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

London, 19 March 2009

WITHDRAWAL ASSESSMENT REPORT
FOR
FACTIVE

International Nonproprietary Name:
Gemifloxacin

Procedure No.EMEA/H/C/995

Day 180 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 review of the data on quality, safety and efficacy, the Rapporteurs consider that the application for Factive, in the treatment of

- Community acquired pneumonia, of mild to moderate severity,
- Acute Exacerbation of chronic bronchitis,
- Acute bacterial sinusitis,

is not approvable since "major objections" have been identified, which preclude a recommendation for marketing authorisation at the present time. The details of these major objections are provided in the preliminary list of questions (Section VI).

The major objections precluding a recommendation of marketing authorisation pertain to the following principal deficiencies:

Quality

The formation of genotoxic impurities is seen as a major risk to the quality of the product. The use of lower chain alcohols with alkyl mesilate during the synthesis of gemifloxacin mesilate, drug substance, can lead to the formation of the potentially genotoxic alkyl mesilates. The presented data are not sufficient to conclude that alkyl mesilates (MMS, EMS, IPMS) cannot occur in the drug substance.

In addition, a GMP inspection was requested by the EMEA for the proposed manufacturing site. The inspection has already taken place in August 2008, with four major deficiencies. The Rapporteur has not yet received any inspection report. Therefore, GMP compliance is still not established for the proposed manufacturing site.

Nonclinical

Gemifloxacin is a more potent clastogen than other fluoroquinolones and provides only a low margin of safety for therapeutic treatment based on exposure levels clastogenic in vivo in rat. As long as there is no proof that gemifloxacin is not more potent a clastogen in vivo than other fluoroquinolones already approved gemifloxacin should only be regarded as last line treatment for the proposed therapeutic indications, given the precondition that the clinical and quality Major Objections will be solved.

Clinical

1. Regarding community acquired pneumonia (CAP) it is considered that 7 days of gemifloxacin is needed even to treat mild to moderate CAP. The risk-benefit relationship remains questionable due to the frequency of drug-related rash and severe adverse events including rashes that are observed with 7 days treatment (Please see C37 and C40). In addition, even 7 day treatment of pneumonia caused by legionella is not considered to be adequate. This must be adequately reflected in the SPC (see Annex).

2. Regarding acute exacerbation of chronic bronchitis (AECB)

The indication AECB is not supported due to the lack of superiority studies and deficiencies of the conducted studies (please see assessment of questions C26 to C30 in the Clinical Assessment Report).

II. EXECUTIVE SUMMARY

II.1 Problem statement

CAP: Community acquired pneumonia (CAP) is a common disease and a frequent cause of morbidity and mortality worldwide. Although precise figures are not available for all European countries, several studies suggest an annual incidence of CAP ranging from 1.6 to 9 cases per 1000 people with a frequency that appears to be age related, the highest rates being observed in the very young and very old segments of the population (with 34/1000 cases/year in people aged ≥75 years up to 52.3/1000 cases/year among those aged ≥ 85 years) [*Woodhead, 2002*; *Jackson et al., 2004*].

Overall, it is estimated that 20-40% of patients with CAP require hospitalisation and that 5-10% of these patients are admitted to intensive care [*Hoare and Lim, 2006*]. The overall mortality from CAP ranges from 7 to 36% [*Valles et al., 2006*] and it represents the major cause of death due to infectious disease in developed countries [*File, 2004*]. The overall economic burden associated with CAP is significant and growing with the ageing population with much of the direct costs attributed to hospitalisation, length of stay, and physician services [*Birnbaum et al., 2002*].

The aetiology of CAP in European countries has been extensively reviewed [*Woodhead*, *2002*] and the leading cause (predominant pathogen) of CAP has been identified as *Streptococcus pneumoniae*, accounting for more than 20-25% of CAP in Europe, followed by *Haemophilus influenzae* (3-10%), *Moraxella catarrhalis, Staphylococcus aureus*, *Legionella* spp. and Gram-negative enteric bacteria (more uncommon in disease managed outside the hospital setting). The frequency of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* cases is rising as illness severity decreases and they account for about 15% and 7% of CAP cases, respectively [*Arnold et al., 2007*].

The changing susceptibility pattern of several respiratory pathogens to antibacterial agents, particularly *S. pneumoniae*, has recently raised concerns about the efficacy of currently available therapies in the treatment of CAP. Antibacterial resistance to *S. pneumoniae* is increasing worldwide [*Appelbaum, 2002; Jenkins et al., 2008*], affecting primarily beta-lactams and macrolides. The frequency of such resistance is highly different among the European countries as reported by the European Antimicrobial Resistance Surveillance System (EARSS). Resistances of *S. pneumoniae* to macrolides in most European countries is increasing ranging between 10% and 25%, and can be as high as 30% in some areas (i.e. France, Italy or Belgium), while penicillin non-susceptible *S. pneumoniae* was reported as varying from 1% in The Netherlands to 32% in France and 38% in Cyprus [*EARSS Annual Report* 2006]. Dual resistance - i.e. resistance to both penicillin and macrolides - was between 5-10% for 8 of the 30 countries, and between 10-20% in a further 4 countries, being even higher in France (26%) and Cyprus (23%) [*EARSS Annual Report, 2006*]. In a recent extensive review the rate of multidrug-resistant *S. pneumoniae* (defined as resistance to two or more of the following classes of drugs: penicillin, second-generation cephalosporins, macrolides, trimethoprim/sulfamethoxazole, and tetracyclines) in Europe ranged from 3.8% (UK) to 71.8% (France), while levofloxacin resistance ranged from 0 (France, Spain, UK) to 5.6% (Italy) [*van Bambeke et al., 2007*].

