on class III antiarrhythmic drug" will be surveyed and the information on patients suspected of having adverse reactions of hypotension or QT interval prolongation based on their symptoms will be gathered via interview, wherever possible. We plan to ask for the completion of a case report form for patients with subjective symptoms of "loss of consciousness, dizziness on standing up, dizziness, sleepiness, malaise, headache dull, etc." for hypotension and those with subjective symptoms of "tachycardia, bradycardia, dizziness, syncope, palpitations, short of breath, malaise, etc." for QT interval prolongation, so as to collect detailed information on the patient background and concomitant medications etc.

The PMDA considers as follows.
Regarding decreased blood pressure and QT interval prolongation, not only information collection via post-marketing surveillance, but also the preparation of information leaflets for patients are needed for the following reasons: (a) due to increased exposure, these events may occur more frequently in Japanese patients than in non-Japanese patients, (b) the product is an oral medicine and patients take the medicine outside the medical institutions. Thus, patients themselves have to pay attention to possible decreased blood pressure and become aware of subjective symptoms of adverse reactions.

As described in (3) - 4) "Pigmentation," the effects of tissue pigmentation on the human body are unclear with the submitted data. It should be necessary to continue to investigate pigmentation associated with GRNX for its mechanism of development, the identification of a causative substance and the effects of tissue pigmentation on the function of pigmented organs, etc.

Other priority items to be studied in post-marketing surveillance will be finalized, taking the comments from the Expert Discussion into account.

III. Results of Compliance Review on the Application Document and Conclusion

1. The PMDA's conclusion on the results of document compliance review

To be reported later.

2. The PMDA's conclusion on the results of GCP on-site inspection

To be reported later.

IV. Overall Evaluation

As a result of a regulatory review of the submitted data, the PMDA has judged that the efficacy of the product has been confirmed and that there should be no major safety problems affecting approval. The dosage and administration for the product has been established from a PK/PD standpoint, taking into account MPC as well and the product may be characterized by its usefulness in terms of not only the efficacy but also public health, i.e. the suppression of the emergence of resistant bacteria. Meanwhile, adverse reactions including decreased blood pressure and pigmentation which is peculiar to the product have also been reported. Concerning the pigmentation issue, since (a) both clinical and non-clinical information available is limited, (b) although a histological investigation has been conducted, the effects on the function are unknown, it is necessary to assess the benefit-risk balance, being well aware of these risks. Therefore, first of all, not only healthcare professionals but also patients should be cautioned by appropriate information provision and then detailed information should continue to be collected in non-clinical as well as clinical settings, also after marketing.

The PMDA has considered that the product may be indicated for infections caused by the microorganisms that were not isolated in Japanese clinical studies because the efficacy can be inferred from recent clinical isolates, pharmacokinetics, and foreign clinical data. This issue will be finalized upon taking the comments from the Expert Discussion into account.

Review Report (2)

May 15, 2007

I. Product Submitted for Registration

[Brand name] Geninax Tablets 200 mg

[Non-proprietary name] Garenoxacin Mesilate Hydrate

[Applicant] Toyama Chemical Co., Ltd.

[Date of application] May 30, 2006

II. Content of the Review

The Pharmaceuticals and Medical Devices Agency (PMDA) sought the comments from the Expert Discussion based on the Review Report (1). The outline of the comments from the Expert Discussion is shown below.

(1) Efficacy against microorganisms that could not be collected in Japanese clinical studies

Although a sufficient number of strains required for evaluation could not be collected for *Escherichia coli*, *Legionella pneumophila, Streptococcus* spp., *Klebsiella* spp., *Enterobacter*. spp., *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* from among the proposed microorganisms, the PMDA considered that the product may be indicated for infections caused by these microorganisms as well for the following reasons.

a. Foreign clinical studies have confirmed the efficacy against these microorganisms.
b. AUC and C_{max} values, which are considered to be correlated with the therapeutic efficacy of fluoroquinolones, were higher in Japanese subjects than in non-Japanese subjects and the efficacy in Japanese patients is unlikely to fall below that in non-Japanese patients.
c. There were no major differences in the drug susceptibility of clinical isolates between Japan and foreign countries.
d. The product is expected to exceed the target value based on the results of PK/PD analysis using the pharmacokinetics in Japanese subjects and the susceptibility of recent clinical isolates of the above microorganisms to GRNX.

