European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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WITHDRAWAL ASSESSMENT REPORT FOR

Garenoxacin Mesylate (garenoxacin)

EMEA/H/C/747

Day 120 Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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I. RECOMMENDATION

Based on the CHMP review of the data on quality, safety and efficacy, the CHMP considers that the application for **Garenoxacin 400 mg tablet** is not approvable for the treatment of community acquired pneumonia (CAP) in hospitalised patients (as follow-on to IV therapy), for acute exacerbations of chronic bronchitis (AECB) or for uncomplicated skin and soft tissue infections (uSSTI).

The 400 mg tablet might be approvable for the treatment of mild to moderate CAP and for acute maxillary sinusitis subject to satisfactory responses to the List of Questions.

The application for **Garenoxacin 600 mg tablet** is not approvable for the treatment of complicated skin and soft tissue infections (cSSTI) or for intra-abdominal infections (IAI) and acute pelvic infections (as follow-on to IV therapy).

The application for **Garenoxacin 2 mg/ml solution for infusion** is not approvable for the treatment of CAP, cSSTI, IAI or acute pelvic infections.

The major objections precluding a recommendation of marketing authorisation pertain to deficiencies on the efficacy demonstration as stated in the list of questions.

II. EXECUTIVE SUMMARY

II.1 Problem statement

The 4-quinolones act by inhibiting two bacterial tetrameric enzymes of the type II topoisomerase class - DNA gyrase and DNA topoisomerase IV (Topo IV). DNA gyrase is composed of subunits GyrA and GyrB while Topo IV is composed of two dimers of the proteins ParC and ParE (termed GrlA and GrlB in *S. aureus*). Although the two enzymes have overlapping activities, DNA gyrase mainly controls DNA supercoiling during replication and transcription while Topo IV exerts decatenation activity that resolves daughter chromosomes following DNA replication. The quinolones bind to DNA and the tetrameric enzymes to form a stable ternary complex that results in inhibition of DNA synthesis and arrest of cell growth, which is followed by cell death. The (fluoro)quinolones currently available show preference for inhibition of the GyrA subunit of DNA gyrase in Gram-negative organisms. In *S. aureus* and *S. pneumoniae* the preferred target is more difficult to discern but the GrlA/ParC subunit of Topo IV is commonly implicated in these species.

Depending on bacterial species and the quinolone, the degree of inhibition of each of these enzymes is variable so that one is designated a primary target and the other is a secondary target. However, few of the quinolones (so far only clinafloxacin and sitafloxacin) appear to meet the criteria for dual target inhibition i.e. often defined as similar inhibition of DNA gyrase and Topo IV as determined by resistance mutation emergence patterns and by in-vitro enzyme inhibition.

In the absence of mutational or acquired mechanisms of resistance, the fluoroquinolones are usually active against the majority of the Gram-negative and Gram-positive pathogens of the upper and lower respiratory tract as well as the organisms associated with atypical community-acquired pneumonia (CAP) such as *M. pneumoniae*, *C. pneumoniae* and *Legionella pneumophila*. Nevertheless, there are some marked differences between compounds in their in-vitro activities against the major gram-positive pathogen - *Streptococcus pneumoniae*. Due to reports of pneumococcal pneumonia developing despite ciprofloxacin oral therapy, doubt has been cast on the in-vivo efficacy of ciprofloxacin against pneumococcal pneumonia. In contrast, levofloxacin and moxifloxacin appear to be effective.

For common Gram-positive pathogens involved in skin and soft tissue infections, activity against β-haemolytic streptococcal species is usually very good and most agents are very active *in vitro* and *in vivo* against staphylococci. Against non-fermenting Gram-negative rods, enterococci and anaerobes the marketed fluoroquinolones show activity that varies between drugs and between species. For example, in general ciprofloxacin is not considered to be reliable monotherapy for infections in which anaerobic species are important.

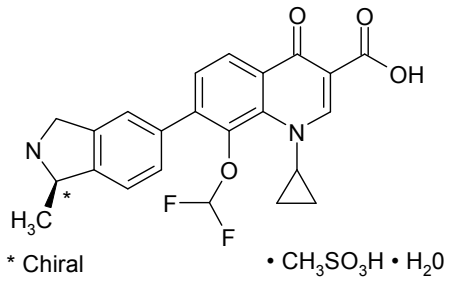
Resistance to the fluoroquinolones commonly involves mutations in one or more of the genes encoding the subunits of DNA gyrase and topoisomerase IV. Other important mechanisms of fluoroquinolone resistance, which may occur alone or in conjunction with topoisomerase mutations and which may affect the class as a whole, are impaired permeability of bacteria to fluoroquinolones and active efflux mechanisms. Since the launch of ciprofloxacin during the 1980s, the prevalence of fluoroquinolone resistance in certain species (particularly *S. aureus*, *S. pneumoniae*, *P. aeruginosa* and *N. gonorrhoeae*) is now a cause for concern in many countries. Indeed, due to co-resistance, the majority of MRSA in some localities are now resistant to these agents.

There are also several well-documented safety issues associated with the fluoroquinolones although the propensity of each agent to cause individual types of adverse reactions is variable. In this regard, structure-activity relationship studies have identified some features of these molecules that may make them more or less likely to be associated with certain types of adverse reactions.

Overall, then, a new quinolone or fluoroquinolone would not be likely to represent a major step forward unless it had some exceptional features related to its antibacterial spectrum, some activity against organisms resistant to existing agents and/or fewer safety issues compared to marketed products.

II.2 About the product

Garenoxacin is a synthetic, des-F(6)-quinolone antibacterial agent. The molecule does not contain fluorine at the C-6 position, which is present in all the fluoroquinolone antibacterial agents.



Chemical Structure of Garenoxacin

Garenoxacin is presented for clinical use as 400 mg and 600 mg film-coated tablets and as a solution for infusion (final concentration 2mg/ml presented in 5% glucose such that a bag of 400 mg/200 ml contains 10 g of glucose monohydrate; 200 ml and 300 ml bags are to be marketed to provide 400 mg and 600 mg doses). These formulations contain the mesylate salt of the (R)-10 enantiomer, for which minimum inhibitory concentrations (MICs) are 4-fold lower than the (S)-enantiomer.

The development of this product for clinical use was based on observations of activity against a range of aerobic Gram-positive and Gram-negative bacteria, *Mycoplasma, Legionella* and *Chlamydia* species and anaerobic bacteria. Also, from what is known about the structure-activity relationships of the fluoroquinolone agents it was expected that the safety profile of garenoxacin might be distinguishable due to the lack of the F atom at C6. Due to the observed spectrum of activity *in vitro*, a previous licensee initiated a programme of clinical studies to evaluate efficacy in infections of the

respiratory tract, uncomplicated or complicated skin and soft tissue infections, intra-abdominal and pelvic infections.

The indications proposed by the applicant (Schering-Plough will be the MAH in the EU) for the oral and intravenous routes of administration are different and are as follows:

Tablets (film-coated 400 mg and 600 mg)

- Acute bacterial exacerbation of chronic bronchitis
- Acute bacterial sinusitis
- Community-acquired pneumonia
- Uncomplicated skin and skin structure infections
- Complicated skin and skin structure infections, including diabetic foot infections
- Complicated intra-abdominal infections, including post-surgical infections and acute pelvic infections.

IV solution of infusion (provided as 400 mg in 200 ml and as 600 mg in 300 ml bags)

- Community-acquired pneumonia
- Complicated skin and skin structure infections, including diabetic foot infections
- Complicated intra-abdominal infections, including post-surgical infections and acute pelvic infections.

The recommended doses and durations of therapy are as follows:

Tablets – 400 mg and 600 mg, SPCs same except for cross-references to other tablet size:

INFECTION	DAILY DOSE	DURATION
Acute bacterial exacerbation of chronic bronchitis	400 mg	5 days
Acute bacterial sinusitis	400 mg	5 days
Community-acquired pneumonia	400 mg	5 to 14 days
Uncomplicated skin and skin structure infections	400 mg	5 days
Complicated skin and skin structure infections, including diabetic foot infections	600 mg*	7 to 14 days
Complicated intra-abdominal infections, including post-surgical infections and acute pelvic infections	600 mg*	5 to 14 days
*Please refer to the TRADEMARK 600 mg film-coated tablets Summary of Product Characteristics (SPC) for full prescribing information.		

IV solution for infusion – single SPC to cover both bag sizes and with reference to oral follow-on therapy:

INFECTION	DAILY DOSE	DURATION
Community-acquired pneumonia	400 mg	5 to 14 days
Complicated skin and skin structure infections, including diabetic foot infections	600 mg*	7 to 14 days
Complicated intra-abdominal infections, including post-surgical infections and acute pelvic infections	600 mg*	5 to 14 days
*Please refer to the TRADEMARK 600 mg solution for infusion Summary of Product Characteristics (SPC) for full prescribing information.		

II.3 The development programme/Compliance with CHMP Guidance/Scientific Advice

No CHMP scientific advice was sought during the development programme. Regulatory Advice was requested and obtained from both European and US Health Authorities. Meetings were held with the Agencies in Belgium, Germany, Hungary, Portugal and Sweden. These meetings prompted the following:

- Belgium (September 10, 2002) - a complete analysis of garenoxacin-associated hypotension, including the theoretical mechanism of action, the target population at risk, and the magnitude of the effect is presented (in 2.7.4).
- Hungary (May 17, 2005) - the correlation between microbiological and clinical outcomes is provided in the individual clinical study reports and the meaning of clinical response (e.g. 'cured' or 'cured + improved') has been clearly defined.
- Germany (June 11, 2002 and May 23, 2005) - a statistical approach to address the imbalance of mortality in the intra-abdominal study is included in the clinical study report for 027. Additionally, the discontinuation rates due to hypotension are presented for the oral and IV formulations in the Integrated Analysis of Safety.
- Sweden (June 22, 2005) - detailed information regarding the activity of garenoxacin against pathogens implicated in atypical community-acquired pneumonia is included in each clinical study report. Additionally, the imbalance of mortality in study 027 is discussed fully in the clinical study report and clinical summary.
- Portugal (July 12, 2005) - a risk management plan has been included in Module 1.9 that includes a study to evaluate the effects of antihistamine administration on hypotension.

II.4 General comments on compliance with GMP, GLP, GCP

The application contains statements of GMP compliance in Module 1 for the EU sites of manufacture, assembly, QC testing and batch release have been provided for tablets and infusion. No GMP inspections are required for these sites prior to MA approval. However, manufacturing of Garenoxacin 400/600mg film coated tablets, testing of the active substance and testing of the finished products is performed at a non-EU site. An EU GMP compliance certificate is required for this latter site of manufacture.

All pivotal toxicology studies are reported to have been performed in compliance with GLP requirements.

The application contains statements of GCP compliance in Module 1, in the Clinical Overview in Module 2 and in individual study reports. The application does not raise any issues for compliance.

II.5 Type of application and other comments on the submitted dossier

This is a stand alone (complete) application made under Articles 3(2) and 8.3 (i) for a new active substance for which the use of the Centralised Procedure is optional.

The worldwide clinical development programme primarily covered the years between 1998 and 2003, and the clinical efficacy studies were mainly performed between 1999 and 2002. As a result, the application does not wholly conform to current CHMP guidance since some of this was not operative during the development period.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug Substance

Garenoxacin mesylate monohydrate is a novel drug substance. The Active Substance Master File procedure has been used to submit data for the drug substance.

Manufacture of the drug substance is a two-step process and is well described. Control of the starting materials and critical intermediate are sufficient to ensure the quality of the final drug substance.

Garenoxacin has been well characterised by appropriate analytical techniques. It is crystalline, soluble in aqueous solutions and is isolated as polymorph A and is the (R)-enantiomer. The configuration of the single chiral centre is retained from the stereo centre of the commercially available starting material phenylethylamine with the known absolute configuration. The purity of the drug substance is controlled by the enantiomeric purity of the starting material.

Potential impurities have been discussed in relation to their origin and potential carry-over in the final drug substance. The manufacturing method provides drug of high quality with very low levels of organic impurities. The drug substance specification is suitable for this compound. Limits of the specified impurities are acceptable, qualified by the specification and toxicological studies.

Stability data demonstrate excellent stability over 48 months.

The API manufacturer had originally licensed a previous licensee to manufacture garenoxacin mesylate in Italy, to the same API synthetic route and chemical scale up processes as used by the proposed API manufacturer in their ASMF. The drug substances from the two sources have been shown to be equivalent and were used for drug process development, registration stability and manufacture of clinical batches. However, only material from one proposed API manufacturer will be used commercially.

The ASMF data are comprehensive and demonstrate that the quality of the drug substance is satisfactory and there are no major objections. However, there are minor concerns which are listed herein.

Drug Product (Tablets)

The drug product is presented as oval, white film-coated tablets containing either 400mg or 600mg garenoxacin (as the mesylate) and packed in PVC/PVdC/Aluminium blister foils.

A number of formulations were used during development and a series of bioavailability studies have been presented to summarise the clinical/formulation development and to compare the bioequivalence

(BE) of those formulations used in Phase I/II studies. These formulations include clinical capsules (25, 100, 200mg), film-coated clinical tablets (200mg, 400mg), film-coated commercial tablets (200, 400, 600mg), clinical powder for oral suspension (40mg/ml), 600mg oral suspension, commercial IV vial (10mg/ml). Appropriate bridging studies are provided to demonstrate bioequivalence of the commercial tablets to the clinical tablets.

The previous licensee transferred the product and analytical technology to Schering-Plough. Manufacture of the product involves standard excipients and processes (dry 'roller compaction', blending, tabletting and film coating). Satisfactory batch equivalence data from the two sites are provided. The development package provided is comprehensive and satisfactory.

The control of the drug product is generally acceptable and the analytical methods, which are same as used by the previous licensee, are well described and suitably validated. Minor deficiencies in the specification are pointed out, including tightening of the shelf life assay limits.

The stability of the product is well demonstrated over a two year period from batches manufactured at the previous licensee's facility. However, only the initial and 3 months stability data are provided for the primary batches from the proposed manufacturing site. Further stability data from more than one site specific primary stability batches provided are requested for each of the two strengths. A post approval stability commitment is provided and accepted. There are no major objections. However, there are minor concerns which are listed in the overview.

Drug Product (Solution for Infusion)

Garenoxacin 2mg/ml Solution for infusion (as mesylate) is available as a single-use, ready-mixed product in IV bag in 5% glucose, 400 mg (200 ml) and 600 mg (300 ml) as base per bag.

The previous licensee developed a vial formulation of the concentrated drug (10mg/ml of free base) which was diluted in 5% Dextrose Injection to a Garenoxacin free base concentration of 2 mg/mL before administration to meet dosing requirements of the product during the intravenous clinical trials. The IV bag was never used in the clinical studies. In-use formulation batch data are requested to determine if the clinical IV formulation is equivalent to the proposed IV bag, in particular the pH of the infusion solution.

The majority of development work for Garenoxacin mesylate IV bag was completed by the previous licensee and the proposed manufacturer of the finished product using the latter's proprietary IV bag technology (PL 2408 container-closure system) and supplemented by Schering-Plough following acquisition of the product from the API manufacturer. Additional pharmaceutical development studies, including the manufacture of site-specific stability batches, have been conducted to support the transfer of European commercial production. Satisfactory batch equivalence data from the two sites are provided. The development package provided is comprehensive and satisfactory.

Manufacture of the product involves filling the formulated active solution into filling into pre-printed PL 2408 plastic container and sealing, enclosing the filled container in foil overpouch and autoclaving the complete product. A validated and automated sterilisation cycle at 121ºC is used, which ensures a minimum F0 exposure of 10 minutes and a Sterility Assurance Level (SAL) of 10-6, or better. Satisfactory validation data are provided for the terminal sterilisation of the bag.

The control of the drug product is generally acceptable and analytical methods are described and suitably validated. The level of drug-dextrose adduct is controlled by the specification, although 5-HMF (5-hydroxy-methylfurfural, a by-product of dextrose degradation) is not. This and other minor deficiencies in the specification are pointed out, including tightening of the shelf life assay limits.

The stability of the product is well demonstrated over a two year period from batches manufactured at the previous licensee's facility. However, only the initial stability data point is provided for the primary batches manufactured at the proposed site. Further site specific primary stability data are

requested. A post approval stability commitment is provided and accepted. There are no major objections. However, there is a list of other concerns in Section VI.1.

III.2 Non clinical aspects

Pharmacology

Note that a summary of microbiology is provided in the clinical section of this overview.

In-vitro studies relating to cardiovascular safety pharmacology included receptor and ion channel binding assays (α_2, β_1 and β_2 adrenergic receptors, endothelin A, L and T type calcium channels, and protein kinase C). Garenoxacin was seen to bind to α_2 adrenoreceptors, but only at concentrations greater than those that were seen to produce effects *in vivo*. Garenoxacin had greater affinity for β_2 adrenoreceptors, where it was seen to demonstrate weak antagonist activity. Additionally garenoxacin was assessed in a hERG assay, where its IC50 was 300μM, which is reported to represent a 30 fold greater exposure compared with the expected Cmax following an intravenous dose of 600mg in humans.

In cardiovascular safety pharmacology studies rapid intravenous dosing of garenoxacin was seen to induce a transient decrease in blood pressure (BP), sometimes accompanied by an increase in heart rate, that was assumed to be compensatory. A number of studies have reported an association between garenoxacin induced hypotension and plasma histamine increases. Additionally, pre-treatment with antihistamines has been shown to inhibit garenoxacin induced BP decreases, and repeated garenoxacin dosing has been shown to lead to a reduced histamine and BP response to garenoxacin. The changes in plasma histamine levels and in blood pressure seen in dogs were shown to be attenuated by extending the infusion period from 12 minutes to 1 hour. Warnings relating to the ability of garenoxacin to induce hypotension following intravenous administration are recommended for the SPC.

Like many quinolones garenoxacin has been shown to induce QTc prolongation. One hour intravenous infusions (doses of 75 and 112 mg/kg) of garenoxacin in cynomolgus monkeys produced QTc prolongation that was not dose dependent. The effect started 30 minutes into the infusion and continued throughout the 1 hour post dosing monitoring period. The mean plasma garenoxacin levels at the end of the monitoring period were 48.14 and 65.62 μg/ml in the 75 and 112 mg/kg groups respectively, and QTc was prolonged by approximately 10% compared to the vehicle control group.

In dogs QTc prolongation following intravenous garenoxacin was observed to be dose dependent. In study 930003330 a 12 minute intravenous injection at a dose of 75 mg/kg induced 18% QTc prolongation immediately following the injection. The mean plasma garenoxacin concentration at this time point was 109.8 μg/ml. Contraindications and warnings relating to the potential of garenoxacin to cause QTc prolongation are recommended for the SPC.