AECB: Chronic bronchitis defined as "*chronic productive cough for 3 months in each of 2 successive years in a patient in whom other causes of productive chronic cough have been excluded*" [*Celli et al., 2004*], whilst considered as a subset of the broader category of Chronic Obstructive Pulmonary Disease (COPD), it remains a clinically and epidemiologically useful term [*Global Inititave of Obstructive Lung Disease* (*GOLD), 2007*].

Chronic obstructive lung disease, including COPD, bronchitis and emphysema, is a major cause of chronic morbidity and mortality throughout the world and according to the latest WHO estimates [*The Global Alliance Against Chronic Respiratory Diseases* (*GARD)*, *2007*], the prevalence of COPD ranges from 4% to 20% in adults over 40 years of age, with a considerable increase by age, particularly among smokers. COPD represents the third most common cause of death (8%) in the 25 member states of the European Union [*Niederlander*, *2006*].

Exacerbations of COPD/AECB, defined as "*an event in the natural course of the disease characterised by a change in the patient's baseline dyspnoea, cough and/or sputum beyond day-to-day variability sufficient to warrant a change in management"* [*Celli et al., 2004*], have serious negative impacts on patients quality of life [*Spencer et al., 2004; Kessler et al., 2006; Bourbeau et al., 2007; Cote et al., 2007*], lung function [*Donaldson et al. 2002; Bai et al. 2007*], and socioeconomic costs [*Wouters, 2003*]. Consequently, according to the current GOLD guideline, the prevention, early detection and prompt treatment of AECB may impact the clinical progression of the disease by ameliorating the effects on quality of life while minimizing the risk of hospitalization [*Wilkinson et al., 2004; Casas et al., 2006*].
AECB is also a major source of medical consultation, with a median number of exacerbations seen in primary care of two per year, and 30% of patients suffering from 3 or more exacerbations in 1 year [*Donaldson and Wedzicha, 2007*]. In light of this and considering that acute exacerbations are the main cause of hospitalization among COPD patients, the economic burden of AECB is considerable [*Anzueto et al., 2007*].
The aetiology of AECB is complex. The majority of exacerbations are infectious in aetiology and bacteria are detected in approximately 50% of the cases while combined bacterial and viral infection can be identified in 25% of the cases [*Sykes et al., 2007; Celli and Barnes, 2007*].
The predominant bacteria recovered from the lower airways of patients with AECB are *H. influenzae*, *S. pneumoniae* and *M. catarrhalis* [*Woodhead et al., 2005*]. So called atypical pathogens, such as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, have been identified in patients with AECB. In patients with mild AECB *S. pneumoniae* is predominant while as FEV_1 declines and patients have more frequent exacerbations and/or concomitant diseases, *H. influenzae* and *M. catarrhalis* become more frequent, and *P. aeruginosa* may appear in patients with severe airway limitation [*GOLD*, 2007].
The benefit of antibiotic treatment of AECB is supported by several publications including a meta-analysis [*Saint et al., 1995*] and by a recent systematic review from Cochrane Centre suggesting a mortality benefit with the use of antibiotics in this indication in comparison with placebo [*Anzueto* et al., *2007*] and a beneficial effect on lung function.
Based on the current available evidence and according to the GOLD guideline [*GOLD, 2007*], antibiotics should be given to:

- Patients with AECB with the following 3 cardinal symptoms: increased dyspnoea, increased sputum volume, and increased sputum purulence (Evidence B).
- Patients with AECB with 2 of the cardinal symptoms, if increased purulence of sputum is one of the two symptoms (Evidence C).
- Patients with severe exacerbation of COPD that requires mechanical ventilation (invasive or non-invasive) (Evidence C).

According to the analyses and recommendations of the recent systematic review of the Cochrane Centre, the use of antibiotics in the indication AECB has to be discussed more thoroughly. According to the results of this review (Ram FSJ et all., First published 19.04.06) "in exacerbations of COPD associated with increased cough and sputum purulence, antibiotic therapy, regardless of choice, significantly decreases short-term mortality, treatment failure and sputum purulence". This benefit of antibiotics however, was observed only in patients requiring hospitalisation. In contrast, analyses restricted to community-based studies did not find differences between antibiotic and placebo.
Superiority studies are considered necessary to show efficacy in this indication. This is in line with the recent draft of the FDA guidance for industry on AECB/COPD which clearly recommends superiority studies in this indication and the FDA draft guidance on non-inferiority studies, which proposed that such a design would not be considered acceptable for AECB. The "Note for Guidance on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95/rev.1)" currently states "If a placebo-controlled study is possible, this would be desirable and applicants should discuss the provision of such a study as part of the clinical development programme with EU Regulators." In the patient population studied, placebo-controlled or comparator-controlled superiority studies are possible and necessary.

II.2 About the product

Gemifloxacin is a synthetic broad-spectrum antibacterial agent that belongs to the fluoroquinolone class of antibiotics and is available in an oral formulation as the mesylate salt in the sesquihydrate form.
Gemifloxacin drug substance was originally discovered by LG Life Sciences Ltd and subsequently developed by SmithKline Beecham (later on GSK) and Oscient Pharmaceutical Co. for the treatment of urinary and respiratory tract bacterial infections. Approved by FDA in April 2003 (Factive®, Oscient Pharmaceutical Co.) gemifloxacin has been launched in the US in September 2004. Currently approved indications in the US include the treatment of acute exacerbation of chronic bronchitis (AECB) and community acquired pneumonia (CAP) of mild to moderate severity including multi-drug resistant strains *Streptococcus pneumoniae* (MDRSP). The recommended dose in both indications is one 320 mg tablet administered once daily for 5 days with the possibility to extend treatment to 7 days in cases of CAP due to known or suspected MDRSP. The drug is also available on the market in other extra European Union (EU) countries, including Brazil, Canada, China, Jordan, Mexico, Saudi Arabia, South Africa, South Korea, Russia and Taiwan. As of today, from available sales data it is possible to estimate a post-marketing exposure of more than 1.6 million patients world-wide (among these ~1.3 million are from use in the US).
In late 2006, Menarini International Operations Luxembourg acquired exclusive rights to register gemifloxacin in all the European countries. The present application has been prepared in support of the three respiratory tract indications: CAP of mild to moderate severity, AECB and acute bacterial sinusitis (ABS).