The PMDA sought the comments from the Expert Discussion on the above conclusion.

The following comments were raised from the Expert Discussion.
These microorganisms are important pathogens of the diseases for which the product will be indicated and although a sufficient number of cases could not be collected in clinical studies, it is obvious from foreign clinical data and PK/PD that the product demonstrates efficacy. Thus, there should be no

problems with designating these microorganisms.
With respect to the description of the designated microorganisms, it was also suggested that some of the resistant bacteria listed should be deleted/amended, upon which the PMDA instructed the applicant to modify the description of the designated microorganisms.

The applicant accepted these modifications and responded that the resistant variants of *Staphylococcus aureus*, *Moraxella (Branhamella) catarrhalis,* and *Haemophilus influenzae* would be deleted and the description of the designated microorganisms would be changed to "garenoxacin-susceptible strains of *Staphylococcus* sp., *Streptococcus* sp., *Streptococcus pneumoniae* (including Penicillin-resistant *Streptococcus pneumoniae*), *Moraxella (Branhamella) catarrhalis*, *Escherichia coli*, *Klebsiella* sp., *Enterobacter.* sp., *Haemophilus influenzae, Legionella pneumophila, Chlamydia pneumoniae,* and *Mycoplasma pneumoniae*." However, the applicant expressed a wish to provide information on multi-drug resistant *Streptococcus pneumoniae* against which the efficacy of the product has been demonstrated by the clinical data presented at this time.

The PMDA accepted this request.

(2) Dosage and administration
The PMDA concluded as follows.
A phase II clinical study (Study 61003) evaluated the safety and efficacy of 200 mg and 400 mg of the product in patients with respiratory tract infections, which showed that the efficacy rate was 96.0% (24/25 subjects) at 200 mg and 87.5% (21/24 subjects) at 400 mg and that there were no major differences in the safety. As the mean AUC in Japanese subjects was approximately 1.5 times that in non-Japanese subjects, the product may be less safe in Japanese patients compared with non-Japanese patients. However, the dose used in a Japanese clinical study which confirmed the non-inferiority of GRNX over LVFX (Study 61005) was 400 mg. In light of these findings, although it is necessary to be cautious about the safety, a dosage regimen of 400 mg once daily may be chosen from the point of view of PK/PD and MPC.

The members of the Expert Discussion accepted the PMDA's conclusion, but suggested the need to give attention to the elderly, especially those aged over 80. Based on the Expert Discussion's comments, the PMDA instructed the applicant to include the age range that was actually studied in the "Use in the Elderly" section of the package insert, and to consider conducting "an investigation of the disposition kinetics of GRNX and adverse events in the elderly (including those aged over 80)" for post-marketing surveillance.

The applicant responded that the product had been administered to elderly patients in Japanese phase II and phase III clinical studies and that the age of elderly subjects actually treated with the product "65-94 years old" and the age of non-elderly "18-64 years old" would be included in the package insert.

Furthermore, the PMDA instructed the applicant to modify the wording about the administration of a lower dose of 200 mg to low-body-weight patients with severe renal impairment. The applicant responded that the wording for the Precautions of Dosage and Administration of the package insert would be changed as shown below, in accordance with the instruction. The PMDA accepted it.

(Before change)
2. When the product is used in low-body-weight (<40 kg) patients with severe renal impairment (Ccr <30 mL/min) who are not undergoing dialysis etc., a lower dose (200 mg) may be given at the discretion of the doctor.

(After change)
2. Use of a lower dose (200 mg) in low-body-weight (<40 kg) patients with severe renal impairment (Ccr <30 mL/min) who are not undergoing dialysis etc. is recommended. [See [Pharmacokinetics]]

[Pharmacokinetics]
6. Blood concentrations in patients with renal impairment
<Reference information>
The mean AUC was 219 μg•hr/mL (calculated value) following multiple administration of 400 mg to low-body-weight (<40 kg) patients with severe renal impairment (Ccr <30 mL/min) who are not undergoing dialysis etc.