Additional pharmacology studies revealed no significant interactions with CNS receptors including GABA receptors *in vitro*, and no synergistic interactions were noted in preclinical models to assess adverse CNS effects of garenoxacin in combination with NSAIDs.

In vivo, intravenous doses of garenoxacin were associated with decreased locomotor activity in mice at a dose of 60 mg/kg. Decreased activity was also noted as an adverse effect in dogs (intravenous doses of 30 mg/kg, Cmax reported as 31.55 μg/ml) and monkeys (at the lowest intravenous dose tested, 75 mg/kg, Cmax reported as 57 μg/ml). In humans the Cmax following repeated intravenous dosing with 600 mg is reported to be 15.6 μg/ml.

Additionally, garenoxacin was seen to have emetic activity in dogs (at 40 mg/kg intravenously) and monkeys (112 mg/kg intravenously). As the vomiting was reduced when dogs were pre-treated with haloperidol the vomiting was considered to be centrally mediated. Nausea and vomiting are included as adverse events in section 4.8 of the SPC.

Pharmacokinetics

In mice, exposure (Cmax and AUC) was seen to increase in a dose proportional manner following single oral doses of garenoxacin. In rats exposure was dose related, although increases in AUC tended to be greater than dose proportional (e.g. in study 910071069 a 5-fold increase in dose led to a 6-fold increase in AUC).

Only one single dose study (in rats – report 91007612) examined sex differences and in this study exposure (AUC) was markedly less in females than in males. This effect was seen following both oral and intravenous dosing, and bioavailability was greater in females than in males. In this study clearance was seen to be 3 times greater in females than in males. The mechanism underlying this effect has not been explored. The applicant reports that in clinical trials gender differences in pharmacokinetic parameters were not seen.

The single dose studies demonstrate that in mice, rats and monkeys bioavailability of garenoxacin is high; between 70 and 98% in mice, between 70 and 85% in rats, and 76% in monkeys. Rat studies demonstrated that the presence of food in the gut significantly reduced bioavailability; bioavailability was reduced from 77% in fasted rats to 26% in fed rats.

In a repeat dose study Cmax was not seen to be significantly different in rats administered a single dose of garenoxacin and in rats administered 21 doses of the drug at 6 hourly intervals. On the other hand, in dogs, AUC was substantially greater (approximately 1.6 fold) following 14 daily intravenous doses of 100 mg/kg garenoxacin compared to after the first dose.

Studies using Caco-2 monolayers suggest that garenoxacin is not a substrate for the P-glycoprotein efflux pump.

In-vitro protein binding data demonstrate that in rats, dogs, monkeys and humans 89, 78, 82 and 87% of garenoxacin was protein bound, respectively. In-vitro studies with human plasma have shown that human serum albumin is the protein responsible for the bulk of the binding.

Tissue distribution studies using rats, dogs and monkeys have shown that radioactivity is rapidly and widely distributed following both intravenous and oral administration. Values for VSS in rats (0.88 l/kg), rabbits (0.60 l/kg), dogs (1.28 l/kg), and monkeys (1.45 l/kg) were larger than the volume of total body water of 0.60 to 0.69 L/kg in these species, suggesting extensive extravascular distribution of garenoxacin. Values for VSS in the animal species were comparable to that reported in humans (0.81 L/kg at a dose of 600 mg). In all species examined, relatively little radioactivity gained access to the brain and spinal cord, while tissues that consistently showed high levels of radioactivity included the liver, kidney, lung and gastrointestinal tract (following both oral and intravenous administration). In rats and dogs, radioactivity levels were seen to accumulate in the thyroid as well as in the aorta. These observations were not investigated further. In monkeys retention of radioactivity was noted in melanin-containing tissues (eye and skin). However, neither non-clinical nor clinical studies revealed evidence of ocular toxicity or phototoxicity.

Within the blood, limited partitioning of radioactivity into red blood cells was observed in dogs (up to 36%) and monkeys (up to 21%).

Rat studies demonstrated fetal and neonatal exposure to garenoxacin following administration to pregnant and lactating rats. Note that concentrations of garenoxacin have also been determined in lactating women administered a single 600 mg garenoxacin dose. Concentrations of garenoxacin in breast milk were 4 μg/ml, and the proportion of the dose secreted in breast milk over a 120 hour period is reported to have been < 0.1%.

The metabolism of garenoxacin has been investigated in rats, dogs, monkeys and humans after oral, intravenous and intra-duodenal administration. Six metabolites (M1 to M6) have been isolated, 4 have been identified (M1, M4, M5 and M6) and one has been tentatively identified (M2). Two metabolites

(M2 and M3) were only seen in animals. In all species the primary metabolite was M1 (a sulphate conjugate).

The major metabolic pathways in humans appear to be similar to those seen in monkeys, dogs and rats. In all species, following administration of ^{14}C-garenoxacin the major radioactive component seen in plasma was unchanged garenoxacin, with no more than 10% of the radioactivity accounted for by the primary metabolite, M1. Radioactivity in the urine was also primarily due to the parent compound, with a small proportion due to M1 (approximately 5%). In all species examined, the bulk of the radioactivity present in faeces was due to a combination of the parent compound and M1. However, studies with bile duct-cannulated rats showed that M6 is also present at high levels in the bile. M6 is a glucuronide metabolite, and it has been suggested that following excretion in the bile, this is hydrolysed back to garenoxacin by intestinal microflora.

Evidence of some covalent binding of radioactivity was seen in dog plasma (reduced extractability over time). Bound radioactivity was seen to be released by treatment with 0.5N NaOH and mass spectral data suggests that the bound material may be structurally related to M5. The applicant reports that in human plasma studies no covalent binding was observed, and M5 is only seen in trace amounts in humans.

Some studies have been performed in an attempt to identify the agent responsible for the reddish-purple discolouration of various tissues seen in the toxicology studies. Ex-vivo and in-vitro analysis of coloured tissues has suggested that the compound may have a bis(isoindolenylidene) structure, and that it may be a dimer. While the chemical structure has not been confirmed, it seems that the coloured compound degrades to metabolites M4 and M5 and a dehydration derivative of M5.

Given the tissue discolorations seen in the repeat dose studies and the covalent binding of radioactivity to plasma proteins seen in dogs, further characterisation of potentially reactive metabolites should be provided, particularly in the light of the potential for liver toxicity in humans. The applicant should consider carrying out a chemically reactive metabolite screen.

In vitro metabolism studies using human and rat systems generally showed no inhibition or induction of cytochrome P450 isoforms following incubation with a range of concentrations of garenoxacin, although a slight inhibition of CYP isoforms in human hepatic microsomes was seen following incubation with a high concentration of garenoxacin (1000 μM). Overall, these results suggest that cytochrome P450 mediated drug interactions between garenoxacin and cytochrome P450 inhibitors, inducers and substrates are unlikely.

Excretion of garenoxacin and its metabolites has been investigated in rats, dogs, monkeys and humans. The data are summarised in the following table.

Summary of excretion of garenoxacin related radioactivity in rats, dogs, monkeys and humans

Species	Dose / Route	Sex	Excretion of Radioactivity (% of dose)[a]		
			Urine	Feces	Total
Rat	5 mg/kg PO	M	13.0	84.8	97.8
	5 mg/kg IV	M	19.0	79.7	98.7
Dog	100 mg/kg IV	M	31.9[b]	64.1[b]	95.9
Monkey	5 mg/kg PO	M	38.9	60.7	99.6
	5 mg/kg IV	M	48.1	50.5	98.6
Human	600 mg PO	M	41.8	45.4	87.2

Rat, dog, monkey and human data derived from reports 910072610, 930000422, 910071078 and 930001963/930001550, respectively.
a: Mean cumulative excretion in urine and faeces over 96 h in rats, 168 h in dogs and monkeys, and over 192 h in humans
b: After repeated administration for 14 days

In rats elimination profiles were seen to remain constant regardless of dose and route, and the bulk of a dose was excreted within 24 hours. Female rats were observed to excrete more of an oral dose as M1 (7.51% in urine and 29.4% in bile) than males (0.96% in urine and 14.1% in bile), while males excreted more as M6 (18.2%, all in the bile) than females (2.82% divided between the bile and urine).

Data from dog studies showed that renal clearance of unbound garenoxacin was less than the glomerular filtration rate, suggesting that garenoxacin undergoes tubular re-absorption. Additionally, garenoxacin is likely to undergo entero-hepatic recirculation

A number of nonclinical studies relating to potential interactions have been performed.

Although increasing garenoxacin concentrations were shown to inhibit warfarin binding to human serum albumin binding site I *in vitro*, concentrations of 100 µg/ml garenoxacin did not inhibit warfarin protein binding overall *in vitro*. *In vivo*, co-administration of warfarin (0.3mg/kg/day) and garenoxacin (up to 60mg/kg/day) in rats did not increase prothrombin time or activated partial thrombin time compared to that seen in animals treated with warfarin alone.

In-vitro studies have shown that garenoxacin does inhibit CYP mediated metabolism of theophylline, although only at concentrations greater than would be expected in the liver following therapeutic doses of garenoxacin. Garenoxacin was less potent in this respect than enoxacin and ciprofloxacin, for which there are clinical reports of interactions with theophylline, but more potent than ofloxacin, for which no clinical interactions have been reported.

As described above, studies using human and rat systems generally showed no inhibition or induction of cytochrome P450 isoforms following incubation with a range of concentrations of garenoxacin. These results suggest that cytochrome P450 mediated drug interactions are unlikely.

Studies in rats have shown interactions between garenoxacin and cimetidine, which was shown to reduce renal clearance of garenoxacin by inhibition of tubular secretion and between garenoxacin and probenecid, which was shown to increase renal clearance possibly by inhibiting tubular re-absorption of garenoxacin.

Finally, the applicant has provided a number of studies that assessed the pharmacokinetics of garenoxacin in uninfected mice and rabbits compared to mice and rabbits infected with *Streptococcus pneumoniae*. In mice serum garenoxacin levels were not significantly influenced by infection. In rabbits CSF garenoxacin levels were seen to be greater in infected than in uninfected animals, and Cmax was seen to increase in a greater than dose proportional manner.

Toxicology

Single-dose toxicity studies of garenoxacin were conducted in mice, rats, and dogs by the oral route at doses of 1000 to 2000 mg/kg and by the intravenous route at doses up to 300 mg/kg. Oral doses of up to 2000 mg/kg were well tolerated in mice and rats, with no findings of note. Dogs were more sensitive with transient clinical signs and changes in haematology and blood chemistry seen, particularly at 2000 mg/kg. No gross pathology was noted in these animals.

Single intravenous dosing led to deaths in mice, rats and dogs at doses of 250 mg/kg, 300 mg/kg and 300 mg/kg respectively. Convulsions were seen in all species, as well as decreased locomotor activity and decreased respiration. Transient changes in haematological parameters and blood chemistry were also observed. While no significant gross pathology was noted in mice and rats, in dogs that died histopathology revealed congestion of the liver and small intestine, leading the applicant to conclude that, in these animals, death was the result of an acute circulatory disorder. In mice and rats the NOAEL was 100 mg/kg, while no NOAEL was established in dogs.

The primary findings from repeat dose studies in rats included effects on the liver (lipid droplets in hepatocytes, inflammatory cell infiltration and necrosis – seen at oral doses of 100 mg/kg in males) and degeneration of articular cartilage (at oral doses of 400 mg/kg in females and at intravenous doses of 100 mg/kg). Other findings, including dilation of the caecal lumen and increased caecal weights, are considered to have been secondary to changes in intestinal microflora. Toxicokinetic data from the pivotal studies show that exposure was dose related, increased with repeat dosing, and was substantially greater in males than in females (in oral and intravenous dosing studies). However, it is noteworthy that in an unscheduled DNA synthesis assay systemic exposure in male rats following oral dosing of 1000 and 2000 mg/kg was not dose related, suggesting that at these high doses the pharmacokinetics of garenoxacin may not be linear in this species. Additionally, non linear increases in exposure were noted in juvenile rats administered increasing intravenous doses of garenoxacin.

Repeat dosing in dogs was associated with lipofuscin deposition in the follicular cells of the thyroid (at oral doses as low as 8 mg/kg in a 6 month study), although thyroid hormone levels were seen to be unaffected. Additionally, liver findings were noted (inflammatory cell infiltration at oral doses of 75 mg/kg) as well as degeneration of articular and epiphyseal cartilage (noted at oral doses of 75 mg/kg and intravenous doses of 50 mg/kg). Reddish-purple discolouration was seen in multiple organs/tissues but was not paralleled by histopathological findings. Additionally, injection site reactions were noted in the intravenous dosing studies (at 50mg/kg). All effects were noted to be at least partially reversed during recovery periods. The 6 month oral administration study in dogs included ultrastructural evaluation of the pancreas, with no notable findings. Toxicokinetic data from the dog studies show that exposure was dose related and did not differ in males and females.

In monkeys repeat dosing was associated with lipofuscin deposition in follicular cells of the thyroid as well as brown foamy cells in the follicular lumen (at oral doses of 100mg/kg), and a slightly elevated T4 level was seen in one high dose female (100mg/kg oral). Additionally, QTc prolongation was noted (at oral doses of 100mg/kg and intravenous doses of 75mg/kg) as well as transient decreases in heart rate, and atrophy of the fundic mucosa in the stomach. Reddish-purple discolouration of numerous organs/tissues was also seen. Additionally, injection site reactions were noted in the intravenous dosing studies at 30mg/kg. Toxicokinetic data show that systemic exposure was dose related and there were no sex differences.

The NOAELs calculated from the repeat dose studies demonstrate that animal to human safety margins are negligible. The table below lists the doses at which some of the adverse effects were seen in the repeat dose studies, along with the relevant animal to human exposure ratios for these effects. Animal to human safety margins are negligible for adverse effects on the liver (lipid droplets in hepatocytes, inflammatory cell infiltration, necrosis), thyroid (lipofuscin deposition) and cartilage. The applicant should comment on the potential clinical safety implications of this.

Doses at which adverse effects were seen in the repeat dose studies and the corresponding safety margins Exposure ratios are calculated based on AUC values from repeat dose testing.

Study	Effect	Dose	Animal : human exposure ratio
Oral dosing in rats	Liver findings (lipid droplets in hepatocytes, inflammatory cell infiltration, some necrosis)	100mg/kg	0.27
Oral dosing in rats	Articular cartilage degeneration	400mg/kg (F)	0.4
Intravenous dosing in rats	Articular cartilage degeneration	100mg/kg	0.479
Oral dosing in dogs	Lipofuscin deposits in thyroid	8mg/kg	0.137
Oral dosing in dogs	Degeneration of articular and epiphyseal cartilage	75mg/kg	2.71
Intravenous dosing in dogs	Degeneration of articular and epiphyseal cartilage	50mg/kg	1.92
Oral dosing in monkeys	Lipofuscin deposits in thyroid	100mg/kg	2.11
Oral dosing in monkeys	QTc prolongation	100mg/kg	2.69
Intravenous dosing in monkeys	QTc prolongation	75mg/kg	2.96
Intravenous dosing in monkeys	Injection site reactions	30mg/kg	0.945

Gene mutation studies using bacteria and Chinese hamster lung cells produced no evidence of genotoxicity.

In a photomutagenicity study in *Salmonella* strains garenoxacin did induce a statistically significant number of revertants/plate in strain TA102 in the absence of UV irradiation. High levels of UV irradiation were actually associated with a decreased number of revertants per plate (compared to in the absence of UV irradiation). As positive responses to garenoxacin were seen in the absence of UV irradiation as well as in the presence of UV irradiation the effect is considered to represent mutagenicity rather than photomutagenicity. The applicant argues that this is not surprising as other quinolone antibiotics have produced positive results in DNA repair-proficient bacterial strains such as TA102. The applicant did not undertake a photomutagenicity study with a metabolising system present and should justify the absence of such studies**.**

Garenoxacin clearly induced chromosome aberrations in cultured mammalian cells (Chinese hamster lung cells). The applicant reports that this too, is an expected result as other fluoroquinolone antibiotics are also known to be clastogenic in these systems, and that the results can therefore be considered a class effect.

In a photoclastogenicity test in CHO cells garenoxacin was shown to be photoclastogenic, as were ciprofloxacin and lomefloxacin. Additionally, a small positive clastogenic response was seen to garenoxacin in the absence of UV light. No such effect was seen with the comparators, ciprofloxacin and lomefloxacin, in the absence of UV light. The applicant should comment further on the potential significance of this finding.

Results from the in-vivo genotoxicity studies (micronucleus assays in mouse bone marrow and an unscheduled DNA synthesis assay in hepatocytes from treated rats) did not reveal evidence of genotoxic potential. Exposure data show that the levels achieved were at least 3 times those expected in humans following multiple dosing (based on AUC).

Additional genotoxicity studies performed to investigate the potential association between the reddish-purple discolouration of tissues (as seen in the repeat dose studies) and genotoxicity revealed no positive findings.

No carcinogenicity studies have been performed. The applicant argues that the profile of results seen in genotoxicity studies is consistent with what would be expected for this class of drug (i.e. garenoxacin was mutagenic in *Salmonella typhimurium* strain TA102 and positive in in-vitro assays

for clastogenicity and photoclastogenicity but produced no evidence of genotoxicity *in vivo*) and that the weight of evidence from human experience indicates that quinolones do not pose a carcinogenic risk. Consequently, and as garenoxacin will only be used short term, no carcinogenicity testing is needed. However, the applicant reports that ciprofloxacin has been seen to be photocarcinogenic in mice. It seems reasonable, therefore, to assume that garenoxacin may also be photocarcinogenic, at least in mice. Section 4.4 of the proposed SPC does include a warning recommending patients avoid exposure to UV irradiation and strong sunlight.

A fertility and early embryonic development study in rats revealed no drug related effects on mating, fertility or reproductive parameters or on early embryonic development at any dose (males administered up to 400 mg/kg/day and females up to 1000 mg/kg/day).

No embryofetal toxicity was seen in the definitive rat embryofetal development study at any dose (pregnant rats administered up to 1000 mg/kg/day orally). However, in the definitive rabbit embryofetal development study garenoxacin was associated with abortions and premature delivery at all doses (i.e. as low as 6.25 mg/kg intravenously). The applicant considers this finding to be secondary to poor nutrition in the dams, resulting from reduced food consumption. Extrapolating from the limited rabbit toxicokinetic data available, the AUC at this dose is likely to have been in the region 39 μg.h/ml, which is four fold less than that seen in humans administered repeat intravenous doses of 600 mg garenoxacin. Fetal findings were also noted in the rabbit study (slightly decreased weight and increased incidence of rudimentary thymus), at 25 mg/kg. Systemic exposure at this dose is likely to have been similar to that expected in humans administered repeat 600 mg doses.