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

In the overall clinical pharmacology program, the pharmacokinetics of oral gemifloxacin have been assessed in a variety of clinical pharmacology studies that included 1197 healthy volunteer subjects, 12 healthy elderly volunteers, 46 patients with renal impairment (including 12 patients who were maintained on chronic haemodialysis), and 33 patients with hepatic insufficiency. Furthermore, the safety and pharmacokinetics of i.v. gemifloxacin have been evaluated in 58 healthy volunteers.

An extensive clinical development program was conducted in more than 8000 patients enrolled in 27 phase II/III clinical studies to evaluate the safety and efficacy of gemifloxacin in the treatment of the main bacterial respiratory tract infections in adults. All of the studies were performed in compliance with the principles of Good Clinical Practice. A special study (Study 344) was conducted to explore the potential relationship between plasma levels of gemifloxacin and its metabolite with the incidence of rash in patients groups with an increased risk of rash development.

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

GLP aspects: Standard safety pharmacology tests were conducted in compliance with GLP and are in accordance with the requirements in ICH S7A for safety pharmacology studies.
The pharmacokinetic studies were not performed according to GLP principles, however, they were adequately performed and in accordance with current guidelines.
All pivotal toxicity studies were conducted in compliance with GLP regulations.

GCP aspects: Overall, studies in the sought indications were conducted in accordance with Good Clinical Practice. However, in several clinical studies an investigator was disqualified based on the findings of a failed GCP audit conducted by the sponsor or the FDA. This led to the exclusion of several patients in the

CAP study 049, the AECB studies 068 and 001, and the ABS studies 009, 010, 186, and 206. The numbers of the patients excluded were always very low compared to the overall number of patients included in the studies. Respective abridged study protocols were provided by the Applicant in each case. These protocols and the conclusions of the Applicant are accepted.

GMP aspects: A GMP inspection was requested by the EMEA for the finished product manufacturer. The inspection has already taken place in August 2008, with four major deficiencies. On the basis of further documents submitted the GMP compliance was confirmed.

Declarations from the Qualified Persons of the Menarini von Heyden GmbH, Dresden, Germany (packaging, batch control and batch release) and Patheon Pharmaceuticals Inc, Ohio, USA (bulk production) that the active substance manufacturer LG Life Sciences, Ltd, Korea operates in compliance with the detailed guidelines on good manufacturing practice for starting materials have been provided.

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

This is an application made under Article 8 (3) of Directive 2001/83/EEC, as amended for an EU marketing authorisation via the Centralised Procedure with Dr. Broich acting as Rapporteur and Dr. Hudson as Co-Rapporteur.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

III.1 Quality aspects

Drug substance

An Active Substance Master File (ASMF) procedure is used for the drug substance gemifloxacin mesylate sesquihydrate. The manufacturer and ASMF holder is sited in Korea.

Gemifloxacin mesylate sesquihydrate (chemical name: (R,S)-7-(3-aminomethyl-4-Z-methoxyimino-1-pyrrolidinyl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-1,8-naphthyridine-3-carboxylic acid methanesulfonate) has one asymmetric centre at C3 but is developed as the racemate. Development of the racemate has been progressed due to equivalent enantiomeric anti-microbial activity and metabolism. Structural isomerism of the oxime group is possible. The syn configuration of this group is ensured by the synthetic route and monitored by chromatographic methods. Different polymorphic forms were isolated and identified by characterisation/polymorphism studies. Pseudopolymorph II (sesquihydrate) is thermodynamically more stable than other solid forms, and has therefore been selected for further development and commercial production.

Different companies have been involved in the development of the drug substance.

A detailed description of the manufacturing process, information on the control of materials, control of critical steps and intermediates, and process validation and/or evaluation are given in the restricted part of the ASMF.

The drug substance specification provided includes test on appearance, identification (IR and HPLC), assay (HPLC), impurities (HPLC: total related, specified identified SB-332408, SB-332409, SB-332410, unspecified; TLC: high molecular weight impurities), residual solvents (GC: total, dichloromethane), water content (Karl Fischer), heavy metals, and residue on ignition.

Analysis data are provided for several qualification, validation, and Iksan Plant commercial batches showing consistent and reproducible quality.

A retest period of 36 months is established. Long term and accelerated stability data are provided for several development, qualification and commercial batches. Photostability studies show a significant degradation of the impurity SB-265805-S indicating that the drug substance should be protected from light.

Drug Product

The drug product is a 533 mg (containing 320 mg gemifloxacin as pure free base) white to off-white, oval, film-coated tablet, debossed GE bisect 320 on both sides. The excipients of the tablet core are microcrystalline cellulose, povidone, crospovidone, magnesium stearate. The film-coating Opadry OY-S-28924 contains hypromellose 5 cP (HPMC 2910), hypromellose 15 cP (HPMC 2910), titanium dioxide, and macrogol 4000. The container closure system is composed of clear PVC/PVDC blister packs with aluminium foil lidding.

The manufacture of the bulk production is sited in USA. Responsible for packaging, batch control and batch release is sited in Germany.
The manufacturing process consists of six steps: granulation, preparation of compression mix (blending and lubrication), compression of the core tablets, preparation of film coating suspension, coating, and packaging).

The release specification includes parameter on description/appearance, identification (HPLC), gemifloxacin content (assay HPLC), uniformity of dosage units, dissolution, moisture content, degradation products (HPLC: SB-332410, any unspecified impurity, and total related substances). The shelf-life specification does not include the parameter identification and uniformity of dosage units.