(3) Post-marketing surveillance etc.
The applicant has submitted the following study plans for post-marketing surveillance.

1) Drug Use Investigation
3,000 cases (a sample size that provides a 95% probability of detecting one case of adverse drug reactions with an incidence of 0.1%) will be collected in order to identify the occurrence of adverse drug reactions under routine drug usage. As the product has the potential for causing an adverse reaction of decreased blood pressure, decreased blood pressure will be designated as a priority item.

2) Specified Drug Use Investigation
Since patients with Legionella pneumonia could not be collected in Japanese clinical studies, the efficacy and safety of the product in the treatment of Legionella pneumonia will be confirmed.

The PMDA considers that it is necessary to actively collect cases of not only Legionella pneumonia but also infections caused by the microorganisms for which a sufficient number of subjects could not be collected in Japanese clinical studies, via post-marketing surveillance. Regarding decreased blood pressure and QT interval prolongation, not only information collection via post-marketing surveillance, but also the preparation of information leaflets for patients are needed for the following

reasons: (a) due to higher exposure, Japanese patients may have higher risk for these events compared to non-Japanese patients, and (b) the product is an oral medicine and patients take the medicine outside the medical institutions. Thus, patients themselves have to become aware of and detect adverse reactions to the product.

The above idea of the PMDA was supported by the members of the Expert Discussion. Moreover, the following comment was raised by the Expert Discussion: abnormal glucose tolerance should also be investigated or that it is necessary to collect information on the safety etc. in elderly patients who could have high exposure.

In view of the comments from the Expert Discussion, the PMDA asked the applicant to consider the following points besides the items already presented, review the overall post-marketing surveillance, and submit the outlines of surveillance studies including individual schedules.

- Actively collect information concerning the diseases/microorganisms for which a sufficient number of cases could not be collected in Japanese clinical studies, e.g. Legionella pneumonia
- Collect information on abnormal glucose tolerance
- Collect information on the disposition kinetics of GRNX and the occurrence of adverse events in the elderly (including those aged over 80)
- Collect information on photosensitivity
- A study on pigmentation <including a non-clinical study>
- Effects on insulin secretion
- A follow-up on pigmentation

The applicant responded as follows.
In a Drug Use Investigation, at least 5,571 cases (at least 3,000 elderly cases) for the safety analysis population will be collected, and blood glucose abnormalities, cadiovascular abnormalities, whether or not concomitant antihypertensive drugs are used, and pigmentation will be chosen as the priority items. The incidence of photosensitivity will also be assessed in the Drug Use Investigation. At least 20 cases of Legionella pneumonia to be included in the analysis will be collected. In non-clinical studies, a substance causing pigmentation will be identified, the function of pigmented organs will be examined as measured by the cardiovascular function of dogs administered multiple doses of the product (blood pressure and heart rate), and insulin secretion in dogs will be investigated.

Concerning a non-clinical study on pigmentation, the PMDA instructed the applicant to also conduct (a) a detailed histological examination by an electron microscope, and (b) *in situ* study on the vascular function etc., using *in vivo* pigmented blood vessels. The applicant accepted it.

(4) Others

Based on the Expert Discussion, the PMDA asked the applicant to prepare patient information leaflets describing specific symptoms in an easy-to-understand manner for pigmentation, decreased blood

pressure, and QT interval prolongation etc., which are adverse drug reactions of concern, so that patients themselves will be able to become aware of these adverse reactions. In addition, given that there are concerns about adverse reactions of hypotension, abnormal glucose tolerance, and convulsion, the PMDA instructed the applicant to include patients with abnormal glucose tolerance and patients with convulsive disease in addition to patients with hypotension and patients with QT interval prolongation in the Careful Administration section of the package insert and advise caution regarding the concomitant use with anti-hypertensives including diuretics or hypoglycemic drugs in the package insert.

The applicant responded that it would prepare patient information leaflets ("*Kusuri-no-Shiori*") containing the following items for providing information to patients, and that they would advise caution in the package insert in accordance with the PMDA's instruction. The PMDA accepted it.

