Efficacy and safety of garenoxacin tablets on bacterial pneumonia: postmarketing surveillance in Japan

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Abstract

We performed a postmarketing surveillance study to determine the efficacy and safety of the oral quinolone antibacterial agent, garenoxacin (Geninax® Tablets 200 mg), against bacterial pneumonia.

Between October 2009 and March 2011, patients with community-acquired pneumonia visited 174 facilities in Japan; we collected survey forms from 739 patients of these patients who were suspected with bacterial pneumonia on the basis of factors, e.g., the presence of purulent sputum or suspected presence of bacterial pathogens in clinical specimens. We examined the safety in 730 patients and the efficacy in 535 patients.

The efficacy rate of garenoxacin for bacterial pneumonia was 92.8% (479/516 patients). The eradication rates for *Streptococcus pneumoniae* and *Haemophilus influenzae*, the major pathogens of bacterial pneumonia, were 98.5% (65/66 strains) and 100% (65/65 strains), respectively.

The incidence of adverse drug reactions (including abnormal laboratory tests) was 7.9% (58/730 patients). Among the main adverse drug reactions, abnormal laboratory tests were observed in 2.1% patients (15/730), hepatobiliary disorders were observed in 1.8% patients (13/730), and skin and subcutaneous tissue disorders were observed in 1.6% patients (12/730).

In conclusion, garenoxacin showed an efficacy rate of greater than 90% for bacterial pneumonia and is considered to be useful in daily practice.

Key words:
garenoxacin, postmarketing surveillance, bacterial pneumonia, clinical efficacy, safety

Text

(1) Introduction

Garenoxacin (GRNX) is an oral quinolone antibiotic manufactured by Toyama Chemical Co., Ltd. (Tokyo, Japan); the company obtained the approval for manufacturing and marketing this medication in July 2007 under the product name Geninax® Tablets 200 mg. GRNX has a novel and unique chemical structure with lack of fluorine atom at the 6-position of the quinolone skeleton, which is normally considered essential to the antibacterial activity of conventional fluoroquinolones. GRNX shows excellent antibacterial activity against major bacterial pathogens in respiratory and otorhinolaryngological infections by inhibiting type II topoisomerases (DNA gyrase and topoisomerase IV), which are involved in bacterial DNA replication. In addition, GRNX shows strong antibacterial activity against penicillin-resistant *Streptococcus pneumoniae*, the increasing prevalence of which in the recent years has become a cause of concern [1, 2]. Further, because this drug shows a large AUC [3] and good tissue penetration [4, 5] after administration of a single dose of 400 mg/day, plasma concentrations in excess of the mutant prevention concentration for *S. pneumoniae* and *Staphylococcus aureus* were obtained for more than 24 h. Thus, GRNX is expected to prevent the emergence of drug-resistant strains [6].

In the clinical development study of GRNX, however, evaluable patients were limited to those who met strict inclusion and exclusion criteria to accurately assess the efficacy and safety of GRNX. Such development study might not necessarily reflect the actual patient population. Thus, we conducted a study in patients treated with GRNX in daily clinical practice basis.

In this study, we performed a specified postmarketing surveillance study to confirm the efficacy and safety of GRNX against bacterial pneumonia (including community-acquired pneumonia and nursing and healthcare-associated pneumonia [NHCAP], not including hospital-associated pneumonia) in daily clinical practice. We collected data regarding efficacy, safety, and causative bacterial pathogens in patients with bacterial pneumonia with various backgrounds.

(2) Patients and methods

(2)-1 Target patients

The study was conducted in patients who were treated at 174 medical institutions

across Japan between October 2009 and March 2011 and who met the following inclusion and exclusion criteria (Table 1).

The inclusion criteria were as follows:

1. Patients who were 15 years or older
2. Patients who had infiltrative shadows that thought to have appeared acutely and newly on chest radiographic images and not exceeding 2/3 of one lung
3. Patients who had purulent sputum or in whom a bacterial pathogen was presumed to be present in clinical specimens (e.g., the sputum) or who had a positive result in urinary antigen test
4. Patients who had respiratory symptoms (e.g., cough, chest pain, or dyspnea)
5. Patients who could ingest orally
6. Patients who had no concomitant atypical pneumonia as confirmed by rapid diagnosis (ImmunoCard® Mycoplasma, Meridian, USA) when GRNX therapy was initiated
7. Patients who did not require a combination of other antibiotics or steroids when GRNX therapy was initiated (however, patients undergoing long-term treatment with a low-dose macrolide antibiotic at a fixed dose or patients receiving a drug with a prednisolone conversion of ≤30 mg/day at a fixed dose continued these regimens)
8. Patients who took no other antibiotics within 7 days before initiation of GRNX therapy (however, patients in whom other antibiotics were considered to be ineffective and infection was detected were allowed)

The exclusion criteria were as follows:

1. Patients who had a history of hypersensitivity to GRNX or other quinolones
2. Patients who were pregnant or possibly pregnant or were lactating
3. Patients who previously enrolled in the study
4. Patients in whom drug efficacy of GRNX was difficult to assess
5. Patients whom the primary physician determined to be inappropriate for registration

(2)-2 Methods

This study was performed as a prospective study using a central registration system. The patients were registered on the registration center until the day after the beginning of GRNX. Informed consent and ethics committee approval were obtained as required for postmarketing surveillance. The survey items were as follows: patient characteristics (sex, age, inpatient/outpatient, weight, infectious disease diagnosis, severity of pneumonia [A-DROP scoring system], underlying diseases [diseases related to

pneumonia], complications [diseases not related to pneumonia], hepatic function disorder before GRNX therapy, renal impairment before GRNX therapy, and history of adverse drug reactions or allergies); antibiotics taken immediately before (within 1 week) initiation of GRNX therapy; administration status of GRNX (dose, number of doses, and administration period); concomitant drugs; combination therapies; clinical symptoms and signs; laboratory tests; bacteriological examinations; clinical efficacy; and adverse events. Rapid diagnosis and serological tests were performed as required.