A shelf-life of 3 years is established without any special declaration of storage conditions. Long term and accelerated stability studies of three validation batches have been provided. Tests have been performed on description/appearance, gemifloxacin content, dissolution, moisture content, and degradation products.

However, the quality of the drug substance and drug product is not adequately demonstrated. There are major objections concerning genotoxic impurities and concerning GMP compliance of the drug product manufacturer and some other outstanding issues (See List of Question.)

III.2 Non-clinical aspects

Pharmacology

Primary pharmacodynamics studies are reviewed in the clinical D80 assessment report.
The safety pharmacology evaluation included the assessment of the potential effects of gemifloxacin on the central nervous system (CNS), including general behaviour, the cardiovascular system and the respiratory system. Supplementary studies included investigations of the renal system, the gastrointestinal system and blood coagulation.
In sum, the safety pharmacology studies did not show any uncommon effects for a drug of the quinolone class.
In comparison with other quinolones the CNS toxicity of gemifloxacin was rather low. Toxic effects were only seen at high doses (at least 160 mg/kg).
In regard to cardiotoxic effects the applicant has conducted a comprehensive package of safety pharmacology studies. In in-vivo studies in dogs there was no effect on heart rate or blood pressure at oral

doses of up to 200 mg/kg. Oral doses of gemifloxacin up to 200 mg/kg induced no arrhythmia, however, gemifloxacin induced prolongation of the QRS complex in the ECG of dogs after oral administration of doses of ≥ 50 mg/kg, and similar effects were observed after an i.v. infusion of 30 mg/kg. The effects on the QRS complex were observed at drug plasma concentrations (about 5 µg/ml at a dose of 50 mg/kg oral, 10 µg/ml at a dose of 30 mg/kg i.v.) only about 3-5-fold higher when compared to therapeutic plasma concentrations in humans (1.2 µg/ml after administration of 320 mg oral). In dog isolated Purkinje fibres, gemifloxacin up to test concentrations of 100 µM had no effects on the maximum rate of depolarisation (V_{max}), indicating no effects on cardiac Na+ channels. To our knowledge, a prolongation of the QRS complex in the ECG has not been observed after administration of any marketed fluoroquinolone derivative. The applicant has not provided an explanation for the mechanism of the prolongation of the QRS complex observed in dogs after administration of gemifloxacin. However, it is stated, that gemifloxacin has a low potential for cardiovascular liabilities due to QRS prolongation for the following reasons: (i) In contrast to the safety pharmacology studies, no gemifloxacin-related ECG abnormalities, including the QRS complex and the QT interval, were detected in dogs dosed orally for up to 13 weeks in repeated dose toxicity studies at doses up to 160 mg/kg/day. (ii) No clear indication of Type I Na^+ channels blockade by gemifloxacin was found in the *in vitro* studies performed in the dog Purkinje fibre preparation. (iii) No evidence for clinically relevant QRS prolongation has been observed in the course of the clinical development.
In dogs given 30 mg/kg gemifloxacin intravenously, QTc increased by up to 16% shortly after a 30-min infusion ended, and returned to near baseline 25 min later. There was no effect at 10 mg/kg i.v. (corresponding to a Cmax of 3.66 µg/mL and AUC of 12.8 µg.h/mL, compared with a mean Cmax of 1.2 µg/mL and AUC of 8.4 µg.h/mL in humans given 320 mg orally). There was also no effect on QTc at an oral dose of 200 mg/kg (Cmax 6.76 µg/mL, AUC 69.7 µg.h/mL).
Gemifloxacin inhibited hERG channel currents in HEK293 cells (stably expressing hERG) by an IC50 of 260 µM. From these observations a value for the ratio hERG IC50/free Cmax of 280 can be calculated. According to Redfern et al (2003), a 30-fold margin between Cmax and hERG IC50 may sufficient for drugs undergoing clinical evaluation. However, the hERG study probably underestimates hERG blockade by gemifloxacin due to methodological deficiencies (external potassium >5meq/l, temperature 32.5°C, measurement of "blunted" tail-currents, unusual voltage clamp protocol), even though an IC50 close to that of moxifloxacin is given.
In a study performed in dog Purkinje fibres, gemifloxacin prolonged the action potential duration (APD) by 9% at a concentration of 100 µM. There were no significant changes at 10 µM.
In sum, gemifloxacin was found to have a low potential to prolong QTc in safety pharmacology studies. This is reflected in a small, not statistically significant, increase (mean 4.1 msec) in QTc in gemifloxacin-treated patients.
Some effects were seen on the respiratory system and the renal system (in rats) and the gastrointestinal system (in rats and mice), however, without exception after high oral gemifloxacin doses.
Oral administration of gemifloxacin up to 200 mg/kg to rats produced no effects on the blood coagulation system parameters.
The applicant has provided two *in vitro* studies to assess gemifloxacin's affinity for (1) 23 different receptors and (2) 7 different ion channels. Gemifloxacin 10 □M (corresponding to 3.3 folds the C_{max} observed in humans after the oral administration of a 320 mg tablet), had a modest inhibition (40-50 %) on the binding to muscarinic (non-selective) receptor and on the opioid (non-selective) receptor, which is considered not a relevant clinical risk. There were no further noteworthy findings.

Pharmacokinetics

The pharmacokinetic parameters of gemifloxacin were determined after oral (gavage) and i.v. administration to rats and dogs, the main species used in the toxicology studies. Some further data have also been obtained in the mouse (CD-1) to support the reproductive toxicology studies in this species and in the hairless mouse (SKH-hrBR) to support the phototoxicity/photocarcinogenicity studies.
Gemifloxacin plasma concentration data were acquired using HPLC fluorescence detection or LC-MS/MS methods.