In the pre and postnatal development study in rats the only effect observed in the F1 generation was increased caecal weights in offspring of dams treated with 1000 mg/kg. No additional drug related findings were noted in the F1 or F2 generation. The proposed SPC reports that garenoxacin is contraindicated in pregnancy and section 4.6 of the SPC reflects this. However, as a full nonclinical reproductive toxicology package has been supplied the statement, in section 4.6 of the SPC, that animal studies are insufficient seems somewhat inappropriate. Alternative text is recommended in the list of questions.

Local tolerance studies have examined reactions to garenoxacin following intra-peritoneal, intravenous, paravenous and intra-arterial administration of garenoxacin. At a concentration of 2 mg/ml (the concentration proposed for use in humans) garenoxacin was not associated with local reactions greater than those seen following administration of control solutions (saline, 5% glucose, 11% glucose and 5% dextrose, depending on the study). Paravenous administration of a solution of 3 mg/ml garenoxacin was slightly irritant, and intravenous administration of 10 mg/ml garenoxacin induced injection site reactions (thrombosis, oedema and inflammatory cell infiltration). However, the local tolerance studies were not performed with the final product.

The antigenic potential of garenoxacin has been investigated in mice and guinea pigs using passive cutaneous anaphylaxis, and in guinea pigs using active systemic anaphylaxis, all with negative results. Additionally, garenoxacin was tested in an in vitro haemagglutination assay, also with negative results.

Drug substance and finished product specifications show that, with the exception of the proposed limit for dextrose adducts present in the intravenous formulation, all impurities are in line with the relevant ICH guidelines. The applicant has provided data from toxicology studies in order to qualify the proposed limit for dextrose adducts. Additionally, the applicant has provided data from toxicology studies relating to a decarboxylated degradant reported to be present in the tablet formulation, although the limits proposed for this impurity (0.2%) are not such that qualification is a regulatory requirement. Dextrose adducts has been qualified by a 2 week repeat intravenous dosing study in rats that included assessment of genotoxic potential in a micronucleus assay, and in an in vitro mutagenicity assay to evaluate mutagenic potential at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus in Chinese hamster lung (V79) cells. Based on the studies with dextrose adducts, the proposed level of 0.5% in the finished product specification can be considered toxicologically qualified.

The phototoxicity of garenoxacin was investigated in a repeat oral dosing study in hairless mice using doses of up to 800 mg/kg/day (the top dose used). At this dose, levels of garenoxacin present in the skin are reported to be approximately 10 times those expected in humans treated with the drug. Mean plasma garenoxacin levels were approximately 3 times the Cmax seen in humans administered repeat intravenous doses of 600 mg/kg/day. Similarly, no evidence of phototoxicity was seen in a single dose guinea pig study in which garenoxacin was administered intravenously. Mean plasma garenoxacin levels were approximately 3.5 times the Cmax seen in humans administered repeat intravenous doses of 600 mg/kg. Data from these studies suggest that garenoxacin may be less phototoxic than levofloxacin and ciprofloxacin.

The ability of garenoxacin to induce crystalluria was investigated in a non-GLP study in which rats were administered single oral doses of up to 400 mg/kg, with no positive findings.

As quinolone antibiotics are known to adversely affect cartilage in developing animals, the effects of garenoxacin were examined in 3 juvenile animal studies. In juvenile dogs both intravenous and oral garenoxacin was seen to induce degeneration of articular cartilage following repeat administration for 1 week. In the oral dosing study toxicity was seen at exposure levels (Cmax) similar to those expected in the human population, while in the intravenous dosing study exposure levels (AUC) similar to those expected in humans were not associated with toxicity – toxicity was seen at exposure levels approximately double those expected in humans. The comparator products, ciprofloxacin and norfloxacin, produced similar toxicity, although the degree of toxicity seen with these comparators was greater than that seen with garenoxacin. This was despite the fact that the plasma and joint levels of the drugs were greatest for garenoxacin. In the intravenous dosing study trovafloxacin was also used as a comparator product, and this was not seen to induce any signs of articular toxicity.

In an investigative study in immature rats electron microscope evaluation of joint cartilage and Achilles tendon demonstrated that oral garenoxacin, ciprofloxacin and ofloxacin induced ultrastructural changes typical of quinolone antibiotics. These effects were seen at exposure levels (plasma Cmax) similar to those expected in humans. The low animal to human safety margins for toxicity to articular cartilage and tendons derived from the juvenile animal studies is particularly relevant given the applicant's paediatric development plans.

The applicant submitted an environmental risk assessment. There are some questions about this which need to be addressed (see list of questions).

III.3 Clinical aspects

Pharmacokinetics

The absolute bioavailability of garenoxacin was determined in fasting healthy subjects. The geometric mean for the absolute oral bioavailability of a 600 mg garenoxacin dose was determined to be 92%. Cmax following IV administration was 35% greater than after the oral dose.

Bioequivalence was demonstrated between the clinical study formulation (one 200 mg + one 400 mg tablet) and commercial tablets (one 200 mg [not to be marketed] + one 400 mg or a single 600 mg tablet).

The effect of food was assessed by administering 2 x 200 mg tablets in the fasting state and after a standard high-fat meal (945 kcal; 55 g fat, 82 g CHO and 32 g protein).

Pharmacokinetic Variable	Geometric Means		Ratio of Fed/Fasted (90% Confidence Interval)
	Fasted	Fed	
Cmax (µg/mL)	5.76	4.69	0.81 (0.71, 0.94)
AUC(INF) (µg•hr/ml)	71.7	63.8	0.89 (0.85, 0.93)

Parameter		Fasted (N = 13)	Fed (N = 13)
Tmax (hr)	Median (Min-Max)	1.0 (0.5 –4.0)	2.0 (0.75 – 3.0)
T-HALF (hr)	Mean (S.D.)	14.1 (2.6)	14.9 (2.7)
AUC(0-T) (µg•h/ml)	Geo. Mean (%CV)	69.6 (24.0)	61.8 (20.0)

In the light of the correlation between the AUC/MIC ratio and efficacy it seemed that the effect of food was not likely to be clinically important and dosing was without regard to food in all Phase III studies.

Single and multiple oral dose studies suggested that increments in Cmax were fairly dose-proportional up to 800 mg but were higher than expected in the 1200 mg dose group. Increments in AUC(TAU) were fairly dose-proportional up to 400 mg but were higher than expected on days 7 and 14 in the 800 mg group and on all 3 days in the 1200 mg group.

	Garenoxacin	**Day 1 (n = 6)**	**Day 7 (n = 6)**	**Day 14 (n = 6)a**
Cmax (µg/ml)	100 mg	1.2 (23.2)	1.5 (23.1)	1.6 (37.0)
Geometric Mean	200 mg	2.4 (15.2)	2.9 (15.9)	3.0 (9.2)
C.V. %)	400 mg	4.6 (14.8)	5.2 (15.8)	5.6 (17.6)
	800 mg	9.5 (12.8)	12.6 (32.2)	14.4 (40.4)
	1200 mg	16.3 (31.8)	21.5 (37.9)	24.0 (34.8)
AUC(TAU)b(µg•h/ml)	100 mg	11.5 (21.3)	15.6 (18.6)	15.7 (20.5)
Geometric Mean	200 mg	23.3 (19.0)	31.0 (17.6)	32.7 (17.3)
(C.V.%)	400 mg	45.2 (15.6)	58.5 (23.1)	58.6 (19.9)
	800 mg	100.7 (10.7)	157.9 (44.5)	180.8 (48.8)
	1200 mg	179.8 (30.0)	271.0 (36.5)	307.3 (31.2)

The applicant concluded that within the 100 mg to 400 mg dose range increases in Cmax and AUC(TAU) on Days 1, 7, and 14 and AUC(INF) on Day 1 were approximately proportionate to dose and were time-independent. At doses of 800 and 1200 mg increases in systemic exposure were somewhat greater than the dose increment and appeared to demonstrate some degree of time dependence.

In a further study the results showed a predictable modest accumulation following 400 mg oral daily doses over 28 days. The pharmacokinetics of garenoxacin was considered to be time-independent following repeated oral administration at this dose level.

Single and multiple intravenous doses indicated that steady state was reached on day 4 at all dose levels (200-800 mg). Cmax and AUC(TAU) on Days 1, 11 and 18 and AUC(INF) on Day 1 increased proportionately to dose. Geometric means for the AUC(TAU) accumulation index (all were from 1.2 to 1.5) appeared to be independent of dose and were similar on Days 11 and 18 (i.e. days 7 and 14 of multiple dosing).

In-vitro protein binding was constant over the range 0.005-0.05 mg/ml in human serum with a mean percent bound of 87%. Binding was mainly to HSA binding site I but there was also binding to other protein fractions. With Cmax values of 15.4 µg/ml and 11.4 µg/ml after 600 mg IV and PO doses, respectively, the protein binding of garenoxacin in serum is predicted to be 83.6% to 83.9%.

In breast milk, 0.07% (0.42 mg) of a 600 mg oral dose was recovered within 120 hour post-dose.

Using Caco-2 cells, results suggested that garenoxacin is unlikely to be a substrate of P-gp.

In-vitro biotransformation studies in human liver microsomes indicated that at concentrations of 10 or 100 µM (4.26 and 42.6 µg/ml) unlabelled garenoxacin there was no NADPH-dependent metabolism, including CYP-mediated oxidative metabolism. Biotransformation of [14C]-garenoxacin was investigated *in vitro* with cDNA expressed human CYP isozymes of types 1A2, 2A6, 2D6, 2E1, 3A4, 2C9 and 2C19. The only positive finding was that CYP2C9 catalysed formation of a minor unidentified metabolite (< 4%) that was not observed in human plasma, urine or faecal samples. The parent compound was the major component in liver S9 incubation samples.

The ability of garenoxacin (40, 200, and 1000 µM [17.1, 85.3, and 426.4 µg/mL]) to inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4 was studied in human hepatic microsomes using appropriate reference substrates. There was <15% inhibition in all cases at up to 200 µM. Results from quantification of CYP gene induction indicated that garenoxacin was not an inducer of CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP2E1 and CYP3A4. Induction was also studied in rats with similar conclusions regarding CYP1A1/2, 2B1, 2C6, 2C11, 2E1, and 3A2.

In a mass balance study most of the radioactivity in plasma (> 94%) and pooled urine (> 95%) was unchanged [14C]-garenoxacin. In urine, two minor metabolites were identified as the acyl glucuronide (M6) and sulphate (M1) conjugates and accounted for 3% and 2% of radioactivity, respectively. In the pooled faeces (0-192 h), unchanged drug amounted to 34% and M1 accounted for 55% of the faecal radioactivity. Some other minor metabolites, including M4 (lactam derivative), were also detected, each accounting for ≤1% of the faecal radioactivity. Garenoxacin did not undergo in-vivo inter-conversion to the S-enantiomer.

There is no major circulating metabolite(s), for instance, the Cmax of total radioactivity was 13% greater and AUC(INF) was approximately 6% greater than corresponding values for garenoxacin. Sampling up to 192 h gave 42% of the radioactivity dose recovered in urine and 45% in faeces. The percentage of the radioactive dose excreted in the urine was similar to the estimate for unchanged garenoxacin (38.9%).

The percentage of the radioactive dose excreted in the urine was similar to the estimate based on unchanged garenoxacin (38.9%). Values for mean renal clearance of unbound garenoxacin following oral administration were similar to or greater than the anticipated glomerular filtration rate, indicating that garenoxacin undergoes both glomerular filtration and tubular secretion. Crystalluria was not detected in urine following 14 days of oral dosing with up to 1200 mg, oral doses of 400 mg for up to 28 days or 14 days dosing intravenously with up to 800 mg daily.

Population PK/PD analyses were performed on data collected from 721 patients with acute bacterial exacerbation of chronic bronchitis (AECB), community acquired pneumonia (CAP) and acute bacterial sinusitis (ABS) who were treated with oral doses of 400 mg once daily for either 5 or 10 days. A one-compartment model with first-order absorption and elimination adequately described the pharmacokinetics of garenoxacin. In the final model, garenoxacin clearance was dependent on estimated creatinine clearance (CLcr), ideal body weight (IBW), age, obesity and concomitant use of pseudoephedrine (see below). Volume of distribution (V/F) was shown to be influenced by body weight and gender, with a 17.7 l increase for males.

Further examination of the significant covariates showed that patients with mild (CLcr 51-80 ml/min) or moderate (CLcr 30-50 ml/min) renal dysfunction have approximately a 14 or 25 mL/min decrease in apparent oral clearance (CL/F), respectively, compared to patients of the same gender and obesity

classification with normal renal function. The CV% for CL/F) was 25% and that for V/F was 19%. The applicant concluded that the relationships detected did not warrant dose adjustment in patients with these covariates. This was based on the similarities in exposures between patients and healthy volunteers and the PK/PD analysis of safety. The applicant considered AUC (range 42.1-216 µg·h/mL) and Cmax (range 3.52-13.6 µg/ml) were not statistically significant predictors of occurrence of AEs and established a wide therapeutic index for garenoxacin.

In a study of renal impairment single 600 mg doses were given to:
Group A: CLcr > 80 ml/min; matched to Group B for age (± 5 years), weight (± 20%) and gender.
Group B: CLcr < 30 mL/min but not requiring dialysis
Group C: needing haemodialysis (HD) dosed 3 hours prior to haemodialysis. A second dose was given 14 days later and immediately after completion of haemodialysis
Group D: needing CAPD dosed immediately prior to the first instillation of dialysate fluid for that day.

Pharmacokinetic Parameter	**Group**	**AdjGeometric Mean**	**Contrast**	**Ratios of Adj. Geo. Means Pt. Estimate (90% CI)**
Cmax (µg/ml)	A	12.6		
	B	10.1	B versus A	0.799 (0.566, 1.129)
AUC(INF)	A	136.4		
(µg•h/ml)	B	205.4	B versus A	1.506 (1.113, 2.038)

The HD extraction ratios were similar (approximately 14%) when HD was performed 3 h post dose (Group C Phase 1) or approximately 68 h post dose (Group C Phase 2). The proportions of the dose removed by HD were approximately 11% and 1.5%, respectively. In CAPD subjects approximately 3% of the dose was removed over 72 h.

Based on this study, the applicant concluded that:
- The decrease in Cmax with renal impairment is not clinically significant since the AUC:MIC ratio is the established pharmacodynamic predictor of efficacy for quinolones.
- The increases in AUC with renal impairment (B and D *vs* A) are not clinically significant because of the broad therapeutic index.
- Garenoxacin may be administered to those with severe renal impairment, including HD or CAPD patients, without dose adjustment. Garenoxacin should be administered after completion of HD.

In a study of hepatic impairment single doses of 600 mg were given with fasting for 2 h either side of the dose to subjects of Child-Pugh A (N=6), Child-Pugh B (N=6), Child-Pugh C (N=2) and Group D of healthy controls (N=6). Without the data from a single outlier, the applicant considered that there was no effect of mild hepatic impairment (A) on Cmax but there was an effect seen for Groups B and C. In contrast, it was concluded that there was no effect for any group with respect to AUC(INF). When the outlier data were included, the comparison of AUC(INF) for group A *vs* D failed to meet the pre-defined 90% CI. The applicant concluded that no dose adjustment is required in patients with hepatic impairment.

Statistical analysis excluding outlier in group A

Pharmacokinetic Parameter		Group	Adjusted Geometric Mean	Contrast	Ratios of Adj. Geo. Means Pt. Estimate (90% CI)
		A	9.76	A versus D	0.889 (0.693, 1.142)
Cmax	(µg/l)	B C	8.34 7.03	B versus D C versus D	0.760 (0.599, 0.964) 0.641 (0.458, 0.897)
		D	10.97	N/A	N/A
AUC(INF)(µg•h/ml)		A B C D	113.9 108.6 113.9 113.0	A versus D B versus D C versus D N/A	1.008 (0.808, 1.258) 0.961 (0.779, 1.187) 1.008 (0.748, 1.358) N/A

The population PK analysis in patients detected a 14% decrease in garenoxacin clearance ($p < 0.00001$) for patients co-administered pseudoephedrine, which may be due to competition for the active tubular secretion pathway involved in garenoxacin elimination.

In an interaction study concomitant intravenous morphine reduced the Cmax and AUC(inf) garenoxacin such that 90% CI around the Cmax ratio were outside the 80, 125 limits while those for the AUC ratio were within these limits but did not span 1.00.

There were increases in Cmax and AUC(tau) digoxin when garenoxacin was added such that 90% CI did not span 1.00 and exceeded 125% for Cmax. However, trough digoxin serum concentrations did not exceed the normal therapeutic range (0.8 to 2.0 ng/mL). Mean digoxin %UR at steady state was not altered by co-administration with garenoxacin and the mean digoxin renal clearance was not affected. However, there were decreases in mean systolic bp on co-administration. While these were not symptomatic in healthy subjects, patients in efficacy studies who received garenoxacin plus digoxin were at higher risk of hypotensive events.

Exposure to garenoxacin was reduced by 58% when co-administered with Maalox. Garenoxacin exposure was not affected when it was administered 4 h prior to Maalox whereas administration 2 h prior to Maalox gave adjusted geometric means of Cmax and AUC(INF) that were 3% and 12% lower compared to garenoxacin alone and the lower 90% CI for the AUC(INF) ratio was 0.77. Exposure to garenoxacin was reduced by 22% and 16% when administered 2 h and 4 h after Maalox, respectively. There was no important effect of omeprazole on the pharmacokinetics of garenoxacin.

Comment on pharmacokinetics

The study of renal impairment does not comply with the CHMP recommendations. As an alternative to performing a new study, the applicant might be able to use PK modelling to derive appropriate recommendations for dose adjustments. The study in persons with hepatic impairment also would not meet CHMP recommendations. While a significant effect of hepatic impairment on garenoxacin would seem unlikely this issue should be explored further to justify the recommendation for no dose adjustment.

There seems to be a potential for interaction with pseudoephedrine at the level of tubular secretion but the exact pathway(s) utilised by garenoxacin has not been elucidated. The slight reduction in exposure on co-administration with IV morphine should at least be reflected in the SPC since a clinically significant interaction with opiate pre-medicants cannot be ruled out. The applicant dismissed the observations made from the interaction study with digoxin. However, reliance on comparisons of mean values may hide significant changes in individual subjects that might occur if the interaction is at the level of renal excretion. The pharmacokinetic data and the potential for hypotensive events on co-administration should be adequately reflected in the SPC. Overall, the applicant needs to further justify

the limited scope of the drug interaction studies thus far and should make proposals to address the potential for interactions at the level of the renal tubule.