[Pigmentation (no reports in humans)] The skin or the inside of the mouth may be colored reddish violet.
[Decreased blood pressure] Symptoms such as dizziness, lightheadedness, feelings of weakness, malaise, headache, and heaviness of head, may occur.
[Blood sugar abnormalities] 1) Hypoglycaemia: Symptoms such as dizziness, hunger, lightheadedness, tremor of hands and feet, feelings of weakness, headache, palpitations, and cold sweat, may occur. 2) Hyperglycaemia: Symptoms such as thirst, excessive drinking, polyuria, the body feels heavy, and feelings of weakness, may occur.
[QT interval prolongation (no reports in humans)] Symptoms such as the pulse quickens, palpitations, shortness of breath, faint, loss of consciousness, strange feeling of chest, and chest pain, may occur.

(5) Stability data on the drug product

Stability data up to 24 months from a long-term testing of the drug product that was ongoing (30℃ /65%RH) was additionally submitted. As a result, based on the ELD/PMSB Notification No. 0603004 dated June 3, 2003 "Guideline for the Evaluation of Stability Data," it has been concluded that the proposed shelf life of 3 years is justified when the drug product packaged in a PTP sheet or a high density polyethylene bottle is stored at room temperature.

III. Results of Compliance Review Concerning the Documents Appended to the New Drug Application and Conclusion by the PMDA

1. The PMDA's conclusion on the results of document compliance review

Document compliance review was conducted in accordance with the provisions of the Pharmaceutical Affairs Law for the documents appended to the new drug application. As a result, although cases of failure to assess the efficacy rate as per the protocol were found sporadically and such judgment was justified by the case review committee for some cases, as there were no major problems, it was concluded that there should be no problem with conducting regulatory review based on the application dossier.

2. The PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Law for the documents appended to the new drug application (CTD: 5.3.3.1.1, 5.3.3.1.2, 5.3.5.A.2.1, 5.3.1.1.2, 5.3.5.A.1.1, 5.3.5.A.2.2, 5.3.3.1.7, 5.3.5.A.2.3, 5.3.5.B.2.1, 5.3.5.A.2.4, 5.3.5.B.2.2, 5.3.3.1.8, 5.3.3.4.2). As a result, the following cases were noted: failure to perform appropriate monitoring activities in accordance with the standard operating procedures (the sponsor); whether or not the appropriateness of conducting a proposed clinical study was adequately reviewed at the IRB could not be confirmed from the retained records at some medical institutions; enrollment of subjects who met the exclusion criteria in relation to illnesses as specified in the protocol into the study; failure to perform tests; and errors and omissions etc. in transcribing data from the source document to the case report form. However, as there were no major problems, the PMDA concluded that there should be no problem with conducting regulatory review based on the application dossier.

IV. Overall Evaluation

The PMDA judged that the submitted data confirms the efficacy of the product and that there should be no major safety problems affecting approval. Also, in the PMDA' opinion, with regard to the issues for which the PMDA considers that information should continuously be collected, the applicant has responded that information will be collected appropriately through the post-marketing surveillance.

As a result of the above review, the PMDA has concluded that the product may be approved for the following indications and dosage and administration. The re-examination period is 8 years, it is appropriate to designate the drug substance as a powerful drug, and the drug product is not classified as a poisonous drug or a powerful drug nor a biological product or a specified biological product.

[Indications] <Microorganisms>
Garenoxacin-susceptible strains of *Staphylococcus* sp., *Streptococcus* sp., *Streptococcus pneumoniae* (including Penicillin-resistant *Streptococcus pneumoniae*), *Moraxella (Branhamella) catarrhalis*, *Escherichia coli*, *Klebsiella* sp., *Enterobacter* sp., *Haemophilus influenzae, Legionella pneumophila, Chlamydia pneumoniae,* and *Mycoplasma pneumoniae*
<Diseases>
Laryngopharyngitis, tonsillitis (including peritonsillitis and peritonsillar abscess), acute bronchitis, pneumonia, secondary infection of chronic respiratory disease, otitis media, sinusitis

[Dosage and administration] The usual adult dosage for oral use is 400 mg of garenoxacin once daily.