In general the PK were comparable in males and females (rats, dogs).
The oral bioavailability of gemifloxacin and its individual (+) and (-) enantiomers in fasted rats and dogs was variable and ranged from 11% to 42% at 16-160 mg/kg (solution formulation) in the rat and 28% to 99% at 8 mg/kg (given as a powder in gelatine capsules) in the dog. Much lower systemic concentrations of gemifloxacin were observed in fed animals (up to ca 19 and 5 times lower in rat and dog, respectively) indicating that the bioavailability is reduced when the compound is administered with food.
Gemifloxacin was rapidly absorbed following oral administration with T_{max} generally lying between 0.5 and 2 hours for the three main animal species examined.
An in vitro study on permeability across various intestinal models provided evidence that gemifloxacin is a substrate for intestinal efflux and/or active secretory mechanisms. However, the applicant has performed a study to evaluate the in vitro interaction of gemifloxacin with P-glycoprotein (P-gp) using a P-gp ATPase activity assay. The results of the study allow the conclusion that there is no significant interaction (as a substrate or inhibitor) between gemifloxacin and P-gp up to 20 µM, that is about 7 folds higher than Cmax achieved at the therapeutic dose (320 mg p.o., once daily).
Toxicokinetic data from the repeated-dose toxicity studies provided neither evidence of accumulation nor sex-related differences in systemic exposure. Cmax and AUC values increased with dose , although not consistently dose-proportionally.
In vitro studies showed that the plasma protein binding of gemifloxacin was moderate and generally similar in all species. The distribution of [14C]Gemifloxacin to blood cells has been investigated in rat, dog and man and was moderate with mean values of 64, 72 and 56 %, respectively.
Following a single oral dose of 16 mg/kg gemifloxacin was distributed into nearly all tissues examined with the highest concentrations occurring in thyroid, lungs, kidney and liver. In common with other quinolone compounds there was evidence for some association with melanin in the pigmented tissues (pigmented skin and uveal tract).
Elimination of radioactivity from most tissues (apart from the walls of the G. I. tract) was generally rapid and essentially complete by 24 h after dosing.
Gemifloxacin was metabolised to a limited extend in animals and man, i.e. the majority of gemifloxacin was excreted unmetabolised. However, there are some differences in metabolism between the animal species investigated and humans. In man three metabolites have been observed in plasma which were not detected in the plasma of the preclinical species. Two metabolites (O-desmethyl gemifloxacin, and the ether glucuronide of hydroxymethyl gemifloxacin) have been observed in relatively low levels in human plasma, however, the metabolite gemifloxacin carbamyl glucuronide represented 11.5% plasma radioactivity in man after a 320 mg dose of [14C]Gemifloxacin. The applicant has carried out a new 2-week repeat-dose toxicology study in rat, with the most relevant human metabolite, i.e. carbamyl glucuronide gemifloxacin (CGG). The applicant has also carried out an additional in vitro study to assess the potential of the two major human metabolites (CGG and O-desmethyl gemifloxacin) to inhibit the mammalian topoisomerase II.
These studies demonstrated that CGG was avoid of any in vivo toxic effect, at drug exposure at least 10 folds higher than in the therapeutic setting and did not affect the mammalian topoisomerase II at concentration 100 folds higher than its presumed Cmax. These considerations can also be applied to the other glucuronide–derivatives observed in human plasma.
The major route of excretion was via the faeces with > 60% of the dose being eliminated by this route in each species. The remainder was largely recovered in the urine.
In human liver microsomes, gemifloxacin caused a 22% and 16% inhibition of CYP1A2 and CYP4A9/11 activities, respectively. The activity of CYP3A4 was increased by about 10%. However, the applicant has provided reassurance on the lack of clinical relevance of the results obtained *in vitro* based on published and proprietary data.

Toxicology

The toxicity of gemifloxacin was evaluated in standard toxicological studies. Additional studies conducted included the examination of phototoxic, photomutagenic, photocarcinogenic and antigenic potential. As gemifloxacin is intended for short-term administration (5-8 days), carcinogenicity studies have not been