GRNX was administered under the approved regimen, and the administration period was not limited. Concomitant drugs and combination therapies were not limited.

The observation period was until the termination of GRNX therapy, and adverse events were monitored until 4 days after GRNX therapy was terminated.

(2)-3 Efficacy evaluation

The clinical efficacy and bacteriological efficacy (prevalence of bacteria) were examined. Clinical efficacy was assessed at the termination of GRNX therapy and was classified as “effective,” “ineffective,” or “evaluation not possible” according to clinical efficacy criteria [7] (Table 2). In patients receiving GRNX for 10 days or more, an additional assessment was made on the 10^{th} day after initiation of GRNX. Bacteriological efficacy (prevalence of bacteria) was classified as bacterial “eradication” or “persistence” according to bacteriological efficacy criteria [7] on the basis the bacteriological examination results before and after GRNX therapy.

Safety was evaluated on the basis of the occurrence of adverse drug reactions. Adverse drug reactions were any events which a causal relationship with GRNX could not be denied during the observation period, such as medically unfavourable and unintended signs and symptoms (e.g., abnormal changes in laboratory tests and clinical symptoms and signs). Exacerbation of the pneumonia because of insufficient response to GRNX was not included.

(2)-4 Assessment of judgment/totalization results

An evaluation committee was formed with 5 members (one principal investigator, three coordinating investigators, and a representative physician) to discuss whether to include the problem cases, the handling of data in cases that deviated from the protocol, the handling of bacterial pathogens, and causal relationships between adverse events and GRNX therapy.

The term “bacterial pathogens” referred to bacteria that were detected at a score of ≥3+ (the level of $\geq 10^5$ colony-forming units/ml) derived from sputum. *S. pneumoniae* and *Haemophilus influenzae* detected at a clear level were classified as bacterial

pathogens. In addition, positive *S. pneumoniae* urinary antigen test results and positive *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* serological test results were also obtained to detect bacterial pathogens.

Adverse drug reactions were analyzed using the Medical Dictionary for Regulatory Activities, Japanese version (MedDRA/J, ver. 15.0).

(2)-5 Analysis sets

Efficacy was evaluated in the patients in the efficacy analysis set, which included patients from whom survey forms were collected and who met the inclusion and exclusion criteria and who received GRNX under the approved regimen. The safety was evaluated in the patients in the safety analysis set from whom survey forms were collected and who received GRNX at least one time.

(2)-6 Statistical analysis

Statistical analysis was performed using χ^2 test for comparison, and when the expected values were 5 or less, Fisher's exact probability test was employed.

(3) Results

(3)-1 Analysis sets and patient characteristics

The analysis sets are shown in Figure 1.

Patient characteristics of efficacy and safety analysis sets are shown in Table 3.

Among the safety analysis set, 59.0% of patients were male with an average age of 61.6 years and 51.8% (of the total set) were elderly (≥65 years). Moreover, 90.5% were outpatients, 62.2% experienced mild pneumonia according to the A-DROP scoring system, and 36.7% experienced moderate pneumonia. Underlying diseases (diseases related to pneumonia) and complications (diseases not related to pneumonia) were observed in 47.1% and 51.2% of the patients, respectively, both accounting for approximately half of the patients. The maximum daily dose of GRNX was 400 mg, which was administered to a majority of the patients (98.2%). In 13 patients, the dose was adjusted to 200 mg per day by attending physicians because of low weight (<40 kg), advanced renal impairment, advanced age (≥75 years), or the presence of adverse events. The average administration period was 8.7 ± 3.6 days, with the greatest number of patients at 3 to 7 days (48.6%), followed by 8 to 14 days (44.2%). Patient characteristics in the efficacy analysis set were almost same as those in the safety analysis set.

In patients from whom survey forms were collected, bacterial culture before GRNX

therapy was performed in the specimens collected from 635 patients. Rapid diagnosis and serological test of bacterial pathogens were performed in 434 patients; *S. pneumoniae* urinary antigen test was performed in 399 patients, *C. pneumoniae* serological test in 88 patients, and *M. pneumoniae* serological test in 191 patients, respectively. We detected 289 strains of bacterial pathogens from 271 patients. The main bacterial pathogens detected were *S. pneumoniae* at 45.3% (131/289 strains), followed by *H. influenzae* at 35.6% (103/289 strains), *Moraxella* (*Branhamella*) *catarrhalis* at 5.9% (17/289 strains), *M. pneumoniae* at 4.2% (12/289 strains), and *C. pneumoniae* at 3.1% (9/289 strains) (data not shown).

(3)-2 Clinical efficacy

The clinical efficacy findings are shown in Table 4.

The efficacy rate of GRNX at the time of the termination, excluding patients with an indeterminate result, was 92.8% (479/516 patients). The efficacy rates according to age were >90% in both the non-elderly and elderly groups. The efficacy rate according to the presence or absence of underlying diseases or complications was 88.9% (209/235 patients) in patients with underlying diseases, 89.3% (243/272 patients) in patients with complications, 96.0% (267/278 patients) in patients without underlying diseases, and 96.7% (236/244 patients) in patients without complications. In addition, the efficacy rate was 97.1% (135/139 patients) in 139 of 143 patients who were evaluated for clinical efficacy on the 10^{th} day after initiation of GRNX administration (Four inevaluable patients were excluded).