Pharmacodynamics

Garenoxacin was highly selective for bacterial compared to human topoisomerase, with estimates of selectivity that ranged from 26 to > 3000, depending on the study and the bacterial topoisomerase. As with other quinolones the primary target in Gram-negative organisms seems to be the GyrA subunit of DNA gyrase. It is more difficult to discern primary targets in Gram-positive organisms but the GrlA subunit of Topo IV is commonly implicated at least in staphylococci.

In a range of studies the *f*AUC/MIC ratios predictive of efficacy for garenoxacin against *S. pneumoniae*, S. *aureus*, Enterobacteriaceae and non-fermentative Gram-negative organisms were ≥ 30, ≥ 60, ≥ 80 and ≥ 90, respectively. Garenoxacin is not predicted to be active against *Pseudomonas spp*.

The extensive in-vitro susceptibility data showed that MIC90 values did not exceed 0.25 mg/l for the majority of species. Notable exceptions included:

- MIC90 for MRSA and MRSE were from 1-8 mg/l. This reflects the co-resistance to quinolones that is observed in methicillin-resistant staphylococci.
- MIC90 for enterococcal species was from 1-8 mg/l
- MIC90 for *Klebsiella*, *Proteus* and *Serratia* were up to 1 mg/l
- MIC90 for *Acinetobacter* and *Pseudomonas* were 8-64 mg/l
- The susceptibility of anaerobes varied, the least susceptible were some *Bacteroides* species.
- *C. difficile* is highly resistant

The evidence generally pointed to cross-resistance between other quinolones and garenoxacin. However, there did seem to be some potential for garenoxacin to retain useful activity against certain pneumococci that showed reduced susceptibility to ciprofloxacin and levofloxacin. There are also data to indicate that garenoxacin may be active against specific staphylococci with certain types of mutational resistance to ciprofloxacin.

Secondary pharmacology

Intravenous garenoxacin is given in 5% glucose so that infusions to healthy subjects were initially accompanied by mild to moderate elevations in serum glucose levels but a mean decrease in glucose of 21.3 ± 11.2 mg/dl was noted at 30 minutes after the end of infusion. In an open label, non-placebo controlled study, after oral dosing serum glucose decreased to a mean value of 79.1 mg/dL (from a baseline of 90.4 mg/dl) at 1 h but this had normalised by 3 h post-dose. A negative change from baseline in serum glucose was noted in all subjects at 40 minutes and 1 hour after oral administration. There was a weak trend towards an increase in mean serum insulin or mean change from baseline that normalised by 1.5 h. The maximum increase was noted at 40 minutes post-dose but not all subjects had a positive change from baseline *vs* time. Mean serum c-peptide did not appear to change.

In a study in healthy subjects no dose-related patterns were observed in any of the simple reaction time (SRT), continuous performance time (CPT) or digit symbol substitution (DSS) test variables when garenoxacin was given at doses of up to 1200 mg administered orally for 14 days.

Intravenous dosing for 14 days at various doses did not adversely affect adrenal function and there was no adverse effect on thyroid function. Photographs and visual inspection were used to assess any effects on the buccal mucosa (particularly discoloration) during 28 days dosing in study 008 but none was observed.

In a study of photosensitivity, the percent decreases in MED were similar between garenoxacin and placebo at 400 ± 30 nm, 430 ± 30 nm and the whole light spectrum. No subjects in the placebo or

garenoxacin groups had a PI > 5.0 on Day 7, suggesting that doses up to 800 mg do not have a potential to cause delayed erythema or pigmentation.

In a study of systolic blood pressure (bp) in sodium chloride-depleted healthy subjects, changes in semi-recumbent systolic bp showed that:

- The infusion rate appeared to affect the profile of ΔSBP and ΔHR within the first 3 h following the start of the infusion on Day 1, with related AEs (i.e., dizziness or symptomatic hypotension) only noted in the 1 h garenoxacin infusion group. A greater incidence of decrease in SBP > 10 mmHg and decrease in HR > 10 bpm was noted for the 1 h garenoxacin infusion group compared to the 3 h garenoxacin or placebo infusion groups.
- The applicant decided that early changes in SBP and/or HR in patients might be mitigated by a longer infusion duration (i.e., 3 h) but decreasing the rate of infusion would likely not mitigate the late changes (> 3.5 h after the start of infusion) in SBP and/or HR.
- Following the first day of dosing, no additional decrease in mean SBP or HR was anticipated to occur on subsequent days of dosing with a 1 h garenoxacin infusion and this period of administration was chosen for the efficacy studies.
- Changes from baseline in histamine concentrations were similar for garenoxacin and placebo groups, were not affected by the rate of infusion and did not correlate with changes in SBP or HR.

The clinical programme did not include a formal study of effects on QTc in accordance with the CHMP NfG. In place of this, the applicant presented:

- An integrated retrospective analysis of QTc data from 5 Phase I studies in healthy subjects
- An integrated analysis of QTc data derived from 5 IV to PO Phase III studies

In the five studies in healthy subjects, serial ECGs were obtained during administration of garenoxacin including doses of 400 mg and 600 mg for up to 14 days. The report includes data from 224 subjects aged from 18-45 years of which 149/224 received garenoxacin (88% male). Regarding QTcB intervals

- No subjects had any QTcB interval > 450 ms for males or > 470 ms for females.
- QTcB intervals between 431-450 ms (males) or 451-470 ms (females) occurred in 2% prior to dosing and in 4% after receiving garenoxacin doses up to 1200 mg orally or up to 800 mg intravenously.
- One male given garenoxacin 400 mg had a ΔQTcB > 60 ms on Day 7 only despite continued dosing.
- The incidence of ΔQTcB 30-60 ms was 25% for placebo, 36% for ciprofloxacin, 22% for lomefloxacin and 27% for garenoxacin.
- There was no clear relationship between dose, route of administration or day of administration for garenoxacin doses up to 1200 mg PO or 800 mg IV, with the exception of 600 mg IV on Day 14.

In the five Phase III studies of IV-to-PO garenoxacin administration ECGs were obtained at baseline, at approximately the end of the infusion on Day 1 and once during treatment on Days 3-5. For garenoxacin patients the mean QTcB change was -8.7 ms on Day 1 and -7.4 ms on Day 3-5. Corresponding mean QTcF changes were -4.7 ms and 4.4 ms. Changes in QTcF or QTcB were similar for patients given garenoxacin or comparators (including levofloxacin).

For garenoxacin patients the frequency of QTc change >60 ms on Day 1 was 1% for both genders, 1% for those <65 years and 2% for those ≥ 65 years, 2% for those with hypokalaemia or on concomitant anti-arrhythmic drugs treatment *vs* <1% for those with neither of these conditions. Similar findings applied on Days 3 through 5. All patients with QTc >500 ms were ≥ 65 years of age. Three patients had a change from baseline of >60 ms that resulted in QTc intervals of >500 ms. One garenoxacin patient (89 year-old female) had a change from baseline of 140 ms on Day 15 with syncope and was discontinued. Eight days later she had another episode of syncope and *Torsade de pointes*, which was attributed by the investigator to sotalol. Another garenoxacin patient (66-year-old male) had self-limiting ventricular tachycardia with prolonged QTc on Day 5 and was discontinued.

Comment on pharmacodynamics

Antibacterial activity
The in-vitro data suggested that garenoxacin was very unlikely to have useful clinical activity against the difficult to treat non-fermenters, including *P. aeruginosa*, some anaerobic species and organisms that have reduced susceptibility to ciprofloxacin and other quinolones except, perhaps, for pneumococci and staphylococci with certain mutations. PK/PD considerations suggested that activity might also be dubious against some of the enterobacterial species even when quinolone-susceptible.

Hypotension
Data in patients demonstrated an association between garenoxacin (especially IV) and reports of hypotension, especially in patients with some other risk factors. The applicant has proposed that histamine release, histamine sensitisation and some affinity of garenoxacin for β-adrenergic receptors may be involved and the issue is discussed further in the section on safety.

Cardiac conduction
The applicant has not conducted a study to investigate effects on the QT interval in accordance with the CHMP guidance. However, the data suggest that garenoxacin likely has a low potential to prolong the QTc interval among the quinolones. The applicant should conduct a study in accordance with CHMP guidance before approval can be considered and the it is SPC should reflect the findings.
Garenoxacin also appeared to have some concentration-dependent effect on the PR interval at least on Day 1 of dosing. The prolongations were limited to first degree AV block, were asymptomatic and reversible. While these effects are unlikely to be clinically significant there could be a potential for an additive effect with any co-administered drug that may also prolong the PR interval and this should be adequately covered as a warning in the SPC.

Glucose homeostasis
If anything, there may be a trend to lower glucose levels associated with garenoxacin. Further analysisare requested. The applicant should perform a well-designed study in diabetic persons (Types 1 and 2 diabetes) to further evaluate this matter. Whether this has to be completed pre-authorisation will be considered in the light of the company's answers. The SPC should reflect the data and all changes in glucose homeostasis should receive special attention in the Risk Management Plan.

Other issues
Garenoxacin did not appear to have significant effects on adrenal or thyroid function. Compared to other quinolones the risk of phototoxicity seems to be low but the applicant has placed a warning statement to avoid undue UV exposure during therapy and this is appropriate. The organ discoloration detected in animals is of unknown clinical relevance if, indeed, it occurs in man.

Clinical efficacy

Choice of dose
There were no dose-response studies although some studies looked at different durations (see below).

From the applicant's report on the population PK analysis and based on outcomes in the three Phase II studies, regression analysis showed that log2(MIC) ($p = 0.0186$) was a significant predictor of clinical failure across all pathogens. An odds ratio of 1.153 indicated that for each doubling of MIC value there was approximately a 15% greater chance of clinical failure. Under this model, the maximum probability of clinical failure, which corresponded to an MIC of 32 μg/ml, was approximately 0.27 while the minimum probability of clinical failure, at an MIC of 0.004 μg/ml, was about 0.055.

- The applicant considered that a dose of **400 mg once daily** for treating respiratory tract-associated infections (including **CAP, AECB and ABS**) would achieve the target *f*AUC/MIC ratio (i.e. ≥ 30) against *S. pneumoniae*.
- In **uSSTI** the applicant calculated that **400 mg once daily** would achieve the target *f*AUC/MIC ratio (i.e. ≥ 60) against quinolone-susceptible *S. aureus*. For quinolone-R staphylococci, with a

MIC90 garenoxacin around 4 µg/ml, the ƒAUC/MIC ratio would be <10 at doses of 400 mg or 600 mg.

- For **cSSTI and IAI** garenoxacin at **600 mg once daily** was expected to provide AUC/MIC and ƒAUC/MIC ratios for the range of possible pathogens that were similar to or higher than those achieved with approved doses of trovafloxacin and ciprofloxacin even though these ratios fell below the target cut-off for predicting efficacy.

Monte Carlo simulation was used to assess the pharmacodynamic target attainment rates for garenoxacin 400 mg once daily against quinolone-susceptible *S. aureus* and *S. pneumoniae*. The AUC24/MIC ratio attainment rates against these organisms were > 97% and so predicted clinical efficacy against these pathogens. Against *S. pneumoniae* garenoxacin had a 98% attainment rate for an AUC24/MIC of 120, which suggested the possibility of clinical efficacy against some levofloxacin-resistant pneumococci.

Efficacy by indication claimed

The data supporting the efficacy of garenoxacin are derived from **19 Phase II/III clinical studies** completed by a previous licensee. The clinical studies were conducted between 1999 and 2003 in North America (USA, including Puerto Rico, and Canada), Europe (including Eastern Europe, Russia, and Turkey) and the rest of the world (Mexico, Argentina, Costa Rica, Brazil, Peru, Chile, Venezuela, Israel, South Africa, Australia, Taiwan and Korea).

- Due to the large number of studies and the range of indications sought, these will be discussed by indication in the sub-sections that follow regardless of whether PO only or IV/PO.
- Due to the length of the clinical study report, only the briefest details of the studies considered to be most important can be described in this Overview.

Features common to the majority or all studies included:

- Prior antibacterial therapy was to be limited to no more than 24 h in the 7 days prior to enrolment.
- It was not required to remove patients from study just because they had a resistant pathogen isolated from baseline samples only after enrolment.
- Randomisation was by automated systems in all studies.

- Phase III studies were double blind and double dummy. In some instances (IV to PO studies) it was necessary that a study site pharmacist was unblinded and also a monitor from the sponsor not otherwise involved in the studies checked drug compliance and accounting.
- Test of cure (TOC) visits were held at least 5 days after the completion of therapy but the acceptable window varied by indication. Later follow-up visits were generally held between 21-28 days post-therapy but were employed in only some indications as detailed below.

- Investigators assigned outcomes in the CRFs. However, the sponsor performed a blinded review of these in order to classify patients with regard to eligibility and evaluability and then outcomes were re-assigned for some patients as seemed necessary before unblinding the database and performing the analyses. Details of the numbers with outcomes re-classified by the sponsor's reviewer are provided by study and generally involved 10% or less of the total study participants. In general, there is no suggestion form these re-assignments that there was any inadvertent unblinding of the sponsor's reviewers and their approach seems to have been conservative.

- The pre-defined populations were:
  1) All Treated = All randomised who received at least one dose of study drug.
  2) Clinically Eligible = All Treated who met the diagnosis
  3) Clinically Evaluable (CE) = All Clinically Eligible who met all of the following criteria:
     a) received pre-specified duration of study drug (usually at least 5 days and at least 3 days if a treatment failure) plus minimum number of IV doses in Iv to PO studies.
     b) received no non-study systemic antibiotic active against the causative pathogens

c) had a TOC visit in the pre-defined window or when declared a failure.

4) Microbiologically Evaluable (ME) = CE with a pathogen

- Straightforward bacteriological studies were performed by local laboratories, where preliminary susceptibility testing was also conducted. Central laboratories were used for referral of isolates after primary culture for confirmation of identity. Central laboratories performed susceptibility testing to garenoxacin and to commonly used agents as appropriate to the species. The analyses used the results from the central laboratories unless these were not available, in which case any available local laboratory results were used.
- In Phase III CAP studies, *M. pneumoniae, L. pneumophila*, and *C. pneumoniae* were identified by culture, PCR and/or serology testing at the University of Louisville, Kentucky, USA. Paired serology was performed for pre-treatment, TOC and FU visit samples and urine was collected for *Legionella* antigen testing. An algorithm was developed to determine the level of certainty of diagnosis of these pathogens based on published work and the experience of the expert laboratory used.

CAP

The studies can be summarised as follows:

Phase II **AI464004**	Open-label, Non-Comparative	400 mg PO (2 x 200 mg) QD 10 days	208	Outpatients	
Phase III		***Oral; garenoxacin 5 days***			
AI464017	R, DB	400 mg PO QD for 5 days vs 500 mg clarithromycin PO BID 7-10 days	310	Outpatients with mild to moderate	
AI464018	R DB	400 mg PO QD for 5 days vs 500/125 mg co-amoxiclav PO q8h for 7-10 days	360	Outpatients with mild to moderate	
AI464081	R, DB	400 mg PO QD for 5 days vs 1 g amoxicillin caps PO q8h for 10 days	308	Mild to moderate	
Phase III		***Oral; garenoxacin 7-10 days***			
AI464019	R, DB	400 mg PO QD vs 500 mg levofloxacin QD Both 7-10 days	270	Outpatients	
AI464029	R, DB	400 mg PO QD vs 500 mg clarithromycin PO BID Both for 7-10 days	315	Outpatients	
Phase III		***IV to PO***			
AI464020	R, DB	400 mg IV QD +/- PO vs 1-2 g ceftriaxone IV QD +/- 0.5-1 g erythromycin IV QID +/- 500 mg clarithromycin PO BID Both 7-10 days (≥2 days IV)	406	Hospitalised	
AI464021	R, DB	400 mg IV QD +/- PO vs 500 mg levofloxacin IV QD +/- 500 mg PO QD Both 7-10 days (≥2 days IV)	328	Hospitalised	
Phase III		***IV to PO or PO only – pneumococcal study***			

AI464073	Open-label, Non-comparative	400 mg IV QD +/- PO or 400 mg PO only QD For 7-14 days	121	Inpatients and outpatients with CAP caused by *Streptococcus pneumoniae*	

Studies enrolled adults with evidence of CAP demonstrated by a new infiltrate(s) on chest x-ray and at least 2 of fever (> 38°C oral, > 38.5°C tympanic or > 39°C rectal), leucocytosis (> 10,000 white blood cells/mm^3 or > 15% band forms), cough, chest pain, rales and/or evidence of pulmonary consolidation on auscultation and sputum production.

Phase III comparative studies aimed to demonstrate non-inferiority between treatments in Clinically Evaluable (CE – see below) patients at the TOC visits (5-18 days post-therapy). The pre-defined delta was 15%. Extended follow-up visits were between 19-28 days post-therapy.

Clinical responses were defined as follows:
Cure: All acute signs and symptoms of pneumonia resolved or improved to a level such that no additional antibiotic therapy was required AND chest X-ray abnormalities had either improved or not progressed
Failure: At least one of death due to pneumonia within 30 days of end of study treatment, persistence or progression of signs and symptoms, development of new findings consistent with pneumonia, additional or alternate antibiotic therapy given.
Unable to determine: Extenuating circumstances precluded classification as Cure or Failure.

Comparative, oral, 5 days garenoxacin

Study 017 in patients with Fine Score ≤ 70 (Class I and II) conducted in N. America in 2000-2002
Cure rates were numerically higher for garenoxacin in each pre-defined population and lower 95% CI were within -5.1%.

	Clinical Response	**Garenoxacin**			**Clarithromycin**	
Clinically Evaluable	N	126			122	
	Cure	120	(95)		110	(90)
	Failure	6	(5)		12	(10)
	95% CI			-2.2, 12.3		
Clinically Eligible	N	140			139	
	Cure	127	(91)		119	(86)
	Failure	11	(8)		17	(12)
	Unable to Determine	2	(1)		3	(2)
	95% CI			-3.2, 13.4		
All Treated	N	154			156	
	Cure	136	(88)		133	(85)
	Failure	16	(10)		20	(13)
	Unable to Determine	2	(1)		3	(2)
	95% CI			-5.1, 11.2		

Clinical responses were 97% for garenoxacin and 88% for clarithromycin for those with ATS mild/moderate infections and 25/28 compared to 27/28 in respective treatment groups for those with severe disease. For Fine class I patients cure rates were 94% and 97% compared to 98% and 80% for

Fine class II. There were two relapses in each treatment group. The table below shows clinical outcomes by pathogen.