conducted (there was an assessment of photocarcinogenicity, however). All definitive studies were conducted according to the requirements of Good Laboratory Practice (GLP). All doses quoted are in terms of gemifloxacin (pure free base).
Pivotal studies were conducted in rats up to 13 weeks and in dogs up to 26 weeks. The highest daily dose in rats was 600 mg/kg corresponding to multiples of human exposure of 80 (male rat) and 100 (female rat) based on AUCs. The highest daily dose in dogs was 192 mg/kg corresponding to multiples of human exposure of 53 (male dog) and 59 (female dog) based on AUCs.
In the rat, the kidney was identified as target organ of toxicity, in dogs, the liver and bile were affected.
In the rat the principal toxicological finding was tubular nephropathy associated with deposition of drug-related crystalline material. Males were affected at lower doses than females. Crystal nephropathy is a well known and well characterised toxic effect of quinolones. The NOEL for tubular nephropathy in male rats was 24 mg/kg and for female rat 168 mg/kg, this corresponds to an AUC of 2.9 µg/h/ml. The human AUC at steady-state was 8.4 µg/h/ml (320 mg/d; combined sexes), i.e. the animal:human exposure ratio at the NOAEL is < 1. Nevertheless, the well characterised mechanism for this effect leads to the assumption that there is no relevant risk for humans for the development of crystal nephropathy. Several quinolones (most notably ciprofloxacin and norfloxacin, and including gemifloxacin), are relatively insoluble at pH ≥ 7. This promotes crystallisation of drug in the renal tubules of rats, which typically form alkaline urine, leading to a foreign-body reaction and tissue damage. Male rat urine tends to be of higher pH than female, correlating with sex-dependent differences in sensitivity to nephropathy. Human urine is normally mildly acidic, favouring dissolution of higher concentrations of gemifloxacin, and minimising likelihood of crystallisation. The corresponding information under SPCs section 5.3 is adequate from the assessor's point of view.
In the dog minimal or slight hepatocellular changes (hepatocellular degeneration, single cell necrosis) and minimal or slight cholangitis/pericholangitis were the main findings. In a 28-day study proliferation of the bile duct epithelium and minimal or slight hepatocellular degeneration with enlarged hepatocytes and single cell necrosis were seen. The NOAEL for this toxic effect was 96 mg/kg/d, the LOAEL was 192 mg/kg/d, corresponding to 2-4 and 6-7 times clinical exposure based on AUCs, respectively. In a 13-week + 4 weeks recovery study no clear NOAEL could be established, however, the liver changes in the low-dose group (48 mg/kg/d, corresponding to 1.7-2 times clinical exposure based on AUC) were generally minor and reversible. In a 26-week minor liver changes were seen at 46 mg/kg/d.
The applicant's explanation regarding the mechanism of these effects (deposition of crystals of gemifloxacin in the biliary tract, followed by local impedance of bile flow, and resulting damage to principally periportal hepatocytes by bile salts and that the stress on the biliary system to eliminate parent drug is greater in dog than in man) sounds plausible. Further, it should be taken into consideration, that the intended treatment period in patients is 5 days, whereas, hepatotoxic effects in animals are only observed after a longer duration of repeated dosing (at least 28 days). Thus, the assessor shares the applicant's view, that the risk for adverse liver effect in humans has to be estimated as low.
In the dog, high dose animals showed erosion of the articular surfaces of one or more joints in the 28-day study (LOEL was 192 mg/kg/d, corresponding to 6-7 times clinical exposure based on AUC). This degeneration was confirmed histologically though there was no evidence of treatment-related lesions in the growth plate cartilage. Arthropathy was not seen in any other study.
Toxicokinetic studies were conducted in satellite groups of animals as part of the repeat dose toxicity studies. Plasma concentration-time profiles for gemifloxacin show that Cmax and AUC values increased with dose, although not consistently dose-proportionally. Evidence was obtained that there was neither accumulation nor sex-related differences in systemic exposure.
Gemifloxacin was extensively tested in an in vitro and in vivo battery of tests on genotoxicity including AMES-test, mutation assay in mammalian cells, clastogenicity assays in mammalian cells, mechanistic studies for topoisomerase II binding in mammalian cells, in vivo clastogenicity assays in mouse and rat and in vivo DNA repair assay in rat liver.
Summarizing the data and weighing the evidence gemifloxacin has to be considered a potent mammalian in vitro and in vivo clastogen with a mode of action closely related to its pharmacological (antibacterial) mode of action. Mammalian topoisomerase II affinity was measured to be higher than for ciprofloxacin and grepafloxacin leading to assume that genotoxic effects in mammalian cells might occur at lower doses

with gemifloxacin. To identify NOEL concentrations in rat plasma an in vivo micronucleus study with continuous infusion to obtain constant plasma concentrations over time was performed in rat. NOEL for clastogenicity in vivo in rat bone marrow was found at continuous mean plasma concentrations of Cmean = 3.66 µg/ml for 2h and provide a margin of safety of 4 when assuming that the plasma concentration in man after a single 320 mg oral dose is constantly above 0.9 µg/ml between 0.5 h and 3 h after dosing. However, in rat concentrations in other tissues like liver, kidney or spleen are multiples above the plasma concentrations and it might be possible that gemifloxacin induced genotoxic effects occur there. As it can be assumed that the respective human organs are also exposed to higher concentrations of gemifloxacin than bone marrow, safety margins might not be present any more. As relevant data of genotoxicity in organs other than bone marrow were missing this had to be addressed thoroughly by the applicant.
In order to answer to this major objection Menarini conducted an additional in vivo study in rat with 2 hour continuous infusion as well as an in vitro study in human lymphocytes to further investigate the genotoxic potential of gemifloxacin.
Summing up the results of the in vivo study (RTC74170) there is an unequivocal NOEL for DNA damage in liver at 24 h only at the lowest dose group of 1 µg/ml target plasma concentration providing only a low margin of safety. There was no justification provided why comparators were not included into the in vivo study as recommended by the CHMP. Menarini performed the in vitro micronucleus assay in human lymphocytes instead. As in vitro studies had not been regarded appropriate for comparing clastogenic potency it remains unclear why Menarini had performed the in vitro study.
The results of the in vitro micronucleus test (RTC74880) clearly demonstrated the high clastogenic potency of gemifloxacin compared to ciprofloxacin and moxifloxacin. Based on the NOELs in this study gemifloxacin is by a factor of at least 7 more potent than ciprofloxacin and by a factor of at least 15 more potent than Moxifloxacin for the induction of micronuclei.
Over all gemifloxacin appears to provide only a lower margin of safety than cipro- or moxifloxacin for therapeutic treatment, based on exposure levels clastogenic in vitro and in vivo.
Based on the current safety profile the risk/benefit evaluation is negative as standard first line therapy in the proposed indications.
However approval should be considered for cases where no safer alternatives for therapeutic treatment remain and gemifloxacin would provide an effective treatment option. This however would need a major revision with appropriate changes and restrictions in the clinical indications in the PI/SPC (the major objection remains).
Gemifloxacin was tested in comparison to lomefloxacin and ciprofloxacin for photoclastogenicity. Lomefloxacin and ciprofloxacin showed the expected increase in clastogenic potential after UV irradiation, whereas gemifloxacin was the most potent clastogen under the conditions of this assay but showed no additional increase of effects after UV irradiation. Gemifloxacin therefore can be regarded as not photoclastogenic.
In a 12-month oral (gavage) photocarcinogenesis study in hairless mice gemifloxacin did not shorten the time to tumour onset nor increasing the tumour burden in UV irradiated mice in comparison to the non treated irradiated controls.
Given the short term duration of therapeutic treatment of 5 days, long term carcinogenicity studies have been omitted.
Gemifloxacin was evaluated in a combined fertility and embryo-foetal development study in rats, embryo-foetal development studies in mice and rabbits and a pre-postnatal study in rats. The drug was applied orally, only in the rabbit study intravenous application was chosen. Studies were conducted according to GLP. Toxicokinetic data were obtained concurrently with the reproductive toxicity studies as were data on placental and milk transfer.
In the fertility study, gemifloxacin did not affect reproductive performance or fertility of male and female rats (AUC 3-4 folds higher than therapeutic exposure). However, foetal growth retardation was observed. Foetal growth retardation was also seen in the embryo-foetal development studies at AUC levels 2- to 3-fold the human therapeutic exposure. Animal exposure at the developmental NOAEL equalled approximately human therapeutic exposure based on AUC. Placental transfer of gemifloxacin was shown in the rat with maternal plasma to foetal ratios of 1 to 2. In the study on pre-postnatal development, head and eye malformations were observed for offspring of the high dose group as were lower body weights