The clinical efficacy for elderly and non-elderly patients is shown in Table 5.

The efficacy rate was slightly lower in elderly patients with moderate pneumonia. The efficacy rate in the elderly with underlying diseases was lower by approximately 6–10% (86.9% [139/160 patients]) than that in the elderly and non-elderly patients with no underlying diseases as well as non-elderly patients with underlying diseases. The efficacy rate in elderly and non-elderly patients with complications was lower by approximately 3–10% than that in patients without complications (89.4% [169/189 patients] in elderly and 89.2% [74/83 patients] in non-elderly with complications).

The efficacy rate in patients receiving antibiotic treatment prior to GRNX therapy (within 7 days before beginning administration) was lower by approximately 3% (89.8%, 53/59 patients) than that in patients not without antibiotic treatment (93.1%, 418/449 patients) (Table 4). The antibiotic treatment before GRNX therapy primarily consisted of oral medications, e.g., clarithromycin (CAM), cefcapene pivoxil (CFPN-PI), and azithromycin (AZM).

The breakdown of 37 patients for whom treatment was determined to be ineffective at

the time of the termination of GRNX therapy according to age and underlying diseases is shown in Table 6.

Efficacy was evaluated in 252 non-elderly patients and 283 elderly patients after the termination of GRNX therapy. The treatment was found to be ineffective in 4.4% (11/252 patients) of the non-elderly and 9.2% (26/283 patients) of the elderly patients. Among the elderly patients with underlying diseases, many had chronic respiratory diseases, and this differed from the underlying diseases of the non-elderly. The elderly and the non-elderly patients had diabetes mellitus, hypertension, rheumatoid arthritis, and other complications, but no differences were observed according to age.

In the efficacy analysis set, 7 patients received concomitant administration of other antibiotics after the initiation of GRNX therapy, and the treatment was effective in 2 out of 6 patients (Table 4). GRNX was determined as ineffective in 4 patients for the following reasons; pyrexia at the termination of GRNX administration, insufficient efficacy at the time of admission for atrial fibrillation, progression to pyothorax, diagnosed with mycobacteriosis after initiation of GRNX administration. In addition, 9 patients were suspected with bacterial pneumonia before GRNX therapy, and the bacterial pathogens in these patients were identified as the atypical pathogens *C. pneumoniae* and *M. pneumoniae* after the initiation of GRNX therapy; the efficacy rate in these patients for infection of only atypical pathogens was 4/6 patients, and for mixed infection of bacterial and atypical pathogens was 3/3 patients (Table 7). GRNX was determined as ineffective in 2 patients for the following reasons; insufficient efficacy and cryptogenic organizing pneumonia.

The overall rate of eradication of bacteria was 98.6% (143/145 strains); that of *S. pneumoniae* was 98.5% (65/66 strains) and *H. influenzae* was 100% (65/65 strains). Species that could not be collected in sufficient quantities at the time of GRNX development were *Streptococcus* species and *Enterobacter cloacae*, the rates of eradication were 2/2 strains and 1/1 strains (data not shown).

(3)-3 Adverse drug reactions

Overall, 71 adverse drug reactions related with GRNX were observed in 58 patients, and the incidence of adverse drug reaction was 7.9% (58/730 patients) (Table 8). Hepatobiliary disorders and skin and subcutaneous tissue disorders were more frequently reported in non-elderly than in elderly patients. However, no remarkable difference in the incidence of adverse drug reactions overall was noted between non-elderly and elderly patients. Four severe adverse drug reactions were reported in 3 patients; one patient had eosinophilic pneumonia, one patient had atrial fibrillation, and one patient had decreased blood pressure and dyspnea. No patients died of these severe adverse drug reactions.

GRNX therapy was discontinued in the two patients who experienced eosinophilic pneumonia and who had decreased blood pressure with dyspnea. The GRNX therapy was continued in the patient with atrial fibrillation. All the 3 patients recovered after treatment.

(4) Discussion

The clinical efficacy (efficacy rate) of GRNX in patients with suspected bacterial pneumonia, not including hospital-acquired pneumonia, was 92.8% (479/516 patients). The efficacy of GRNX was good (89.8% [53/59 patients]) even in patients who had received antimicrobial therapies, e.g., CAM, CFPN-PI, and AZM within 1 week before the initiation of GRNX administration and were considered clinical failures. GRNX showed high efficacy (>90%) in non-elderly and elderly patients, but the efficacy rate was significantly lower in the elderly patients ($p = 0.0264$). Of the elderly patients, only 30% had mild pneumonia and >60% had moderate pneumonia, based on the severity scoring system A-DROP, while among the non-elderly patients, 90% had mild pneumonia. Patients with underlying diseases accounted for approximately 60% of elderly patients; in contrast, only 30% of non-elderly patients had underlying diseases. We hypothesize that the difference in the efficacy rate between elderly and non-elderly patients was because of differences in the severity of pneumonia and in the prevalence of underlying diseases. The elderly patients in whom GRNX therapy failed often had chronic respiratory diseases (Table 6), and these patients might have developed pneumonia due to acute exacerbation of chronic respiratory diseases. Bacterial pathogens were not detected in most of these patients, and opportunistic pathogens (e.g., *Pseudomonas aeruginosa*, *Escherichia coli*, and *Nocardia* species) were detected in the amount of + or 2+ score.