Clinical Cure Rate by Pathogen, Clinically Evaluable Subjects with Pathogen(s)

	Number Cured/Number with Pathogen (%)		
Pathogen a/Subtype	**Garenoxacin N = 100**	**Clarithromycin N = 88**	
	95 / 100 (95)	**79 / 88**	**(90)**
S. pneumoniae	29/32 (91)	20/23	(87)
Pen-S	22/24 (92)	14/15	(93)
Pen-I	5/6 (83)	5/7	(71)
Pen-R	2/2 (100)	0	--
Pen-Unknown	0 --	1/1	(100)
H. influenzae	7/7 (100)	8/10	(80)
M. catarrhalis	10/10 (100)	5/5	(100)
S. aureus	17/18 (94)	16/18	(89)
MS/QR	1/1 (100)	0	--
C. pneumoniae	17/18 (94)	13/13	(100)
L. pneumophila	11/11 (100)	8/9	(89)
M. pneumoniae	32/35 (91)	36/39	(92)

Among the 12 evaluable patients who failed clarithromycin therapy two had clarithromycin-resistant *S. pneumoniae* at baseline, one had a clarithromycin-resistant *S. aureus* and one had an intermediately-susceptible *H. parainfluenzae*. There were two patients with pneumococcal bacteraemia per treatment group and all four had documented eradication.

Study 018 in patients with Fine Score ≤ 70 (Class I and II) conducted in S. America, S. Africa, Europe and Russia in 2000-2002

Cure rates at TOC were similar between treatments and lower 95% CI were within -5%. Of seven failures in the CE population given garenoxacin, two had *S. pneumoniae* and one had *H. influenzae* susceptible to garenoxacin at baseline and two had evidence of *M. pneumoniae*.

Clinical responses were 96% and 93% in respective treatment groups for those with ATS mild/moderate infections and 31/34 compared to 26/28 for those with severe disease. For Fine class I cure rates were 96% and 93% compared to 94% for both treatments for Fine class II. There were no confirmed relapses.

	Clinical Response	Garenoxacin	Co-amoxiclav
Clinically Evaluable	N	148	149
	Cured, n (%)	141 (95)	139 (93)
	Failure, n (%)	7 (5)	10 (7)
	95% CI	(-4.0, 7.9)	
Clinically Eligible	N	168	165
	Cured, n (%)	159 (95)	154 (93)
	Failure, n (%)	8 (5)	10 (6)
	Unable to Determine, n (%)	1 (1)	1 (1)
	95% CI	(-4.4, 7.0)	
All Treated	N	186	174
	Cured, n (%)	173 (93)	157 (90)
	Failure, n (%)	11 (6)	15 (9)
	Unable to Determine, n (%)	2 (1)	2 (1)
	95% CI	(-3.5, 9.1)	

Cure rates for pneumococcal infections were 14/16 for garenoxacin and 25/27 for co-amoxiclav compared to 25/26 and 20/23 for *H. influenzae*.

Phase III studies – comparative, oral, 7-10 days garenoxacin

Study 019 conducted in S. America, Europe, Israel and Russia in 2000-2001
Clinical cure rates at TOC were similar between treatments and the lower 95% CI were ≤ 11% (and -9.5 for CE patients). Cure rates were not affected by age. In those with mild/moderate pneumonia by the ATS classification 92% per group were cured compared to 34/39 given garenoxacin and 35/38 given levofloxacin who were classed as severe at baseline. The small numbers in Fine classes III or IV make it impossible to determine a trend although cure rates for those in predictive class I (95% per treatment group) were a little higher than seen for those in class II (83% and 85% per group).

	Clinical Response	Garenoxacin	Levofloxacin
Clinically Evaluable	N	124	124
	Cured, n (%)	112 (90)	114 (92)
	95% CI	(-9.5, 6.3)	
Clinically Eligible	N	134	133
	Cured, n (%)	118 (88)	121 (91)
	Unable to Determine, n (%)	1 (1)	1 (1)
	95% CI	(-11, 5.2)	
All Treated	N	136	134
	Cured, n (%)	120 (88)	121 (90)
	Unable to Determine, n (%)	2 (1)	2 (1)
	95% CI	(-10, 6.1)	

Overall cure rates in the ME population were 55/60 for garenoxacin and 69/76 for levofloxacin. Rates for those with pneumococcal infections were 6/7 and 17/18, respectively. However, note that only one garenoxacin and two levofloxacin patients had this organism isolated from blood. Numbers with *H. influenzae* were better balanced between groups with 12-13 cases of each per treatment. However, all these numbers are too small to comment on any apparent differences in cure rates. Bacteriological outcomes reflected cure rates by pathogens.

Study 029 conducted in N. and S. America in 2001-2002

Clinical cure rates at TOC were similar between treatments and the lower 95% CI were ≥ 8%. Cure rates were not affected by age. In those with mild/moderate pneumonia by the ATS classification 94% and 89% per group were cured compared to 29/32 given garenoxacin and 25/26 given clarithromycin who were classed as severe at baseline. The small numbers in Fine classes III or IV make it impossible to determine a trend and cure rates for those in predictive class I (97% and 93% per treatment group) were generally similar to those in class II (93% and 90% per group). Among four garenoxacin and two clarithromycin patients with pneumococci in the blood at baseline there was only one failure (described above for the clarithromycin resistant organism).

	Clinical Response	**Garenoxacin**		**Clarithromycin**	
Clinically Evaluable	N		128	137	
	Cured, n (%)	119	(93)	124	(91)
	Failure, n (%)	9	(7)	13	(9)
	95% CI			(-4.9, 9.8)	
Clinically Eligible	N		148	148	
	Cured, n (%)	133	(90)	132	(89)
	Failure, n (%)	15	(10)	14	(9)
	Unable to Determine, n (%)		--	2	(1)
	95% CI			(-7.0, 8.3)	
All Treated	N		159	156	
	Cured, n (%)	141	(89)	139	(89)
	Failure, n (%)	17	(11)	15	(10)
	Unable to Determine, n (%)	1	(< 1)	2	(1)
	95% CI		(-8.0, 7.2)		

Cure rates in the ME population were 96% for garenoxacin and 87% for clarithromycin as shown below.

Pathogen a/Subtype	**Garenoxacin N = 86**		**Clarithromycin N = 94**	
Number Cured/Number of Subjects with Pathogen (%)	**82/86**	**(96)**	**85/94**	**(87)**
S. pneumoniae	15/17	(88)	17/21	(81)
H. influenzae	6/6	(100)	8/9	(89)
M. catarrhalis	5/6	(83)	3/5	(60)
S. aureus	5/5	(100)	11/13	(85)
MS/QNR	5/5	(100)	10/12	(83)

MR/QR	0		1/1	(100)
K. pneumoniae	2/2	(100)	1/1	(100)
M. pneumoniae	29/31	(94)	36/39	(92)
C. pneumoniae	12/12	(100)	15/16	(94)
L. pneumophila	14/14	(100)	9/10	(90)

Microbiological responses in evaluable patients were similar to those for clinical cure rates by pathogen. For all patients with a pathogen, eradication rates for pneumococci were 17/21 for garenoxacin and 21/25 for clarithromycin. For *H. influenzae*, corresponding rates were 7/8 and 11/13.

Phase III studies – comparative, IV to oral, 7-14 days garenoxacin
Patients were to have been hospitalised for < 24 h prior to study entry. All patients were to receive at least two doses IV and a switch to oral therapy could occur when pre-specified criteria were met:

Study 020 conducted in N and S. America, S. Africa and Australia in 2000-2002
According to the modified ATS criteria, 73% and 74% of patients per treatment group had severe CAP. Overall, 3% of patients received mechanical ventilation at some time. The differentiation by Fine classes showed that a slightly smaller proportion of garenoxacin patients were in classes IV or V while 56% and 54% per treatment group fell into classes I or II.

More than half (57%) of comparative group patients received only 1 g daily ceftriaxone. While 40% overall received erythromycin, mostly at 1 g 6 hourly, a higher proportion of those treated with 2 g ceftriaxone daily received erythromycin (49% *vs* 37% among those treated with 1 g daily ceftriaxone).

The cure rates by population (shown below) were similar between treatments and the lower 95% CI were within -10%. The single patient who relapsed had been treated with ceftriaxone.

		Number of Subjects (%)				
	Clinical Response	**Garenoxacin**			**Ceftriaxone**	
Clinically Evaluable	N	161			167	
	Cured	141	(88)		147	(88)
	Failure	20	(12)		20	(12)
	95% CI			(-8.1, 7.2)		
Clinically Eligible	N	193			194	
	Cured	162	(84)		166	(86)
	Failure	31	(16)		28	(14)
	95% CI			(-9.3, 6.0)		
All Treated	N	203			203	
	Cured	167	(82)		167	(82)
	Failure	36	(18)		36	(18)
	95% CI			(-7.9, 7.9)		

Responses by potential risk factors showed that 89% of those aged 65 years or less were cured per treatment group with rates of 43/51 (84%) for garenoxacin and 66/76 (87%) for ceftriaxone among those aged > 65 years. For those with ATS severe disease respective cure rates were 89% and 85%. Rates by Fine classification are shown below. It is difficult to interpret these due to the relatively small

numbers per group but, if anything, garenoxacin achieved lower cure rates than ceftriaxone for categories III-V.

Fine Classification	Garenoxacin		Ceftriaxone	
Class I	44 / 48	(92)	38 / 41	(93)
Class II	44 / 48	(92)	44 / 50	(88)
Class III	30 / 35	(86)	25 / 27	(93)
Class IV	20 / 25	(80)	34 / 40	(85)
Class V	3 / 5	(60)	6 / 9	(67)

Of 17 cases of pneumococcal bacteraemia four were treated with garenoxacin and 13 with ceftriaxone. Only one failed, although post-baseline blood cultures were negative, and this patient received garenoxacin. Clinical responses by pathogen (next table) were generally similar between treatments as far as can be judged from the 86 garenoxacin and 104 ceftriaxone patients said to have a pathogen.

Pathogen a/Subtype	**Garenoxacin N = 86**				**Ceftriaxone N = 104**			
N Cured/N with pathogens (%)	**75**	**/**	**86**	**(87)**	**90**	**/**	**104**	**(87)**
S. pneumoniae	23	/	27	(85)	36	/	42	(86)
H. influenzae	15	/	19	(79)	3	/	4	(75)
M. catarrhalis	4	/	5	(80)	5	/	5	(100)
S. aureus	8	/	11	(73)	12	/	14	(86)
S. aureus(MS/QNR)	8	/	10	(80)	11	/	13	(85)
C. pneumoniae	14	/	17	(82)	14	/	15	(93)
L. pneumophila	2	/	3	(67)	16	/	16	(100)
M. pneumoniae	26	/	28	(93)	23	/	27	(85)

The microbiological outcomes in the evaluable patients closely mirrored the clinical outcomes. Eradication rates for all pathogens in this study were a little different in that for pneumococci the rates were 25/32 (78%) for garenoxacin and 43/49 (88%) for ceftriaxone. New infections were described in 27 (13%) garenoxacin and in 22 (11%) ceftriaxone group patients. The most common new infection was oral candidiasis (in 10 and 5 per group) while 3 and one per group had *C. difficile* diagnosed.

Study 021 conducted in Europe, Russia, Israel, Turkey and Argentina in 2001-2002

The clinical cure rates at TOC indicated non-inferiority between garenoxacin and levofloxacin with lower 95% CI within -7% for all three comparisons. Of the 19 treatment failures among CE patients, two in the levofloxacin group had pneumococcal infection at baseline, one in the blood. Of the 10 other patients in this study with pneumococcal bacteraemia, 8 received garenoxacin and 2/8 were not CE and were deemed to have failed in the secondary analyses. Only one patient (treated with garenoxacin) relapsed.

		Number of Subjects (%)			
		Garenoxacin		Levofloxacin	
Clinically Evaluable	N	141		145	
	Cured, n (%)	133	(94)	134	(92)
	Failure, n (%)	8	(6)	11	(8)
	95% CI		(-4.5, 8.4)		
Clinically Eligible	N	163		159	
	Cured, n (%)	147	(90)	143	(90)
	Failure, n (%)	15	(9)	16	(10)
	Unable to Determine, n (%)	1	(< 1)	0	
	95% CI		(-6.9, 7.4)		
All Treated	N	164		164	
	Cured, n (%)	148	(90)	146	(89)
	Failure, n (%)	15	(9)	18	(11)
	Unable to Determine, n (%)	1	(< 1)	0	
	95% CI		(-6.0, 8.4)		

Responses by prognostic factors showed a small effect of increasing age and of ATS classification as severe. There was no detectable difference for garenoxacin outcome across the four Fine classes for which enough data are available for review and no consistent trend for levofloxacin.

	Garenoxacin			**Levofloxacin**		
≤ 65 Years	89 / 93	(96)		83 / 88	(94)	
> 65 Years	44 / 48	(92)		51 / 57	(89)	
Severity of Pneumonia (Modified ATS)						
Mild/Moderate	71 / 73	(97)		72 / 75	(96)	
Severe	62 / 68	(91)		62 / 70	(89)	
Fine Classification						
Class I	54 / 57	(95)		39 / 41	(95)	
Class II	23 / 24	(96)		37 / 38	(97)	
Class III	32 / 34	(94)		31 / 36	(86)	
Class IV	22 / 23	(96)		23 / 26	(88)	
Class V	2 / 3	(67)		4 / 4	(100)	

The overall eradication rates in clinically evaluable patients (as counted by the applicant) were 93% for garenoxacin and 89% for levofloxacin. These rates included eradication of 20/21 and 20/23 pneumococci in respective treatment groups. For all pathogens in all treated patients the rates for pneumococci were 20/26 (77%) for garenoxacin and 20/24 (83%) for levofloxacin.

Organism	Garenoxacin				Levofloxacin			
S. pneumoniae								
Pen-S	18	/	18	(100)	15	/	18	(83)
H. influenzae	13	/	13	(100)	13	/	14	(93)
M. catarrhalis	1	/	1	(100)	0			
S. aureus	9	/	9	(100)	9	/	10	(90)
MS/QR	0				1	/	1	(100)
MS/QNR	6	/	6	(100)	7	/	8	(88)
MS	1	/	1	(100)	0			
MR/QR	1	/	1	(100)	1	/	1	(100)
MR/QNR	1	/	1	(100)	0			
M. pneumoniae	25	/	26	(96)	23	/	24	(96)
C. pneumoniae	11	/	11	(100)	9	/	9	(100)
L. pneumophila	8	/	9	(89)	12	/	12	(100)

New infections were reported in 8% and 12% of all treated patients in respective treatment groups but these were very mixed in nature.

Comment on CAP studies

Many patients (e.g. up to about 20% in PO studies and up to > 50% in IV ± PO studies) had received a systemic antibacterial agent within 7 days of study entry. Although this was mostly confined to a single dose, some of the agents given were parenteral and/or had long half-lives. The applicant should summarise the administration of systemic antibacterials potentially effective in CAP that were given within 7 days of study entry across studies and should provide analyses of outcomes according to whether or not patients received such an agent.

The quoted reference for the ATS definitions of CAP severity require further justification and explanation of the categorisations applied.

The vast majority of cases in which *M. pneumoniae*, *C. pneumoniae* or *L. pneumophila* were implicated were based on serological findings. The applicant should review clinical outcomes for these patients by study according to the diagnostic criteria in order to try to ascertain any differences and whether there is any indication that longer term therapy might be needed for one or more of these species.

In the three studies in which **5 days of oral garenoxacin** was administered (**017, 018 and 081**) non-inferiority was demonstrated with respect to three alternative antibacterial regimens. However, the evaluable patients in 017 and 018 were all Fine class I or II and in all three studies most patients (about 75%) were in the ATS mild to moderate category. In the two studies in which **7-10 days of oral garenoxacin** was administered (**019 and 029**) non-inferiority was demonstrated for the evaluable populations. However, around 80% of the evaluable patients in these studies were Fine class I or II and about 70% were in the ATS mild to moderate category i.e. similar to the populations studied compared to those in 017 and 018. This makes it difficult to be precise about recommendations for treatment except to say that those with mild to moderate CAP could be treated for 5-10 days. The distribution of patients according to ATS and Fine classifications should be mentioned in section 4.4 of the SPC.

In the two studies in which **7-14 days of IV ± PO garenoxacin** was administered (**020 and 021**) non-inferiority (with lower 95% CI within -10%) was demonstrated for the evaluable, eligible and all

treated patient populations. However, there are two main areas of difficulties in interpreting these studies:

- In 020 57% received 1 g ceftriaxone daily and this could be considered questionable for hospitalised patients with CAP. Also, only 40% overall received erythromycin. In 021, the dose of levofloxacin was 500 mg once daily. Twice daily dosing is generally considered to be appropriate for higher risk patients, including those > 65 years (who accounted for 35% and 39% per group in this study) and those with underlying medical conditions at risk of a poor outcome.
- In 020 near to 75% had severe CAP by ATS criteria and 42-45% were in Fine Classes III-V while in 021 about 50% had ATS severe CAP although 43-44% were in Fine Classes II-V. Although denominators in subgroups are small, study 020 suggested slight disadvantages for garenoxacin for those > 65 years (with anyway a baseline imbalance of 34% garenoxacin and 44% ceftriaxone patients in this age category) and those in Fine Classes III-V (with 43 garenoxacin and 59 ceftriaxone group patients in IV or V).

Putting together these issues it is considered that these two studies are not adequate to support the use of 400 mg garenoxacin daily by IV and then PO routes in hospitalised patients with CAP.

AECB

The studies can be summarised as follows:

AI464003	R, DB to compare 5 and 10 days of garenoxacin (no other comparator)	400 mg PO (2 x 200 mg) QD for 5 days followed by placebo for 5 days vs 400 mg PO (2 x 200 mg) QD for 10 days	294
AI464022	R, DB vs azithromycin	400 mg PO QD for 5 days vs 500 mg azithromycin PO on Day 1;250 mg days 2-5	786
AI464023	R, DB vs co-amoxiclav	400 mg PO QD for 5 days vs 500/125 mg co-amoxiclav PO q8h for 7-10 days	445

The studies enrolled adults with chronic bronchitis (i.e. chronic cough and sputum production on most days for 3 consecutive months for more than 2 consecutive years) and:

- Production of purulent sputum as defined in a preliminary sputum smear from the site or local laboratory by the presence of > 25 polymorphonuclear leucocytes per low power field
- Presence of 2 or more of increased cough and/or dyspnoea, increased sputum production or purulence

The studies classified patients according to type 1 or type 2 exacerbations as defined by Anthonisen but there was no pre-stratification by Anthonisen type.