compared to controls at birth and during lactation. These findings occurred at a mean systemic exposure of about 8-times that in women given the therapeutic dose of gemifloxacin. Offspring neurobehavioral and reproductive functions were not affected at any dose. Gemifloxacin and its metabolites were excreted into the milk of lactating rats with milk levels being up to 15-times higher than plasma levels.
Gemifloxacin's antigenic potential was examined in Guinea pigs using an active anaphylaxis test and a study to generate anti gemifloxacin antibodies, further, in mice using a passive cutaneous anaphylaxis test and a passive haemagglutination test. It is concluded that gemifloxacin was not antigenic in these systems.
In a single dose phototoxicity study in hairless mice gemifloxacin was a less potent photosensitiser than lomefloxacin or enoxacin but roughly equipotent to ciprofloxacin. In a subchronic oral (gavage) study on dermal phototoxicity in hairless mice gemifloxacin did not induce any dermal phototoxicity.
The Rapporteur appreciates the commitment of the applicant to submit the missing phase II additional data and asks the applicant to clarify at which time these data will be available. Additionally to the announced studies the applicant is asked to submit the study protocols for the determination of the n-octanol-water-partition coefficient.
The study (OECD 301B) to determine the biodegradability of the active ingredient gemifloxacin can be assessed as valid and plausible. The study results show that after 28 days the active ingredient gemifloxacin was degraded to 31 %. Therefore gemifloxacin can be considered as not readily biodegradable and a water-sediment-study according to OECD 308 should be presented.

III.3 Clinical aspects

Pharmacokinetics

In the overall clinical pharmacology program, the pharmacokinetics of oral gemifloxacin have been assessed in a variety of clinical pharmacology studies that included 1197 healthy volunteer subjects, 12 healthy elderly volunteers, 46 patients with renal impairment (including 12 patients who were maintained on chronic haemodialysis), and 33 patients with hepatic insufficiency.

In addition, the population pharmacokinetics of gemifloxacin were characterised in patients with community-acquired infections as community acquired pneumonia [CAP], acute exacerbation of chronic bronchitis [AECB], acute bacterial sinusitis [ABS] and complicated urinary tract infection [UTI] during the Phase III program.

The absolute bioavailability of gemifloxacin is, on average, 61% and limited by the extent of absorption rather than by significant first-pass metabolism. Absorption of gemifloxacin is rapid, with maximum serum/plasma concentrations generally observed between 0.5 and 2.0 hours post-dose at all dose levels in the fasted state. Thereafter, gemifloxacin concentrations generally decline in a bi-exponential manner, with a terminal phase half-life (T1/2) of approximately 7 hours (4-12 hours), irrespective of dose. The pharmacokinetics of gemifloxacin are approximately linear over the dose range of 20 mg to 800 mg, although mean Cmax tend to increase slightly less than proportionately with increasing dose between 600 mg and 800 mg. Following oral administration of gemifloxacin, AUC and Cmax data exhibit low intra-subject (CVs of 25% and 23%, respectively) and inter-subject (CVs of 27% and 30%, respectively) variability. Following repeat administration of gemifloxacin, there is virtually no accumulation of gemifloxacin at doses up to 640 mg once daily in young subjects and up to 480 mg once daily in the elderly. Urinary excretion of gemifloxacin generally accounts for 20%-40% of the administered dose.
Gemifloxacin is widely distributed into tissues. It is not extensively bound to plasma proteins (70%) and plasma protein binding is independent of concentration up to at least 50-fold higher concentrations than those seen clinically. Concentrations in bronchoalveolar macrophages, bronchial mucosa and nasal secretion exceeded those in plasma while concentrations in epithelial lining fluid were similar to those in plasma.

Gemifloxacin is not extensively metabolised and is excreted predominantly unchanged (approximately 65% of dose) following oral administration. Biotransformation pathways appear to be independent of the dose route. Gemifloxacin is also the predominant drug-related component in plasma up to 12 hours after dosing. The metabolites are minor and include those arising from glucuronidation, N-acetylation and isomerisation. The involvement of cytochrome P450 enzymes in the metabolism of gemifloxacin is negligible. The acyl and carbamyl glucuronides have been observed in plasma and urine.
In patients with a creatinine clearance of $\geq$ 40mL/min dose reduction is not necessary.

There is no major impact of gender and race on the pharmacokinetic of gemifloxacin while weight and age influence PK-data but the observed changes are not considered of clinical impact.

Gemifloxacin did not inhibit any of the important hepatic cytochrome P450 enzymes including CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 or CYP4A9/11 at concentrations at least 50-fold greater than those achieved clinically. Therefore, gemifloxacin would not be predicted to affect the pharmacokinetics of other drugs via a mechanism mediated by cytochrome P450 enzymes. In preclinical studies, gemifloxacin was not an inducer of important hepatic cytochrome P450 enzymes. Furthermore, involvement of cytochrome P450 enzymes in the metabolism of gemifloxacin is negligible and other drugs that inhibit or induce P450 enzymes would not be predicted to alter the pharmacokinetics of gemifloxacin.