Furthermore, the efficacy rate of GRNX in the elderly patients might have been lower than that in the non-elderly patients because the elderly patient group included patients with intractable conditions (e.g., aspiration pneumonia). In Japan, the clinical practice guidelines for NHCAP published in 2011 indicate that NHCAP develops frequently in elderly patients with aspiration pneumonia [8]; however, we were unable to consider this point since this study was conducted before the announcement of the guidelines. In the clinical practice guidelines for NHCAP, GRNX is recommended as one of the empirical treatment drugs for patients who do not require hospitalization [8]; in this study, the efficacy rate of GRNX was high (>85%) in the populations which could include patients with intractable NHCAP, i.e., elderly patients with moderate pneumonia or with underlying diseases related to pneumonia.

Our results were consistent with those of a GRNX efficacy analysis in >6,000 patients

reported by Hori et al. [9]; they reported that the efficacy rate was >90% and that age, underlying diseases, and complications reduced the effectiveness of GRNX therapy.

In this study, we confirmed the efficacy of GRNX for the administration period in clinical practice, and there was no statistical difference in the efficacy rates between the administration periods of 6–7 days, 8–10 days, and 11–14 days. In patients with mild and moderate pneumonia, the efficacy rates by the administration period of 6–7 days, 8–10 days, and 11–14 days was approximately 90%. As shown in Table 5, >90% of the patients with moderate pneumonia were elderly. Considering the fact that the efficacy rate in these patients was equivalent to that in the non-elderly patients with pneumonia of the same severity, GRNX is expected to have a therapeutic effect for an administration period of 6–7 days, regardless of whether the patient is elderly or non-elderly. An overseas postmarketing surveillance study of moxifloxacin (MFLX) showed that the clinical efficacy of MFLX was 96.6% for an administration period of 5–10 days in patients with bacterial pneumonia [10], and we consider that we obtained similar results in our study. Furthermore, 36 patients received long-term GRNX therapy (≥15 days) in the efficacy analysis set. Of these patients, 19 exhibited an improved outcome on the 10th day after the initiation of GRNX therapy, but the therapy was continued in these patients. In future studies, it is important to clarify the duration of GRNX outpatient treatment.

The major bacterial pathogens were *S. pneumoniae* at 45.3% (including 10.7% with positive results only in the urinary antigen test) and *H. influenzae* at 35.6%. These findings were similar to those reported by Saito et al. [11] and Miyashita et al. [12]. The eradication rates of *S. pneumoniae* and *H. influenzae* were >95%, and the overall eradication rate was 98.6%. In the efficacy analysis set, the indicated bacteria were not detected as bacterial pathogens in 345 patients, but GRNX showed high efficacy in these patients at the time of GRNX therapy termination (90.6% [288/318 patients]).

The incidence of adverse drug reactions was 7.9% (58/730 patients). There were no serious issues regarding safety, because no adverse drug reaction specific to GRNX was observed.

In conclusion, we confirmed the usefulness of GRNX for mild to moderate bacterial pneumonia in daily clinical practice. Further studies would be required to clarify the appropriate timing of GRNX termination.

(5) Acknowledgments

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Conflict of interest

Akira Watanabe has received honoraria and lecture fees from Taisho Toyama Pharmaceutical Co., Ltd.; has received subsidies or donations from Astellas Pharma Inc.; chairs endowed departments from Toyama Chemical Co., Ltd.

Tadashi Ishida has received honoraria and lecture fees from Taisho Toyama Pharmaceutical Co., Ltd. and Astellas Pharma Inc.

Hiroaki Hosono and Satoru Kushimoto are employees of Toyama Chemical Co., Ltd.

Shigeru Kohno has received honoraria and lecture fees from Toyama Chemical Co., Ltd., Astellas Pharma Inc. and Taisho Toyama Pharmaceutical Co., Ltd.; has received research grants from Astellas Pharma Inc.

All other authors report no conflicts of interest.