Cure was defined as all acute signs and symptoms of acute infection resolved, or improved to a level such that no additional antibiotic therapy was required, with no new signs and symptoms of acute infection and resolution of any fever.

Phase II study – duration of garenoxacin 400 mg once daily

Study 003 conducted in Europe and N. America in 1999-2000

Unfortunately, 130 patients were lost from the planned analysis of efficacy because they were enrolled at sites later found to be under investigation by FDA for irregularities. Clinical response rates showed overlapping 95% CI between the treatment duration groups in all three patient populations. However, there was a consistent numerical superiority for 10 days over 5 days therapy. Analyses of outcomes by prognostic factors did not show any consistent trends.

		5-day	10-day
Clinically Evaluable	N	139	141
Subjects	Cured: n (%)	122 (88)	133 (94)
	Failure: n (%)	17 (12)	8 (6)
	95% CI	(81.1%, 92.7%)	(89.1%, 97.5%)
Clinically Eligible	N	145	145
Subjects	Cured: n (%)	124 (86)	135 (93)
	Failure: n (%)	17 (12)	8 (6)
	Unable to Determine:	4 (3)	2 (1)
	95% CI	(78.7%, 90.8%)	(87.7%, 96.6%)
All Treated Subjects	N	147	147
	Cured: n (%)	125 (85)	137 (93)
	Failure: n (%)	17 (12)	8 (5)
	Unable to Determine: n	5 (3)	2 (1)
	95% CI	(78.2%, 90.4%)	(87.9%, 96.7%)

Outcomes by the most likely important pathogens also suggested that 10 days might be better.

Pathogen	**5-day**	**N = 139**	**10-day**	**N = 141**
S. pneumoniae	19/22	(86)	17/18	(94)
H. influenzae	21/23	(91)	14/15	(93)
M. catarrhalis	14/18	(78)	23/24	(96)
S. aureus	21/25	(84)	20/21	(95)
H. parainfluenzae	22/24	(92)	31/31	(100)

Phase III studies – garenoxacin for 5 days vs active comparators

Study 022 conducted in N. and S. America and Australia in 2000-2001
Clinical responses at TOC showed that lower 95% CI were within -8% for all three populations.

Clinical Response		**Garenoxacin**	**Azithromycin**
Clinically Evaluable	N Cured: n (%) Failure: n (%) 95% CI	365 305 (84) 60 (16) -7.6, 2.5	356 310 (87) 46 (13)
All Treated	N	400	386
	Cured: n (%) Failure: n (%) Unable to Determine: n (%) 95% CI	328 (82) 68 (17) 4 (1) -7.6, 2.6	329 (85) 51 (13) 6 (2)
Clinically Eligible	N Cured: n (%) Failure: n (%) Unable to Determine: n (%) 95% CI	386 318 (82) 64 (17) 4 (1) -7.2, 3.0	376 321 (85) 50 (13) 5 (1)

Azithromycin achieved numerically higher cure rates by population and for outcomes by potential prognostic factors as shown below.

	Garenoxacin		Azithromycin	
Type 1	275/330 (83)		278/319 (87)	
Type 2	30/35 (86)		32/37 (86)	
Duration of Current Episode (days)				
0 - 7	138/167	(83)	148/166	(89)
> 7	165/196	(84)	159/184	(86)
Systemic Steroid	25/40 (63)		26/31 (84)	
No Systemic Steroid	280/325 (86)		284/325 (87)	
Acute Systemic Steroid User	20/29 (69)		19/23 (83)	
Chronic Systemic Steroid User	5/11 (45)		7/8 (88)	
Not a Systemic Steroid User	280/325 (86)		284/325 (87)	
Smoker	132/154	(86)	158/172	(92)
Non-smoker	173/211	(82)	152/184	(83)

It was notable that 104 evaluable patients failed the assigned treatment. However, documented persistence was seen in only 3 garenoxacin and 7 azithromycin patients and, even in these cases, the species found were usually of dubious relevance.

Pathogen	**Garenoxacin**	**Azithromycin**
Number cured/N (%)	**212/248 (85)**	**205/238 (86)**
S. pneumoniae	47/55 (85)	46/51 (90)
H. influenzae	37/39 (95)	34/40 (85)
M. catarrhalis	41/48 (85)	37/38 (97)
S. aureus	43/54 (80)	39/44 (89)
S. aureus (MS/QNR)	37/47 (79)	36/41 (88)
S. aureus (MR/QR)	5/6 (83)	3/3 (100)
H. parainfluenzae	47/52 (90)	35/43 (81)

Study 023 conducted in Europe, Turkey, S. America and S. Africa in 2000-2001
Clinical responses at TOC showed that the lower 95% CI were within -10% for each study population.

	Clinical Response	**Garenoxacin**		**Co-amoxiclav**	
	N	159		161	
Clinically Evaluable	Cured: n (%)	139 (87)		143 (89)	
	Failure: n (%)	20 (13)		18 (11)	
	95% CI	-8.7, 5.3			
Clinically	N	189		183	
Eligible	Cured: n (%)	163 (86)		163 (89)	
	Failure: n (%)	25 (13)		19 (10)	
	Unable to Determine	1 (< 1)		1 (< 1)	
	95% CI	-9.6, 3.5			
All Treated	N	227		218	
	Cured: n (%)	195	(86)	192	(88)
	Failure: n (%)	30	(13)	24	(11)
	Unable to Determine: n (%)	2	(< 1)	2	(< 1)
	95% CI	-8.5, 3.8			

Those with Type 2 exacerbations and not on steroids had slightly higher response rates.

Prognostic Factor	**Garenoxacin**	**Co-amoxiclav**
Type 1	122/141 (87)	128/145 (88)
Type 2	17/18 (94)	15/16 (94)
Duration of Current Episode at Entry (days)		
0 - 7 Days	85/97 (88)	87/95 (92)
> 7 Days	54/60 (90)	54/64 (84)
Acute Systemic Steroid User	13/16 (81)	15/19 (79)
Chronic Systemic Steroid User	8/9 (89)	4/5 (80)
Not a Systemic Steroid User	118/134 (88)	124/137 (91)
Smoker	52/57 (91)	57/66 (86)
Non smoker	87/102 (85)	86/95 (91)

Outcomes by major pathogens are shown below.

Pathogen /Subtype	Garenoxacin	Co-amoxiclav
Number Cured/ Number with Pathogens (%)	**76/89 (85)**	**77/90 (86)**
S. pneumoniae	16/16 (100)	23/26 (88)
H. influenzae	31/36 (86)	22/27 (81)
M. catarrhalis	3/4 (75)	6/6 (100)
S. aureus	4/4 (100)	5/6 (83)
K. pneumoniae	4/4 (100)	4/4 (100)

Comment on AECB studies
Overall, in an indication in which very high cure rates are expected, the results of 003 and the lower 95% CI observed in the evaluable populations in 022 and 023 (-7.6 and -8.7, respectively) suggest that 5 days garenoxacin might not be an optimal regimen for AECB.

The applicant's summary of AECB studies mentions that approximately 32% of patients in these studies were at least 65 years old and 9% were > 75 years. Details of age distributions and outcomes should be provided by study in case this might throw some light on the findings.

Acute Bacterial Sinusitis (ABS)

There was one Phase II study to evaluate treatment duration and which included sinus aspiration. The single comparative Phase III study also evaluated duration but sinus aspiration was not demanded.

AI464005	Open-label, Non-comparative	400 mg PO (400 mg or 2 x 200 mg) QD for 5 or 10 days	543	ABS (un-complicated, maxillary) with sinus aspiration
AI464024	R, DB vs co-amoxiclav	400 mg GRN PO tablet QD for 5 days followed by placebo QD for 5 days vs 400 mg GRN PO tablet QD for 10 days vs 500 mg amox/125 mg clav PO tablet qh8 for 10 days	722	ABS (un-complicated, maxillary)

Eligible adults had a diagnosis of acute maxillary sinusitis as demonstrated by:
- Facial pain/tenderness over one or both maxillary areas lasting ≥ 5 (005) or 7 days (024) but < 28 days
- Two or more of fever, leucocytosis, nasal congestion, post nasal drainage, frequent coughing, headache
- At least one of purulent discharge from the maxillary sinus orifice, nose or back of the throat
- Radiological documentation of sinusitis by x-ray or CT scan with at least one of the following in one or both maxillary sinuses − opacification, air/fluid level or mucosal thickening of ≥ 5mm (for 10-day cohort of 005 only).

Maxillary sinus aspiration was to occur within 48 h prior to starting study therapy in study 005 only.

There were 4 analysis groups similar to those defined for CAP.
Cure was defined as cardinal signs and symptoms resolved or improved to a level such that no additional antibiotic therapy was required with no new signs and symptoms of acute infection. If available, the radiographic appearance of the sinuses was at least stable
There was a follow-up visit at 3-4 weeks post-therapy but this was only a telephone contact.

Phase II study – garenoxacin for 5 or 10 days with sinus aspiration

Study 005 conducted in N. and S. America and Europe in 1999-2002
Of the 546 from qualifying study sites, 543 were treated, 539 (99%) were Clinically Eligible, 519 (96%) were CE and 311 (60%) were ME. Only four and two patients per duration group had received a systemic antibacterial agent within 7 days of study entry. There were slightly more females than males enrolled into the study (58% in the 10-day and 56% in the 5-day cohort) and the median ages were 40 and 39 years. The proportions of patients with fever or leucocytosis (as defined in the inclusion criteria) at baseline are not reported or discussed. Sinus X rays showed that infections involved only one or both maxillary sinuses in 68% and 77% of respective cohorts and the rest had additional involvement of other sinuses.

Clinical responses by population showed that 95% CI around the cure rates overlapped between the treatment duration groups and there was no advantage for 10 days of therapy over 5 days.

		10 Day	**5 Day**
Clinically Evaluable	N	266	253
	Cured	243 (91)	236 (93)
	Failure	23 (9)	17 (7)
	95% CI	(87% - 94%)	(89% - 96%)
Clinically Eligible	N	280	259
	Cured	248 (89)	240 (93)
	Failure	27 (10)	18 (7)
	Unable to Determine	5 (2)	1 (0)
	95% CI	(84% - 92%)	(89% - 96%)
All Treated	N	281	262
	Cured	249 (89)	243 (93)
	Failure	27 (10)	18 (7)
	Unable to Determine	5 (2)	1 (0)
	95% CI	(84% - 92%)	(89% - 96%)
Microbiologically Evaluable	N	152	159
	Cured	138 (91)	149 (94)

Outcomes by prognostic factors also suggested no advantage for longer therapy except for patients with multiple previous episodes and those who had undergone previous sinus surgery. However, the denominators in at least some of these subgroups are small.

	10 day (243/266)	**5 day (236/253)**
No History of Sinusitis	118/125 (94)	132/141 (94)
History of Sinusitis	125/141 (89)	104/112 (93)
No Allergic Rhinitis	159/173 (92)	169/180 (94)
Allergic Rhinitis	84/93 (90)	67/73 (92)
Number of Episodes < 3	223/245 (91)	224/239 (94)
Number of Episodes ≥ 3	20/21 (95)	12/14 (86)
No Sinus Surgery	216/235 (92)	226/240 (94)
Sinus Surgery	27/31 (87)	10/13 (77)

Clinical outcomes by pathogens and did not suggest a disadvantage for 5 days compared to 10 days treatment. Microbiological outcomes were very similar to clinical outcomes for pathogens from evaluable and from all treated patients.

Phase III study – garenoxacin for 5 or 10 days vs active comparators

Study 024 conducted in N. and S. America, Europe and Australia in 2000-2002
As documented by sinus x-ray, infection was confined to one or both maxillary sinuses 79% of the 5-day group, 74% of the 10-day group and in 72% treated with co-amoxiclav and infection was bilateral in 35-38%. The patterns of infection for the specific sites of right or left sinus were similar across treatment groups. The actual X-ray findings are summarised in the next table.

Finding	Garenoxacin 5-day N = 245		Garenoxacin 10-day N = 240		Co-amoxiclav N = 237		Total N = 722	
Normal	**3**	**(1)**	**3**	**(1)**	**1**	**(< 1)**	**7**	**(1)**
Abnormal	**242**	**(99)**	**237**	**(99)**	**236**	**(100)**	**715**	**(99)**
Opacification Only	146	(60)	149	(62)	156	(66)	451	(62)
Air/Fluid Level Only	30	(12)	23	(10)	35	(15)	88	(12)
Opacification and Air/Fluid Level	66	(27)	65	(27)	45	(19)	176	(24)

Clinical responses suggested no disadvantage for 5 days compared to 10 days therapy. Co-amoxiclav gave slightly lower cure rates than seen in the garenoxacin groups.

		Garenoxacin 5 days		Garenoxacin 10 days		Co-amoxiclav	
Clinically Evaluable	N	199		193		190	
	Cured	182	(91)	170	(88)	159	(84)
	Failure	17	(9)	23	(12)	31	(16)
	97.5% CI	-0.2, 15.8		-4.1, 12.9			
Clinically Eligible	N	233		226		228	
	Cured	209	(90)	196	(87)	187	(82)
	Failure	21	(9)	28	(12)	37	(16)
	Unable to Determine	3	(1)	2	(1)	4	(2)
	97.5% CI	0.0, 15.4		-3.4, 12.8			
All Treated	N	245		240		237	
	Cured	219	(89)	209	(87)	196	(83)
	Failure	22	(9)	29	(12)	37	(16)
	Unable to Determine	4	(2)	2	(1)	4	(2)
	97.5% CI	-0.8, 14.2		-3.4, 12.1			

For outcomes according to prognostic factors (see below) there was no disadvantage for 5 days of garenoxacin compared to 10 days in any subgroup. In most cases there was a numerical inferiority for co-amoxiclav.

Comment on ABS studies
The diagnosis of an acute sinusitis based on X-ray findings is not without pitfalls. However, only the 10-day group in study 005 included patients with mucosal thickening, which is probably a less reliable finding than the others allowed per protocol.

Establishing the aetiology is not possible without sinus puncture and even then the organisms cultured may include colonisers of the nasal passage that contaminated the aspirate. Nevertheless, the applicant has conducted one sinus puncture study and one comparative non-puncture study that would be in accordance with the recommendations made by FDA and by IDSA/ESCMID. It is also notable that 60% of patients in 005 had a pathogen, although not all of these may have come strictly from within the sinuses.

The results of the two studies consistently suggest that there is no advantage for 10 days over 5 days garenoxacin. An indication could be given for *Acute maxillary sinusitis* at a dose of 400 mg once daily. Since the indications will be introduced by text that includes *the following bacterial infections* it is not necessary to include the word *bacterial* in this indication.

SSTI

The studies are summarised below.

AI464015	R, DB vs co-amoxiclav	400 mg PO QD for 5 days vs 500/125 mg co-amoxiclav PO suspension q12h for 7-10 days	442	uSSTI	
AI464025	R, DB vs piptazobactam IV ± PO co-amoxiclav	600 mg IV solution QD +/- 600 mg PO QD vs piptazobactam 3/0.375 g IV q6h ± 500/125 mg co-amoxiclav PO q8h	389	cSSTI	7-14 days
AI464026	R, DB vs ciprofloxacin + metronidazole	600 mg PO QD vs ciprofloxacin 500 mg PO BID + metronidazole 500 mg PO TID	466	cSSTI	7-14 days

Follow-up at 21-28 days was by telephone contact only in study 015 and with visits in 025 and 026.
Cure was defined in uSSTI and cSSTI studies as all acute signs and symptoms related to the infection either resolved or improved to such an extent that no further antibiotic therapy was necessary.

Uncomplicated SSTI

Study 015 conducted in N. America, Europe and Israel in 2000-2001
It is not understood why the suspension of co-amoxiclav rather than tablets was used in this study in adults or why the dose chosen was 500/125 mg twice daily. Adults were stratified by type of infection diagnosis (i.e., impetigo; erysipelas or cellulitis; wound infection; or abscess or folliculitis) at the time of randomisation. Delta was pre-defined at 15%.

The commonest baseline diagnoses were infected wound (28%), cellulitis (24%) and abscess (16%). Clinical responses at TOC indicated that garenoxacin was non-inferior to co-amoxiclav.

		Garenoxacin	Co-amoxiclav
Clinically Evaluable	N Cured: n (%)	200 170 (85)	182 159 (87)
	Failure: n (%)	30 (15)	23 (13)
	95% CI		(-9.8%, 5.1%)
Clinically Eligible = All Treated	N Cured: n (%)	227 190 (84)	215 185 (86)
	Failure: n (%)	34 (15)	28 (13)
	Unable to Determine: n (%)	3 (1)	2 (1)
	95% CI		(-9.5%, 4.8%)

Denominators are not large by diagnoses but there was an indication of relatively low cure rates for garenoxacin in cellulitis. Among the 12 failures with cellulitis in the garenoxacin group 7 had persistence of *S. aureus* while 7 failures in the co-amoxiclav group included two with persistence of *S. aureus*.

	Garenoxacin N = 200	**Co-amoxiclav N = 182**
Abscess	29/36 (81)	24/29 (83)
Cellulitis	34/46 (74)	41/48 (85)
Erysipelas	8/10 (80)	6/6 (100)
Folliculitis	20/26 (77)	22/27 (81)
Impetigo	24/24 (100)	20/22 (91)
Infected wound	55/58 (95)	46/50 (92)

Clinical outcomes by (sponsor-designated) pathogen in the evaluable population were as follows:

N Cured/N with Pathogens (%)	**Garenoxacin 129/152 (85)**	**Co-amoxiclav 111/128 (87)**
Gram-positive	**124/147 (84)**	**105/119 (88)**
S. aureus	57/71 (80)	41/48 (85)
S. aureus (MR/QNR)	2/3 (67)	4/5 (80)
S. aureus (MR/QR)	1/2 (50)	0/1 (0)
S. aureus (MS/QNR)	51/63 (81)	37/42 (88)
S. aureus (MS/QR)	3/3 (100)	0
S. pyogenes	11/11 (100)	12/13 (92)
S. agalactiae Other Gram-positive	9/10 (90) 54/63 (86)	3/4 (75) 45/49 (92)
Gram-negative (Aerobic) **Gram-negative (Anaerobic)**	**26/32 (81)** **3/5 (60)**	**23/29 (79)** **2/3 (67)**

Complicated SSTI – 600 mg once daily garenoxacin IV/PO

Eligible for enrolment were newly hospitalised (< 72 hours) adults with clinical evidence of at least one of

- Infected pressure sore without underlying osteomyelitis
- Infected diabetic foot ulcer without underlying osteomyelitis
- Major abscess:
- Post surgical wound infections with purulent drainage

Patients were stratified by infection to ensure an approximate balance between treatments and delta was pre-specified at 15%.