Table 1. List of the investigating medical institutions

Yamamoto Kumiai Hospital	Eiju General Hospital	Tokyo Medical University Kasumigaura Hospital
JR Tokyo General Hospital	St. Luke’s International Hospital	Nakano General Hospital
NTT WEST Kyushu Hospital	Jyuzen General Hospital	The Jikei University Hospital
Saitama Red Cross Hospital	Ohta Nishinouchi Hospital	Tokyo Women’s Medical University Medical Center East
Aichi Medical University Hospital	Nagano Municipal Hospital	Tokyo Metropolitan Hiroo Hospital
Toyota Kosei Hospital	Tenri Hospital	Tokyo Metropolitan Fuchu Hospital
Kyorin University School of Medicine	Ebara Hospital	Higashiosaka City General Hospital
Isesaki Municipal Hospital	Jusendo General Hospital	Toho University Sakura Medical Center
Izumikawa Hospital	Nissan Tamagawa Hospital	Toho University Ohashi Medical Center
Aino Hospital	Southern Tohoku General Hospital	Toho University Omori Medical Center
Mito Chuo Hospital	Saitama Medical Center	Fujita Health University Hospital
St. Mary’s Hospital	Mie Prefectural General Medical Center	Bell Land General Hospital
Nippon Steel Yawata Memorial Hospital	University of Occupational and Environmental Health	National Hospital Organization Matsumoto Medical Center Chushin Matsumoto Hospital
Hanzomon Hospital	Itami City Hospital	National Hospital Organization Ibarakihigashi National Hospital
Niigata Rinko Hospital	Kofu City Hospital	National Hospital Organization Ureshino Medical Center
Nishifukuoka Hospital	Yokkaichi Municipal Hospital	National Hospital Organization Kanazawa Medical Center
Kusatsu General Hospital	Suita Municipal Hospital	National Hospital Organization Kyushu Medical Center
Fukuoka Seisyukai Hospital	Ikeda City Hospital	National Hospital Organization Kumamoto Medical Center
Tenshi Hospital	Toyonaka Municipal Hospital	National Hospital Organization Kumamoto Saishunso National Hospital
Sasaki Naika	Shiga Medical Center for Adults	National Hospital Organization Kochi National Hospital
Tsuchiura Kyodo General Hospital	Jichi Medical University Saitama Medical Center	National Hospital Organization National Disaster Medical Center
Ibaraki Seinan Medical Center Hospital	Jichi Medical University Hospital	National Hospital Organization Sanyo National Hospital
Yokosuka City Hospital	Saiseikai Suita Hospital	National Hospital Organization Shiga National Hospital
Okazaki City Hospital	Saiseikai Nagasaki Hospital	National Hospital Organization Mito Medical Center
Shimonoseki City Central Hospital	Tokyo Saiseikai Central Hospital	National Hospital Organization Nishibeppu National Hospital
Kitasato University Kitasato Institute Hospital	Saiseikai Utsunomiya Hospital	National Hospital Organization Omuta National Hospital
Kansai Electric Power Hospital	Kyoto-Katsura Hospital	National Hospital Organization Nagasaki Medical Center
Nishimino Kosei Hospital	Shinrakuen Hospital	National Hospital Organization Tenryu Hospital
Miyazaki Prefectural Nobeoka Hospital	Seirei Yokohama Hospital	National Hospital Organization Tokyo Medical Center
Japanese Red Cross Kyoto Daini Hospital	Seirei Mikatahara General Hospital	National Hospital Organization Higashihiroshima Medical Center
Kanazawa Medical University Hospital	Seirei Hamamatsu General Hospital	National Hospital Organization Minami Kyushu National Hospital
Isahaya Health Insurance General Hospital	The Fraternity Memorial Hospital	National Hospital Organization Himeji Medical Center
Kinki Central Hospital of Mutual Aid Association of Public School Teachers	Utsunomiya Social Insurance Hospital	National Hospital Organization Hamada Medical Center
Kyushu Central Hospital of Mutual Aid Association of Public School Teachers	Tohoku Kosei Nenkin Hospital	National Hospital Organization Fukuoka Higashi Medical Center
Chugoku Central Hospital of Mutual Aid Association of Public School Teachers	Nagoya Ekisaikai Hospital	Kyushu Rosai Hospital, Japan Labour Health and Welfare Organization

Kanzaki Municipal General Hospital
Yokohama City University Medical Center
Yokohama City University Hospital
Fukushima Medical University Hospital
Naga Hospital
Onomichi General Hospital
Hiroshima General Hospital
Hiroshima City Asa Hospital
Toranomon Hospital
Sasebo Kyosai Hospital
Tokyo Kyosai Hospital
Hamanomachi Hospital
Asahikawa Medical University Hospital
Kanazawa University Hospital
Kyushu University Hospital
Kumamoto University Hospital
Gunma University Hospital
Kochi Medical School Hospital
Mie University Hospital
Shiga University of Medical Science Hospital
Niigata University Medical & Dental Hospital
Nagasaki University Hospital
The University of Tokyo Hospital
National Center for Geriatrics and Gerontology
Sasaki Institute Kyoundo Hospital
Akashi Medical Center
Juntendo University Urayasu Hospital
Juntendo University Hospital
Showa University Fujigaoka Hospital
Sado General Hospital
Niigata Prefectural Central Hospital
Niigata City General Hospital
Isehara Kyodo Hospital
St. Marianna University Yokohama City Seibu Hospital
St. Marianna University Hospital
Nishinomiya Municipal Central Hospital
Shizuoka City Shimizu Hospital
Ishikawa Prefectural Central Hospital
Kawasaki Municipal Ida Hospital
Funabashi Municipal Medical Center
Osaka Saiseikai Nakatsu Hospital
Japanese Red Cross Otsu Hospital
Oita Prefectural Hospital
Oita Red Cross Hospital
Osaka Prefectural Medical Center for Respiratory and Allergic Diseases
Nagasaki Municipal Medical Center
Teikyo University Chiba Medical Center
Teikyo University School of medicine University Hospital, Mizonokuchi
Tonosho Central Hospital
Tokai University Tokyo Hospital
Chiba Rosai Hospital, Japan Labour Health and Welfare Organization
Tokyo Rosai Hospital, Japan Labour Health and Welfare Organization
Nippon Medical School Chiba Hokusoh Hospital
Japanese Red Cross Nagasaki Genbaku Hospital
Japanese Red Cross Nagasaki Genbaku Isahaya Hospital
Ohtawara Red Cross Hospital
Nihon University Itabashi Hospital
Iida Municipal Hospital
Iwata City Hospital
Toyama Prefectural Central Hospital
Toyama University Hospital
Fukui Prefectural Hospital
Fukui Social Insurance Hospital
Fukuoka University Hospital
Takarazuka City Hospital
Toyohashi Municipal Hospital
Hokkaido Social Insurance Hospital
Kitasato University Hospital
Dokkyo Medical University Koshigaya Hospital

Table 2. Clinical efficacy criteria

Evaluation	Evaluation criteria
Effective	Of the conditions (1) to (3) below, if the following items are met; condition (1) fulfills its condition; either condition (2) or (3) satisfies these conditions; and remaining condition does not lead to exacerbation, it is classified as “effective.” (1) Improvement or disappearance of the symptoms and signs of pneumonia A determination of maximum body temperature, cough, sputum (amount, properties), dyspnea, chest pain, or chest rales. (a) Improvement in the symptoms and signs of 1 item or more. (b) In cases of fever at the initiation of administration (or registered), the fever must improve. If the fever declines after the initiation of administration (or registered), even if body temperature is 37.0°C or more, it will be treated as an improvement. (2) If all abnormalities in chest X-ray shadows improve or disappear Determined on the basis of the density and spread of the chest X-ray shadow. (3) Improvement or disappearance of inflammation No exacerbated items and if the following 2 items are met, “Improvements to 9000/μl or less of the peripheral blood white blood cell count” or “Decline from the highest value of CRP.” The change within the range of normal level is not considered.
Ineffective	If the above criteria are not “effective,” the case is determined to be “ineffective.”
Evaluation not possible	If it is not possible to determine either “effective” or “ineffective,” it is classified as “evaluation not possible.”

Table 3. Patient characteristics

Item	Category	Safety analysis set Number of patients	(%)	Efficacy analysis set Number of patients	(%)
Number of patients for analysis		730		535	
Sex	Male	431	(59.0)	321	(60.0)
	Female	299	(41.0)	214	(40.0)
Age	Non-elderly (<65 years of age)	352	(48.2)	252	(47.1)
	Elderly (≥65 years of age)	378	(51.8)	283	(52.9)
	Mean	61.6		62.1	
Inpatient/Outpatient	Inpatient	69	(9.5)	47	(8.8)
	Outpatient	661	(90.5)	488	(91.2)
Weight (kg)	Mean	55.05		55.22	
Severity of pneumonia (A-DROP scoring system)	Mild	454	(62.2)	327	(61.1)
	Moderate	268	(36.7)	202	(37.8)
	Severe	3	(0.4)	2	(0.4)
	Extremely severe	5	(0.7)	4	(0.7)
Underlying diseases	No	382	(52.3)	286	(53.5)
	Yes	344	(47.1)	246	(46.0)
	Unknown	4	(0.5)	3	(0.6)
Bronchial asthma		102	(14.0)	71	(13.3)
COPD		91	(12.5)	65	(12.1)
Bronchiectasis		53	(7.3)	44	(8.2)
Emphysema		50	(6.8)	34	(6.4)
Interstitial lung disease		21	(2.9)	14	(2.6)
Other		104	(14.2)	74	(13.8)
Complications		374	(51.2)	284	(53.1)
Hypertension		149	(20.4)	119	(22.2)
Diabetes mellitus		64	(8.8)	51	(9.5)
Hyperlipidemia		56	(7.7)	44	(8.2)
Insomnia		39	(5.3)	26	(4.9)
Constipation		32	(4.4)	22	(4.1)
Other		290	(39.7)	218	(40.7)
Antibiotic taken immediately before the initiation of GRNX	Yes	95	(13.0)	62	(11.6)
	Unknown	12	(1.6)	8	(1.5)
Maximum daily dosage (mg)	200	13	(1.8)	7	(1.3)
	400	717	(98.2)	528	(98.7)
	Mean	396.4		397.4	
Administration period (days)	<3	6	(0.8)	2	(0.4)
	3−7	355	(48.6)	262	(49.0)
	8−14	323	(44.2)	242	(45.2)
	15−21	41	(5.6)	26	(4.9)
	22≤	5	(0.7)	3	(0.6)
	Mean	8.7		8.7	
	S.D.	3.6		3.4	
Concomitant drug	No	69	(9.5)	50	(9.3)
	Yes	661	(90.5)	485	(90.7)
Antibiotic	No	704	(96.4)	528	(98.7)
	Yes	26	(3.6)	7	(1.3)

COPD: chronic obstructive pulmonary disease

Table 4. Clinical efficacy according to patient characteristics

Item	Category	Termination of administration				
		Number of patients	Clinical efficacy			Efficacy rate (%)
			Effective	Ineffective	Evaluation not possible	
Number of patients for efficacy analysis		535	479	37	19	92.8
Sex	Male	321	280	30	11	90.3
	Female	214	199	7	8	96.6
Age	Non-elderly (<65 years of age)	252	233	11	8	95.5
	Elderly (≥65 years of age)	283	246	26	11	90.4
Inpatient/Outpatient	Inpatient	47	40	4	3	90.9
	Outpatient	488	439	33	16	93.0
Severity of pneumonia (A-DROP scoring system)	Mild	327	298	17	12	94.6
	Moderate	202	176	20	6	89.8
	Severe	2	2	0	0	2/2
	Extremely severe	4	3	0	1	3/3
Underlying disease	No	286	267	11	8	96.0
	Yes	246	209	26	11	88.9
	Unknown	3	3	0	0	3/3
Complication	No	251	236	8	7	96.7
	Yes	284	243	29	12	89.3
Antibiotic taken immediately before the initiation of GRNX	No	465	418	31	16	93.1
	Yes	62[a]	53	6	3	89.8
	Unknown	8	8	0	0	8/8
Concomitant drug	No	50	43	5	2	89.6
	Yes	485	436	32	17	93.2
Antibiotic	No	528	477	33	18	93.5
	Yes	7	2	4	1	2/6
Administration period (days)	2–3	10	2	5	3	2/7
	4–5	38	28	6	4	82.4
	6–7	216	199	13	4	93.9
	8–10	143	135	5	3	96.4
	11–14	99	92	3	4	96.8
	15–21	26	21	4	1	84.0
	22≤	3	2	1	0	2/3