Study 025 conducted in N. and S. America, Europe and Australia in 2001-2002

Very high proportions (60% and 57% per group) had received prior systemic antibacterial therapy and 28% and 32% per group had received more than 24 h. The clinical cure rates (with 95% CI adjusted for the stratification factor) at TOC all gave lower 95% CI within -6% and were as follows:

		Garenoxacin		Piptazobactam
Clinically Evaluable	N	150		147
	Cure: n (%)	125 (83)		120 (82)
	Failure: n (%)	25 (17)		27 (18)
	95% CI		-5.5, 10.8	
Microbiologically Evaluable	N	133		121
	Cure: n (%)	112 (84)		98 (81)
	Failure: n (%)	21 (16)		23 (19)
	95% CI		-4.4, 13.6	
Clinically Eligible	N	174		174
	Cure: n (%)	139 (80)		139 (80)
	Failure: n (%)	27 (16)		28 (16)
	Unable to Determine	8 (5)		7 (4)
	95% CI		-5.1, 10.7	
All Treated	N	195		194
	Cured: n (%)	153 (78)		154 (79)
	Failure: n (%)	31 (16)		30 (15)
	Unable to Determine	11 (6)		10 (5)
	95% CI		-5.8, 9.2	

Of the 52 evaluable treatment failures, 3 and 5 per treatment group had documented pathogens at TOC but these organisms were susceptible to garenoxacin or piptazobactam. Presumed persistence in the piptazobactam group was the outcome for four patients with resistant *S. aureus* at baseline. The listing of reasons for failures mentions one garenoxacin patient with a *Peptostreptococcus* in blood at the time of failure (Day 5).

Outcomes by diagnoses and selected clinical factors were as follows:

	Garenoxacin		Piptazobactam	
Prognostic Factor/Subcategory	**N = 150**		**N = 147**	
Major Abscess/Complicated	97/112	(87)	94/109	(86)
Cellulitis	13/17	(76)	18/21	(86)
Abscess with cellulitis	27/30	(90)	23/25	(92)
Perineal abscess / cellulitis	18/19	(95)	13/16	(81)
Post traumatic wound infection	24/30	(80)	22/26	(85)
Post Surgical Wound Infection	13/17	(76)	11/16	(69)
Diabetic Foot Ulcer Infection	13/17	(76)	15/21	(71)
Diabetic Foot Ulcer	12/16	(75)	16/22	(73)
Traumatic lesions	44/54	(81)	42/48	(88)
Dermatologic Condition	10/11	(91)	15/17	(88)
Peripheral Vascular Disease	11/11	(100)	15/19	(79)
Underlying Medical Condition				
Peripheral Vascular Disease	20/24	(83)	26/33	(79)
Diabetes Mellitus	38/47	(81)	31/40	(78)
Glycosylated Haemoglobin (%)				
≤ 6.5	47/62	(76)	45/54	(83)
> 6.5	26/34	(76)	24/32	(75)

Of 19 total patients with *S. pyogenes* at baseline 16/19 were cured. Microbiological response rates for this species were 7/9 for garenoxacin and 9/10 for piptazobactam.

Clinical outcomes by pathogen	**Garenoxacin N = 133**		**Piptazobactam N = 121**	
Patients with Pathogen	**112/133**	**(84)**	**98/121**	**(81)**
Aerobes (Gram-positive)				
E. faecalis	9/12	(75)	10/11	(91)
Viridans Streptococci	6/6	(100)	6/7	(86)
S. constellatus	3/4	(75)	3/5	(60)
Other Streptococci	32/36	(89)	27/32	(84)
S. agalactiae	15/15	(100)	16/17	(94)
S. aureus	57/67	(85)	51/64	(80)
S. aureus (MS/QNR)	50/55	(91)	41/50	(82)
S. aureus (MS/QR)	1/1	(100)	2/3	(67)
S. aureus (MR)	0/1	(0)	0	
S. aureus (MR/QNR)	4/6	(67)	5/7	(71)
S. aureus (MR/QR)	2/4	(50)	3/5	(60)
S. aureus (unknown)	1/1	(100)	1/2	(50)
Other Gram-positive Aerobes	21/29	(72)	26/32	(81)

Anaerobes				
B. fragilis	6/7	(86)	9/9	(100)
B. thetaiotaomicron	1/1	(100)	1/1	(100)
B. fragilis group	4/5	(80)	0	
C. perfringens	1/1	(100)	1/1	(100)
Clostridium sp.	1/1	(100)	0	
Peptostreptococcus sp.	12/15	(80)	11/12	(92)
Prevotella sp.	14/15	(93)	6/7	(86)

There were four patients in the garenoxacin group that relapsed and one treated with piptazobactam who had MRSA at the time of relapse. New infections occurred in 23 (12%) in the garenoxacin group and 28 (14%) piptazobactam patients and included 29 types of new infections. A new cellulitis occurred in 4 and 3 patients in respective groups and osteomyelitis was found in 2 and 3 patients.

Complicated SSTI – 600 mg once daily garenoxacin PO only vs oral comparators

Study 026 conducted in N. and S. America and Europe in 2001-2002
Clinical responses at TOC (95% CI adjusted by stratum) showed that the lower 95% CI for the overall comparisons of outcomes in each population were within -8.

Data Set	Clinical Response	Garenoxacin	Ciprofloxacin/Metronidazole
Clin Evaluable	Cure: n (%)	155/182 (85)	149/185 (81)
	Failure: n (%)	27 (15)	36 (19)
	95% Confidence Interval		(-2.9, 10.3)
Clin Eligible	Cure: n (%)	167/206 (81)	167/214 (78)
	Failure: n (%)	29 (14)	39 (18)
	Unable to Determine: n (%)	10 (5)	8 (4)
	95% Confidence Interval		(-3.2, 11.1)
Micro Evaluable	Cure: n (%)	124/150 (83)	132/163 (81)
	Failure: n (%)	26 (17)	31 (19)
	95% Confidence Interval		(-7.7, 7.8)
All treated	Cure: n (%)	186/227 (82)	188/239 (79)
	Failure: n (%)	29 (13)	42 (18)
	Unable to Determine: n (%)	12 (5)	9 (4)
	95% Confidence Interval		(-3.7, 10.4)

Among the failures, one (garenoxacin susceptible) and 9 (three appear to have been ciprofloxacin-R at baseline) in respective groups had persistence of *S. aureus*. Five of 11 persisting organisms in the garenoxacin group and 3/14 in the comparator group showed a decrease in susceptibility from baseline.

Outcomes according to various clinical factors were as follows:

Prognostic Factor/Subcategory	Garenoxacin N = 182		Cipro/Metro N = 185	
Disease Diagnosis				
Major Abscess/Complicated	87/103	(84)	84/105	(80)
Cellulitis	1/2	(50)	5/6	(83)
Abscess without cellulitis	19/21	(90)	19/21	(90)
Abscess with cellulitis	18/22	(82)	19/28	(68)
Perineal abscess/cellulitis	8/9	(89)	6/7	(86)
Post-traumatic wound infection	30/36	(83)	27/34	(79)
Other	11/13	(85)	8/9	(89)
Post-surgical Wound	22/23	(96)	26/27	(96)
Diabetic Foot Ulcer	37/47	(79)	32/45	(71)
Infected Pressure Sore	9/9	(100)	7/8	(88)
Underlying Medical Condition				
Peripheral Vascular Disease	22/26	(85)	24/32	(75)
Diabetes Mellitus	60/74	(81)	51/70	(73)
Glycosylated Haemoglobin				
≤ 6.5%	84/97	(87)	89/107	(83)
> 6.5%	53/65	(82)	50/65	(77)

There were 11 patients with *S. pyogenes* at baseline and it appears that 5/8 in the garenoxacin group and 2/3 in the comparative group were eradicated. The study report does not mention any cases of pathogens in blood at baseline or the outcomes.

	Garenoxacin N = 182		Cipro/Metro N = 185	
N with Pathogen	**124/150**	**(83)**	**132/163**	**(81)**
P. aeruginosa	14/19	(74)	9/14	(64)
E. faecalis	13/18	(72)	16/21	(76)
Other Streptococci	22/27	(81)	27/32	(84)
S. agalactiae	12/14	(86)	20/25	(80)
S. aureus	61/69	(88)	60/77	(78)
S. aureus (MS)	7/8	(88)	6/8	(75)
S. aureus (MS/QNR)	38/44	(86)	44/54	(81)
S. aureus (MS/QR)	3/3	(100)	0/1	(0)
S. aureus (MR)	4/4	(100)	1/2	(50)
S. aureus (MR/QNR)	0		3/3	(100)
S. aureus (MR/QR)	3/3	(100)	2/2	(100)
S. aureus (unknown)	5/6	(83)	4/7	(57)

Comment on SSTI studies

uSSTI is not an acceptable indication. Reasons include:

- Study 015 used a total daily dose of co-amoxiclav that is considered to be inadequate. Despite this likely inadequate comparative regimen, the lower 95% CI was very near to -10%.
- Garenoxacin was numerically inferior in the subgroup with cellulitis and with respect to cure and eradication rates in patients with *S. aureus* (both in evaluable and in all treated patients).
- The inclusion criteria would seem to allow for patients with very minor infections to be enrolled that might not even require systemic antibacterial therapy.

cSSTI is also rejected at present.

- There is concern regarding the proportions given antibacterial therapy within 7 days.
- In 025, the lower 95% CIs were within -6% for each defined patient population. However, the overall cure rates were very high for a cSSTI study and raise some questions over the exact nature of the infections studied. The applicant should provide a further analysis of outcomes according to the number of signs and symptoms present at baseline in order to provide further reassurance regarding the patient population.
- In 026, clinical cure rates were again very high for such a population and this raises further questions about the patient population. Finally, it is not clear what was so different about this patient population, enrolled mainly in similar areas of the world, that investigators were willing to use only oral therapy whereas initial IV therapy was required in 025.

Intra-abdominal and pelvic infections

AI464027	R, DB	600 mg IV QD +/- 600 mg PO QD vs piptazobactam 3/0.375 g q6h ± co-amoxiclav 500/125 mg PO q8h	452	Complicated intra-abdominal infections	5-14 days
AI464028	R, DB	600 mg IV QD +/- 600 mg PO QD vs 3 g ampicillin/sulbactam IV q6h ± 500/125 co-amoxiclav PO q8h	261	Women with acute pelvic infections	5-10 days

In both studies cure was defined as all acute signs and symptoms related to the original infection had resolved, or had improved to such an extent that no further antibiotic therapy was necessary.

Study 027 conducted in N. and S. America, Russia and Europe in 2001-2002
Eligible adults were to have a complicated IAI requiring anti-infective therapy. Patients were stratified on the basis of APACHE II scoring (≤10 or > 10) and by the presence or absence of a primary diagnosis of complicated appendicitis. The TOC visit was the sole follow-up assessment and was held at any time from 10-42 days post-therapy.

APACHE II scores > 15 occurred in 8% of garenoxacin and 6% of piptazobactam patients. Overall, 45% had appendicitis as a diagnosis and 55% had other infections. At baseline, documented fever was present for about one third in each group and 73-78% per group had leucocytosis as defined per protocol.

The majority (351; 78%) had received systemic antibacterials within 7 days of study entry but most of these (293/351) had received only one day while 21 received 2 days and 37 had received at least 3 days. This number included 23 patients per group who had received prior piptazobactam and 95 and 102 per group who had received a parenteral cephalosporin.
The clinical responses at TOC showed lower 95% CI (adjusted for stratification factors) within -4.1%. Outcomes by diagnosis and site or aetiology of infection were generally similar between treatments.

		Garenoxacin			Piptazobactam		
Clinically	N		185			192	
Evaluable	Cure	159		(86)	162		(84)
	Failure	26		(14)	30		(16)
	95% CI			(-3.1, 10.1)			
Microbiologically	N		145			155	
Evaluable	Cure	124		(86)	128		(83)
	Failure	21		(14)	27		(17)
	95% CI			(-3.0, 12.3)			
Clinically Eligible	N		216			217	
	Cure	176		(81)	175		(81)
	Failure	30		(14)	35		(16)
	Unable to Determine	10		(5)	7		(3)
	95% CI			(-4.1, 9.8)			
All Treated	N		226			226	
	Cure	183		(81)	181		(80)
	Failure	32		(14)	36		(16)
	Unable to Determine	11		(5)	9		(4)
	95% CI			(-3.9, 9.9)			

Outcomes by some prognostic factors and by strata are shown below.

Prognostic Factor/ Subcategory	**Garenoxacin N = 159/185**	**Piptazobactam N = 162/192**	**Total N = 321/377**
Stratification Groups			
Appendicitis/ ≤APACHE II 10	64/70 (91)	68/79 (86)	132/149 (89)
Appendicitis/ > APACHE II 10	7/9 (78)	11/12 (92)	18/21 (86)
Other Infect/ ≤APACHE II 10	67/72 (93)	59/68 (87)	126/140 (90)
Other Infect/ > APACHE II 10	21/34 (62)	24/33 (73)	45/67 (67)
APACHE II Score (Protocol Categorisation)			
≤10	131/142 (92)	127/147 (86)	258/289 (89)
> 10	28/43 (65)	35/45 (78)	63/88 (72)
APACHE II Score (Literature Categorisation)			
≤15	153/172 (89)	153/180 (85)	306/352 (87)
> 15	6/13 (46)	9/12 (75)	15/25 (60)

While caution is needed in interpreting outcomes for the smaller subgroups there appeared to be a consistently lower cure rate for garenoxacin among the patients with the highest APACHE scores. Cure rates computed solely by age were 87% in the garenoxacin group (150/173) and 79% in the piptazobactam group (132/168) for those < 65 years. In contrast, among those aged 65-74 years cure rates were 62% (18/29) and 89% (33/37), respectively, with rates of 13/17 and 14/19 for those aged 75-84 and 3/7 compared to 2/2 for those aged at least 85 years.

The clinical outcomes by pathogen showed a possible disadvantage for garenoxacin for *P. aeruginosa* and the enterococci. The microbiological outcomes by pathogen generally reflected the clinical outcomes although the differences between treatments for the above species were less marked.

Pathogen a/subtype	**Garenoxacin**	**Piptazobactam**			
Subjects with Pathogen	**124/146 (85)**	**128**	**/**	**155**	**(83)**
E. coli	74/87 (85)	68	/	83	(82)
K. pneumoniae	14/17 (82)	20	/	27	(74)
Other *Klebsiella* sp.	2/3 (67)	9	/	10	(90)
P. aeruginosa	12/17 (71)	12	/	14	(86)
Citrobacter sp.	5/7 (71)	6	/	8	(75)
Enterobacter sp.	6/7 (86)	6	/	7	(86)
Providencia sp.	3/4 (75)	4	/	6	(67)
E. faecalis	6/11 (55)	15	/	20	(75)
E. faecium	5 / 8 (63)	6	/	7	(86)
Other Enterococci	9 / 11 (82)	8	/	8	(100)
Viridans Streptococci	22 / 28 (79)	11	/	15	(73)
S. constellatus	26 / 29 (90)	8	/	12	(67)
Other Streptococci	14 / 18 (78)	15	/	21	(71)
S. aureus	7 / 8 (88)	5	/	7	(71)
Methicillin sensitive	5 / 6 (83)	3	/	3	(100)
Methicillin resistant	2 / 2 (100)	2	/	4	(50)
B. fragilis	39 / 43 (91)	35	/	43	(81)
B. thetaiotaomicron	20 / 22 (91)	17	/	18	(94)
B. uniformis	7 / 10 (70)	5	/	7	(71)
B. fragilis group	14 / 19 (74)	16	/	22	(73)
C. perfringens	5 / 6 (83)	8	/	8	(100)
Clostridium sp.	16/19 (84)	10	/	11	(91)
Peptostreptococcus sp.	16 /18 (89)	17	/	21	(81)
Prevotella	14 /15 (93)	13	/	16	(81)

There were only 24 evaluable patients with bacteraemia with cure rates of 8/12 in both treatment groups. Regarding organisms found in blood, 10/14 (71%) in the garenoxacin group and 12/15 (80%) in piptazobactam patients were eradicated or presumed eradicated. Presumed persistence occurred in two garenoxacin (one *E. faecalis*) and three piptazobactam patients.

Study 028 conducted in N. and S. America in 2001-2003

Eligible for enrolment were females aged at least 16 years with an acute pelvic infection other than acute pelvic inflammatory disease and/or sexually transmitted infection. Patients were to have fever, leucocytosis and one of the following related to recent (within 10 days) pregnancy, abortion or gynaecological surgery. There was stratification by presence or absence of post-partum endomyometritis and delta was pre-specified at 15%.

The clinical outcomes at TOC showed that although the actual cure rates were very similar, the lower 95% CI (adjusted for stratification) fell between -12.1 and -15.1. The small number of patients who

failed did not have any unusual or common features or pathogens resistant to the assigned therapy at baseline.

Data Set	Clinical Response	Garenoxacin		Ampicillin/ Sulbactam
Clinically Evaluable	N	107		90
	Cure	101 (94)		86 (96)
	Failure	6 (6)		4 (4)
	95% CI		-14.8, 11.4	
Clinically Eligible	N	128		113
	Cure	117 (91)		103 (91)
	Failure	8 (6)		6 (5)
	Unable to Determine	3 (2)		4 (4)
	95% CI		-12.6, 18.0	
Micro Evaluable	N	92		80
	Cure	87 (95)		76 (95)
	Failure	5 (5)		4 (5)
	95% CI		-15.1, 12.3	
All Treated	N	136		125
	Cure	124 (91)		110 (88)
	Failure	9 (7)		8 (6)
	Unable to Determine	3 (2)		7 (6)
	95% CI		-12.1, 16.4	

All but one of the 12 and 17 per group with bacteraemia who were evaluable were cured. Clinical outcomes according to potential prognostic factors did not show any numerical inferiority for garenoxacin. Cure rates by pathogens in evaluable patients were 87/92 (95%) for garenoxacin and 76/80 (95%) for ampicillin/sulbactam.