Efficacy rate = (Number of patients considered as “Effective”) / (Number of patients considered as “Effective” and “Ineffective”)

[a]clarithromycin, 18 patients (including 1 patient: concomitant lincomycin injection); cefcapene pivoxil, 8 patients; azithromycin, 7 patients; levofloxacin, 4 patients; others, 25 patients

Table 5. Clinical efficacy according to elderly/non-elderly classification (at termination of garenoxacin therapy)

Item	Category	Non-elderly (<65 years of age)					Elderly (≥65 years of age)				
		Number of patients	Clinical efficacy			Efficacy rate (%)	Number of patients	Clinical efficacy			Efficacy rate (%)
			Effective	Ineffective	Evaluation not possible			Effective	Ineffective	Evaluation not possible	
Number of patients for efficacy analysis		252	233	11	8	95.5*	283	246	26	11	90.4*
Sex	Male	140	129	8	3	94.2	181	151	22	8	87.3
	Female	112	104	3	5	97.2	102	95	4	3	96.0
Inpatient/Outpatient	Inpatient	18	17	0	1	100	29	23	4	2	85.2
	Outpatient	234	216	11	7	95.2	254	223	22	9	91.0
Severity of pneumonia (A-DROP scoring system)	Mild	235	217	10	8	95.6	92	81	7	4	92.0
	Moderate	14	13	1	0	92.9	188	163	19	6	89.6
	Severe	0	0	0	0	-	2	2	0	0	2/2
	Extremely severe	3	3	0	0	3/3	1	0	0	1	-
Underlying disease	No	174	162	6	6	96.4	112	105	5	2	95.5
	Yes	77	70	5	2	93.3	169	139	21	9	86.9
	Unknown	1	1	0	0	1/1	2	2	0	0	2/2
Complication	No	165	159	2	4	98.8	86	77	6	3	92.8
	Yes	87	74	9	4	89.2	197	169	20	8	89.4
Administration period (days)	2–3	2	1	1	0	1/2	8	1	4	3	1/5
	4–5	19	15	2	2	88.2	19	13	4	2	76.5
	6–7	107	104	3	0	97.2	109	95	10	4	90.5
	8–10	66	62	2	2	96.9	77	73	3	1	96.1
	11–14	46	41	1	4	97.6	53	51	2	0	96.2
	15–21	10	9	1	0	90.0	16	12	3	1	80.0
	22≤	2	1	1	0	1/2	1	1	0	0	1/1

Efficacy rate = (Number of patients considered as “Effective”) / (Number of patients considered as “Effective” and “Ineffective”)

* p = 0.0264

Table 6. List of ineffective cases with patients' underlying diseases according to age

Item		Cases considered as "Ineffective"		
			Age	
		Total	Non-elderly (<65 years of age)	Elderly (≥65 years of age)
Number of cases considered as "Ineffective"		37	11	26
Underlying disease	No	11	6	5
	Yes	26	5	21
COPD		6	0	6
Bronchial asthma		6	1	5
Emphysema		6	0	6
Bronchiectasis		4	0	4
Chronic bronchitis		2	1	1
Upper respiratory infection		1	0	1
Diffuse panbronchiolitis		1	0	1
Malignant neoplasm of lung		3	1	2
Non-small cell lung carcinoma		1	1	0
Bronchopulmonary aspergillosis		1	0	1
Pulmonary tuberculosis		2	1	1
Interstitial lung disease		1	0	1

COPD: chronic obstructive pulmonary disease

Table 7. Clinical efficacy according to the classification of bacterial pathogens

Causative micro-organism	Termination of administration				
	Number of patients	Clinical efficacy			Efficacy rate (%)
		Effective	Ineffective	Evaluation not possible	
Efficacy analysis set	535	479	37	19	92.8
Undetected	333	288	30	15	90.6
Bacterial pathogens	193	184	5	4	97.4
Atypical pathogens	6	4	2	0	4/6
Bacterial pathogens + atypical pathogens	3	3	0	0	3/3

Efficacy rate = (Number of patients considered as “Effective”) / (Number of patients considered as “Effective” and “Ineffective”)

Table 8. Adverse drug reactions

Category of adverse drug reactions	Incidence (%) n = 730					
			Age			
	Total		Non-elderly (<65 years of age)		Elderly (≥65 years of age)	
Number of patients with adverse drug reactions	58	(7.9)	31	(4.2)	27	(3.7)
Number of adverse drug reactions	71		38		33	
Infections and infestations	1	(0.1)	1	(0.1)	0	(0)
Blood and lymphatic system disorders	3	(0.4)	1	(0.1)	2	(0.3)
Nervous system disorders	2	(0.3)	1	(0.1)	1	(0.1)
Cardiac disorders	1	(0.1)	0	(0)	1	(0.1)
Respiratory, thoracic and mediastinal disorders	4	(0.5)	3	(0.4)	1	(0.1)
Gastrointestinal disorders	8	(1.1)	3	(0.4)	5	(0.7)
Hepatobiliary disorders	13	(1.8)	9	(1.2)	4	(0.5)
Skin and subcutaneous tissue disorders	12	(1.6)	8	(1.1)	4	(0.5)
Renal and urinary disorders	3	(0.4)	0	(0)	3	(0.4)
General disorders and administration site conditions	3	(0.4)	1	(0.1)	2	(0.3)
Investigations	15	(2.1)	6	(0.8)	9	(1.2)
Alanine aminotransferase increased	2	(0.3)	2	(0.3)	0	(0)
Aspartate aminotransferase increased	2	(0.3)	2	(0.3)	0	(0)
Blood creatine phosphokinase increased	1	(0.1)	1	(0.1)	0	(0)
Blood lactate dehydrogenase increased	1	(0.1)	1	(0.1)	0	(0)
Blood pressure decreased	1	(0.1)	0	(0)	1	(0.1)
Blood urea increased	2	(0.3)	0	(0)	2	(0.3)
Eosinophil count increased	1	(0.1)	0	(0)	1	(0.1)
Platelet count decreased	1	(0.1)	0	(0)	1	(0.1)
White blood cell count decreased	6	(0.8)	4	(0.5)	2	(0.3)
White blood cell count increased	1	(0.1)	0	(0)	1	(0.1)
Platelet count increased	1	(0.1)	0	(0)	1	(0.1)
Hepatic enzyme increased	1	(0.1)	0	(0)	1	(0.1)

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Figure legends

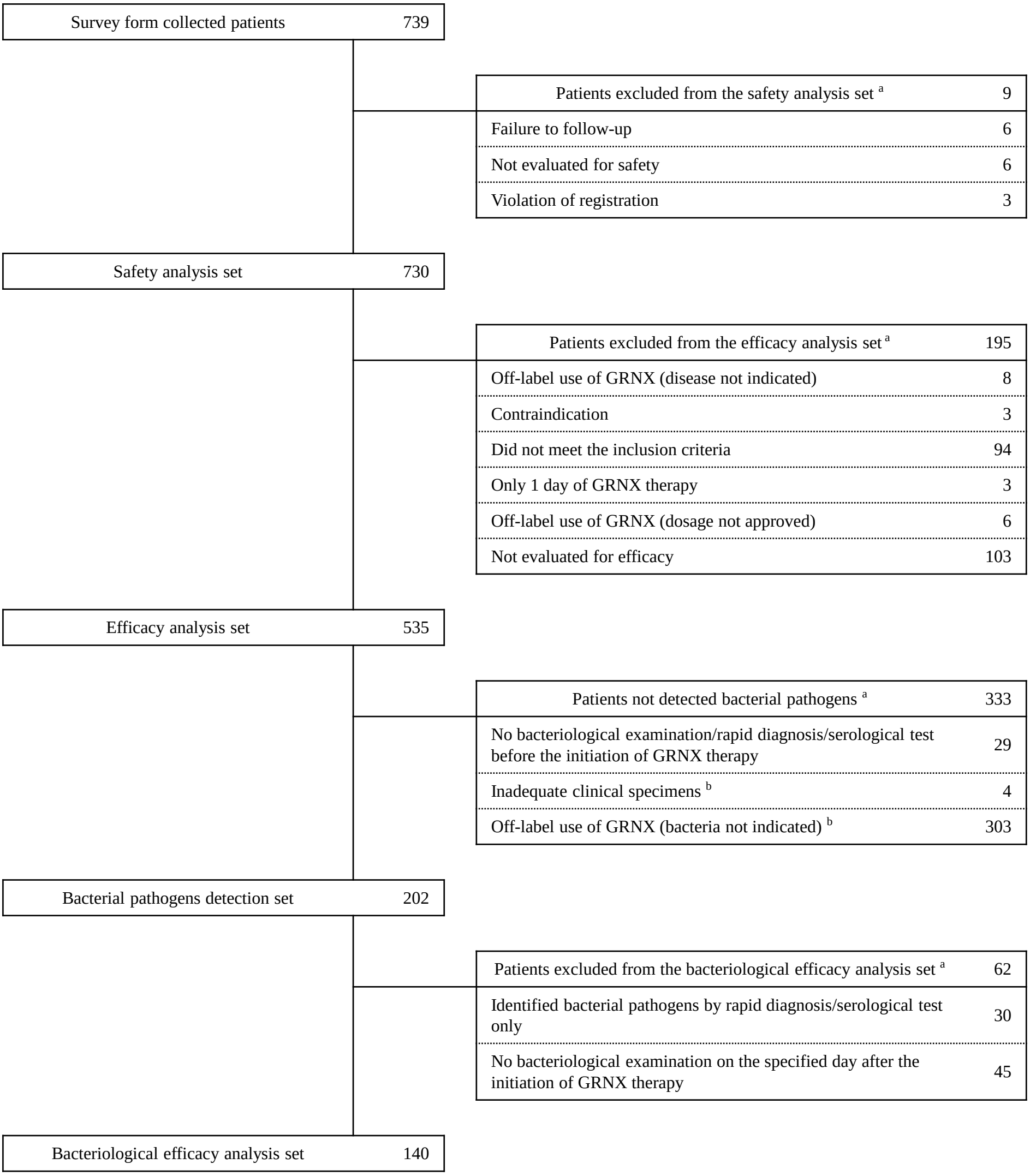
Figure 1

This figure shows the number of patients for included or excluded each analysis set.

Patients placed "[a]" include those with duplicated reasons for exclusion.

Patients placed "[b]" exclude those who tested positive for *S. pneumoniae* in the urinary antigen test.

Figure 1. Analysis sets



[a] Including patients with duplicated reasons for exclusion

[b] Excluding patients who tested positive for *S. pneumoniae* in the urinary antigen test