Comment on IAI and acute pelvic infections

With regard to IAI, it is a concern that 38% in the garenoxacin group and 42% in the piptazobactam group had a diagnosis of appendicitis and an APACHE score ≤ 10 at baseline. Also, only 23% per group had an APACHE score > 10 at baseline and only 7% had a score > 15. Outcomes in subgroups with APACHE scores > 10 or >15 (admittedly with very small denominators for the latter group) were consistently lower for garenoxacin. There is also concern about the very high rate of prior antibacterial therapy in this study (78% of all patients), which requires further explanation and analysis. At present, the CHMP considers that an indication for use in IAI (without the term complicated) cannot be granted since further reassurance is required regarding the suitability of the patient population enrolled to support this indication and the influence of any prior therapy needs to be explored.

Study 028 predominantly enrolled women who were post-abortion or post-partum with very few other infection types included so that a general indication for acute pelvic infections could not be supported (which anyway should not be combined with IAI). In addition, in a patient population with such high cure rates the observed lower 95% CI (-12 to -15) are considered too wide to support a conclusion of non-inferiority of garenoxacin with respect to ampicillin-sulbactam.

Clinical safety

Data are available from > 8000 healthy subjects and patients who received garenoxacin, another study drug or placebo. Numbers of garenoxacin patients in Phase II/III studies are summarised below.

Dose – Oral Regimen	
400 mg	3229
600 mg	227
Total Subjects (Oral Regimen)	3456
Duration of Treatment – Oral Regimen	
5 Days	2000
7 – 14 Days	1456
Dose – IV to PO Regimen	
400 mg	430
600 mg	557
Total Subjects (IV-to-PO Regimen)	987
Mean Duration (IV), Days	
Garenoxacin	4.32
Comparator	4.54

AEs in patients – PO

Drug-related AEs with oral dosing were reported by 19.4% of all garenoxacin patients and diarrhoea (4.4%) and nausea (4.0%) were the most frequently reported. In the comparative studies only, drug-related AEs occurred in 19.6% of garenoxacin and 26% of pooled comparator group patients. Severe or very severe drug-related AEs occurred in 67 (1.9%) patients given garenoxacin and included headache, nausea and abdominal pain. AEs related to garenoxacin occurred at a higher rate with the 600 mg dose (26.0%) compared with the 400 mg dose (18.9%). Also, rates were highest among patients with cSSTI (26.0%) or CAP (21.7%) and lowest among those with AECB (14.4%) but rates were similar between 7-14 (21.6%) and 5-day regimens (17.7%).

AEs in patients – IV ± PO

Of the 987 patients treated with IV ± PO garenoxacin regimens 681 (69%) experienced at least one AE compared to 70% of patients given comparator agents. IV site reactions reported as AEs were slightly more common with garenoxacin (2.1% and 1.3%). However, the information captured in CRFs showed that the incidence of any injection site intolerance was 22.6% for garenoxacin and 12.7% for comparators. From the CRFs, the individual event rates that were higher for garenoxacin than for comparators were infiltration (9.0% *vs* 5.4%), redness (6.5% *vs* 2.9%), phlebitis (5.4% *vs* 3.5%), pain (4.0% *vs* 1.8%), burning (3.0% *vs* 1.5%), discomfort (2.6% *vs* 1.2%), swelling (2.6% *vs* 0.8%) and itching (1.8% *vs* 0.2%).

Drug-related AEs were reported from 234/987 (23.7%) patients given garenoxacin and from 28.1% of those who received comparators. Slightly higher rates were seen with garenoxacin for IV site reaction (1.3% *vs* 0.8%), hypotension (1.4% *vs* 0.5%) and rash (1.8% *vs* 1.3%). Of those given garenoxacin 2.2% experienced a drug-related event that was categorised as severe/very severe and these included hypotension (0.6%), abdominal pain (0.3%) and two cases of each of allergic reaction, colitis and kidney failure. Rates of garenoxacin-related AEs were generally similar for the 400 mg (25.3%) and 600 mg (22.4%) doses although IV site reactions (1.6%) and pruritus (1.1%) occurred more frequently with 600 mg doses compared to 400 mg (0.9% and 0.2%, respectively). Rates were also similar between studies in different indications (CAP, 25.3%; cSSTI, 24.6%; pelvic infections 22.1% and IAI, 20.8%).

AEs of special interest

Hypotension and heart rate
Hypotension was an issue for IV garenoxacin administration as shown below.

Incidence of Hypotension AEs across Garenoxacin Studies; All Treated Subjects

Study Type	Number with a Hypotensive Event / Number Assessed (%)			
	Garenoxacin		Comparators	
	All Events	SAE	All Events	SAE
Total, All PO Studies	14/3456 (0.4)	8/3456 (0.2)	2/2071 (0.1)	0/2071
Total, IV-to-PO Studies During IV Treatment Phase	63/987 (6.4)	23/987 (2.3)	29/912 (3.2)	8/912 (0.9)
Total, IV-to-PO Studies 400 mg	33/430 (7.7)	15/430 (3.5)	11/367 (3.0)	6/367 (1.6)
Total, IV-to-PO Studies 600 mg	37/557 (6.6)	11/557 (2.0)	25/545 (4.6)	7/545 (1.3)

In IV-to-PO studies in which serial or paired ECGs were collected garenoxacin was associated with a slightly greater reduction in heart rate on Day 1 than the comparators and the decrease in heart rate was greater in those experiencing hypotensive events compared to those who did not. This decrease in heart rate on Day 1 was most marked in the elderly (≥ 65 years) and those treated with a diuretic. No association was seen between decrease in heart rate and garenoxacin plasma concentrations. It appeared that some individuals who became hypotensive after administration of IV garenoxacin were unable to mount an appropriate tachycardia in response to the hypotension.

Investigation of potential risk factors for hypotension showed a 2-fold (unadjusted) increase with garenoxacin *vs* pooled comparators. Patients with baseline systolic bp <90 mmHg, below normal BMI, age ≥ 65 years, Fine Class IV/V (CAP) or APACHE II >10 (IAI) were more likely to have a hypotensive event. With the exception of baseline bp and Fine Class, the odds ratio (OR) point estimates suggested stronger associations for these factors with hypotensive events in patients treated with garenoxacin compared to other therapies.

Garenoxacin-treated subjects who received diuretics, digoxin, nitrates, inotropic agents or beta-blockers were more likely to have a hypotensive event than those who did not. In contrast, a lower rate of hypotensive events was observed in those who received antihistamines compared to those who did not receive them.
It was proposed that IV garenoxacin may trigger hypotensive events in some individuals probably by causing histamine release (although in healthy subjects plasma histamine was similar between garenoxacin and placebo groups). In addition, garenoxacin may have a secondary effect to decrease heart rate or prevent a reflex stimulated increase in heart rate possibly due to its affinity for β-adrenoceptors. In subjects who are borderline compensated or already decompensated haemodynamically and who are on cardiovascular drugs, IV garenoxacin administration may be a sufficient additive or synergistic insult to result in the development of significant, sustained hypotension of varying degrees of severity.

Cardiac conduction
For oral studies, the incidence of arrhythmia events was only very slightly higher for garenoxacin than for comparative group patients.

The rate of bradycardia was slightly higher (1.4%) for garenoxacin in IV to PO studies than for comparators (0.9%) although sinus bradycardia occurred in 0.1% and 0.3%, respectively. In contrast, the incidence of tachycardia was higher with comparative therapy (2.1%) than with garenoxacin (0.9%) and the incidence of ventricular tachycardia was similar between treatments.

The applicant identified 11 patients with possible VT that included two patients treated with garenoxacin with narratives that included the term *Torsade de pointes* although these were not coded as such. One of these was a female aged 89 years with an IAI who had a QTcB of 517 ms on Day 5 compared to 403 ms pre-dose on Day 1. On Day 15 there was a SAE of syncope with long QTc, which resolved on the same day. Garenoxacin was discontinued but there was another episode described as

syncope and *Torsade de pointes* on Day +8 that was attributed to sotalol by the investigator. The second was a 30-year-old male who received two doses of oral garenoxacin when he was admitted to the ICU with worsening heart failure, hepatitis (ascribed to ischaemic injury) and kidney failure. One day +3, while in the intensive care unit, there was VF with *Torsade de pointes* that resolved the same day and the events were judged to be unrelated to garenoxacin.

CNS effects
In the Phase II/III studies of PO dosing 284/3456 (8.2%) garenoxacin and 168/2071 (8.1%) comparative group patients had an AE mapped to the nervous system but there were no major differences between agents. When garenoxacin was compared only to other quinolones the incidence of nervous system events was again similar (8.6% for garenoxacin *vs* 9.1% for other quinolones).
In the IV-to-PO studies 17.5% garenoxacin and 19.7% comparative group patients had an AE mapped to the nervous system of which the commonest were insomnia, anxiety, confusion, dizziness, vasodilatation and agitation. When garenoxacin was compared to levofloxacin in study 021 the incidence of nervous system events of any causality was similar at 11% for garenoxacin and 10% for levofloxacin.

Phototoxicity
In the PO dosing studies of efficacy 124 (2.2%) patients had at least one AE potentially associated with phototoxicity but rates were 1.7% for garenoxacin, 6.2% for other quinolones, 2.6% for beta-lactams and 2.1% treated with macrolides. The most frequently reported AEs were rash (1.2%) and erythema (1.0%) but most seem unlikely to have been due to phototoxicity.
In the IV-to-PO studies 116 (6.1%) had at least one AE potentially associated with phototoxicity including 5.9% given garenoxacin, 1.2% treated with quinolones and 7.5% treated with beta-lactams. Again the most frequently reported events (rash in 3.5% and erythema in 2.6%) did not seem to be due to phototoxicity.

Arthrotoxicity and tendonitis
In Phase II/III studies rates of AEs related to joints and tendons were similar for patients given garenoxacin and other agents. Overall tendon and articular AEs were infrequently reported with no change in incidence with increasing age. Rates of tendonitis were similar for garenoxacin and beta-lactams, which are not associated with joint and tendon disorders.

Deaths
In the comparative PO studies the death rates were similar for garenoxacin and comparative treatments (4/2353 and 3/2071) and none was judged by the investigator to be related to study drug.

There were 49 deaths reported during the IV ± PO studies with rates of 31/990 (3.1%) for garenoxacin and 18/914 (2.0%) for comparators but none was considered related to therapy by the investigators. These total figures reflect an imbalance in death rates that was seen in one study (027) in which the 30-day mortality rates were 13/226 (5.8%) for garenoxacin and 3/226 (1.3%) for piptazobactam and the total mortality rate was 3.5%. According to the investigators and a retrospective review performed by an independent, 3-member expert panel of surgeons, study drug did not directly contribute to death in any of these 16 patients. The two primary causes of death were IAI (under study) and co-morbid medical conditions (e.g. six in the garenoxacin group who died had a malignancy compared to none in the comparator arm).

Serious Adverse Events
In PO studies 138/3680 (3.8%) garenoxacin patients experienced at least one SAE and more than half had a respiratory event with the most frequently reported being pneumonia (0.8%) and lung disorder (0.3%). Drug-related SAEs occurred in 0.3% of garenoxacin patients and 0.1% in the comparative group but no obvious pattern emerged.

In IV to PO studies 15.2% given garenoxacin had at least one SAE compared to 14% for patients given other therapies. Drug-related SAEs occurred in 1.6% garenoxacin and 1.1% comparative group patients and the main difference was for digestive system SAEs that occurred in 0.7% and 0.1% in respective groups.

Laboratory abnormalities

With PO regimens most laboratory abnormalities in patients were Grade 1. Elevations in ALT, AST, amylase and glucose were the most frequently reported in both treatment groups. Hypoglycaemia (6.8% *vs* 3.8%), changes in haemoglobin (8.3% *vs* 6.7%) and elevations in creatinine (5.8% *vs* 3.3%) occurred at higher rates with garenoxacin while hyperglycaemia (in fasted subjects) was more common in comparator-treated patients (23.9% *vs* 18.8%, respectively). Males treated with garenoxacin were more likely than females to have hyperglycaemia (23.7% *vs* 11.9%), thrombocytopenia (3.1% *vs* 1.4%), elevated ALT (15.7% *vs* 7.0%) and total bilirubin (4.9% *vs* 1.9%).

In patients in the comparative studies with abnormal laboratory results at baseline, worsening of elevated creatinine (12.2% *vs* 5.3%), eosinophilia (5.6% *vs* 3.5%) and neutropenia (20.7% *vs* 18.8%) occurred slightly more often in the garenoxacin group. One garenoxacin-treated patient had worsening hypoglycaemia and the incidence of worsening hyperglycaemia was also slightly higher for garenoxacin (19.1%) than for comparators (16.8%).

With IV to PO regimens most laboratory abnormalities were Grade 1 or 2. Abnormalities in renal function were slightly more frequent in the garenoxacin group but hypo- and hyperglycaemia were slightly less common with garenoxacin. The most common Grade 3 or 4 laboratory abnormalities were in amylase (1.8% garenoxacin *vs* comparator, 2.0%), hyponatraemia (1.3% *vs* 1.4%) and hyperkalaemia (1.4% *vs* 0.8%). Males treated with garenoxacin had higher rates of ALT (32.2% *vs* 22.5%), amylase (17.5% *vs* 9.5%) and hyperglycaemia (34.4% *vs* 19.0%) compared to females. In contrast females showed higher rates of hypernatraemia (5.2% *vs* 1.4%), hyperchloraemia (13.3% *vs* 1.7%) and hypoglycaemia (7.9% *vs* 3.3%).

Worsening of abnormal baseline values occurred more commonly in garenoxacin patients for creatinine (14.5% *vs* 6.3%), BUN/urea (6.7% *vs* 1.2%) and bilirubin (10.1% *vs* 5.9%). Also, clinically relevant worsening was higher in the garenoxacin group for AST (5.9% *vs* 2.0%), bilirubin (5.4% *vs* 2.5%) and hyperglycaemia (5.6% *vs* 3.5%).

Discontinuation due to AES

In PO studies 2.4% of patients given garenoxacin and 3% who received comparative therapies discontinued therapy prematurely due to an AE. Twice as many in the comparative groups discontinued study drug prematurely due to digestive system events (1.6% *vs* 0.8%).

In IV to PO studies 53/987 (5.4%) discontinued garenoxacin due to an AE, mainly for rash (0.6% *vs* 0.2% for comparators) and allergic reaction (0.5% *vs* 0.1%) while the rate was 4.5% for all comparative group patients. Ten patients (6 garenoxacin) had a laboratory abnormality that led to discontinuation and in 5/6 in the garenoxacin group and 2/4 patients given piptazobactam these were abnormal LFTs.

Pharmacovigilance system

The Pharmacovigilance system has been described and appears to be satisfactory.

Risk Management Plan

This identifies the following risks that require further evaluation:

- Hypotension
- Cardiac conduction
- Drug interactions

Risk Minimisation Plan

The following is proposed:

1. An education program targeted to key healthcare professionals minimise the risk of cardiovascular and/or hypersensitivity events associated with administration of intravenous garenoxacin.

2. A Phase IV randomised clinical study to evaluate whether pre-treatment with antihistamines reduces the incidence of cardiovascular and/or hypersensitivity events.
3. Through a clinical pharmacology trial, further assess the cardiac electrophysiology of subjects who receive intravenous garenoxacin.
4. To continuously assess the safety profile of garenoxacin by an enhanced pharmacovigilance program in order to identify any emerging safety signals in a timely manner.

Comment on safety

In the comparative studies dizziness and somnolence were more common with garenoxacin than pooled comparators. The higher rates of AEs seen with 600 mg doses compared to 400 mg doses may reflect the more serious infections treated with the higher dose.

Intravenous therapy with garenoxacin was associated with higher rates of problems at infusion sites than observed with the various comparators and this must be clearly reflected in the SPC. The applicant should revisit the data in healthy subjects in which 1 h and 3 h infusions were compared and provide further justification for the final choice of 1 h durations for the Phase III studies. This justification should also take into account the association between duration of infusion, hypotension-related AEs observed in IV to PO studies that occurred during the IV or PO periods of treatment and the possible effects of a longer infusion time on efficacy.

The major issue for garenoxacin is drug-related hypotension. Very detailed investigations of possible risk factors identified several that included both host characteristics and concomitant medications. These must all be described in detail in the SPC.

The data available suggest that the risk of clinically important QTc prolongation with garenoxacin is probably low.. The applicant should conduct a study of the effect on QTc in accordance with CHMP guidance before approval can be considered and the SPC should reflect the findings. This issue must also be appropriately addressed in the Risk Management Plan. There is also some potential for PR prolongation but without progression beyond first degree heart block. Adequate warnings should be placed in the SPC.

Pruritus, rashes and allergic reactions have been reported. It is not clear whether some of the early hypotension cases observed might in some way reflect serious hypersensitivity. The applicant should review the database carefully for all events that might have represented hypersensitivity reactions and provide a detailed summary and discussion of these cases. The applicant should also provide a detailed rationale for the selection of hypersensitivity as a matter for enhanced surveillance in the RMP.

The laboratory data in patients suggest an association between raised/worsening creatinine and urea with garenoxacin. There may also be some association with worsening LFTs and hypoglycaemia. These issues merit further investigation and discussion by the applicant, including comparisons between garenoxacin and individual comparators and by indication and dose. The applicant should also perform a well-designed study in diabetic persons to further evaluate effects on glucose homeostasis. Whether this has to be completed pre-licensure will be considered in the light of the company's answers. The SPC should reflect the data and all changes in glucose homeostasis should receive special attention in the Risk Management Plan.

The gender differences in laboratory data merit further scrutiny including an examination of gender imbalances according to distributions of underlying diseases.

The Risk Management Plan is considered to be inadequate at present. The applicant should amend this to reflect special attention to all AEs associated with fluoroquinolones at least during the initial post-marketing period. As mentioned, changes in blood glucose, abnormal LFTs and decreased renal function should be covered. The applicant should provide details of plans to further investigate histamine release.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

Subject to adequate responses to the LOQ and to provision of a satisfactory Risk Management Plan, the risk benefit relationship might be considered favourable for **Garenoxacin 400 mg tablet** in the treatment of mild to moderate community-acquired pneumonia (CAP) and for acute maxillary sinusitis but not for acute exacerbations of chronic bronchitis (AECB).

Due to inadequate evidence of efficacy at this time in the claimed indications, the risk benefit relationship is unfavourable for:

- **Garenoxacin 600 mg tablet** for the treatment of complicated skin and soft tissue infections (cSSTI) or for intra-abdominal infections (IAI) and acute pelvic infections (as follow-on to IV therapy).
- **Garenoxacin 2 mg/ml solution for infusion** for the treatment of CAP (400 mg) or for cSSTI, IAI and acute pelvic infections (600 mg).