Urinary excretion data for gemifloxacin suggested that active renal secretion might be involved, at least in part, in gemifloxacin elimination, and hence the possibility of competition with other drugs for active transport could not be entirely excluded. Therefore the effect of co-administration with probenecid was studied to investigate the effect of inhibition of active renal secretion on gemifloxacin elimination. The data and analyses of these studies indicate that interactions are not a major problem with gemifloxacin.

The PK of gemifloxacin has been intensively studied and the data provided by the Applicant allow for an appropriate PK characterisation of gemifloxacin in healthy volunteers and patients in the sought indications.

Pharmacodynamics

Gemifloxacin has a in-vitro antibacterial activity against *S. pneumoniae, H. influenzae, M. catarrhalis, L. pneumophila, C. pneumoniae,* and *M. pneumoniae*, which are commonly responsible for community acquired respiratory tract infections. The minimum bactericidal concentrations (MBCs) of gemifloxacin are similar to its minimum inhibitory concentrations (MICs).

The use of subinhibitory concentrations *in vitro* leads to a significant increase in MICs towards gemifloxacin. For many pathogens, the potential of gemifloxacin to induce resistance is lower than the potential of ciprofloxacin. Of note, mutant prevention concentration (MPC) of gemifloxacin was lower compared to other quinolones.

Fluoroquinolones exhibit concentration-dependent bactericidal activity. Pharmacodynamic studies of fluoroquinolones in animal infection models and in human trials have indicated that the primary determinant of efficacy is the AUC_{24}/MIC_{90} ratio. For fluoroquinolones the target AUC_{24}/MIC_{90} ratio associated with efficacy is $\geq$ 125, except for *S. pneumoniae* for which an AUC_{24}/MIC_{90} ratio $\geq$ 30 is considered acceptable. A target C_{max}/MIC_{90} ratio of 10 predicts a high probability of efficacy and a low potential for development of resistance. Gemifloxacin has demonstrated high free drug AUC_{24}/MIC_{90} ratio compared to other quinolones used to treat respiratory tract infections (levofloxacin, gatifloxacin, and moxifloxacin).
Gemifloxacin demonstrates a Post-Antibiotic Effect (PAE) of >6 hours at four-times the minimum inhibitory concentration (MIC) against *H. influenzae* and *P. aeruginosa*. These concentrations are easily

achieved in serum at the recommended dose. For other species, including *S. pneumoniae* and *M catarrhalis*, PAE's are similar to those of other quinolones (0.5-1.5 hours).

Clinical efficacy

Community acquired pneumonia, of mild to moderate severity (CAP):
Overall, a total of 7 clinical studies were conducted in accordance with Good Clinical Practice (GCP) to support the use of gemifloxacin 320 mg once daily for the treatment of CAP. A total of 2055 patients with CAP received treatment with gemifloxacin 320 mg once daily versus 926 patients treated with an active comparator. The clinical program was originally based on clinical studies evaluating the efficacy of gemifloxacin administered for at least 7 days in the treatment of CAP and included four pivotal studies, three of which were double-blind, randomised, active-controlled studies (Studies 011, 012, and 049) and one open label, active-controlled study (Study 185). In the clinical studies 012, 049 and 185 the total treatment duration for both gemifloxacin and active comparator could be extended from 7 to 14 days if the patient had a severe infection, a probable or confirmed diagnosis of pneumonia due to an atypical pathogen, or otherwise at the investigator's discretion. The clinical trial program was subsequently completed with Study OP-634-001, conducted to demonstrate that a 5-day regimen of gemifloxacin 320 mg once daily is equivalent in terms of efficacy to the 7-day regimen. In addition to the controlled studies, two supportive uncontrolled studies (Studies 061 and 287) were conducted.
Patients aged ≥ 18 years with a diagnosis of CAP based both on clinical and radiological findings and, where appropriate, on a microbiological confirmation of the diagnosis obtained from pre-entry specimens, were enrolled in the clinical trials. Generally, patients at entry were required to have a clinical diagnosis of CAP characterised by fever and at least two of the following signs and symptoms: new or increased cough, purulent sputum, or a change in sputum characteristics, auscultatory findings on pulmonary examination of rales and/or evidence of pulmonary consolidation (dullness on percussion, crackles on auscultation, bronchial breathing) or dyspnoea. Patients were also to have had a chest radiograph showing the presence of new or progressive infiltrate(s), consolidation, or pleural effusion consistent with pneumonia.

The following table summarises the most important features of the CAP studies:

Protocol No.	No. of Centres: Location	Study Design	Treatment Dose	Treatment Duration
Study 011	102 Centres: France Poland South Africa	Randomised, double-blind, double-dummy, parallel-group	Gemifloxacin 320 mg od oral or Co-amoxiclav 1g/125 mg tid oral	Gemifloxacin 7 days Co-amoxiclav 10 days
Study 012	109 Centres: US, Canada, Europe, Switzerland ,South Africa	Randomised, double-blind, double-dummy, parallel-group	Gemifloxacin 320 mg od oral or Cefuroxime axetil 500 mg bid oral + Clarithromycin 500 mg bid oral	Gemifloxacin 7-14 days Cefuroxime (1-7 days) + Clarithromycin 1-13 days
Study 049	72 Centres: Mexico, Spain, US	Randomised, double-blind, double-dummy, parallel-group	Gemifloxacin 320 mg od oral or Trovafloxacin 200 mg od oral	Gemifloxacin 7-14 days Trovafloxacin 7-14 days

Study 185	69 Centres: Australia, Europe, Guatemala, Lebanon, Philippines, Singapore and North America	Randomised, open, parallel-group	Gemifloxacin 320 mg od oral or i.v. Ceftriaxone 2 g od followed by Cefuroxime 500 mg bid oral ± macrolide	Gemifloxacin 7-14 days Ceftriaxone/ Cefuroxime 7-14 days
Study OP-634-001	68 Centres: Bulgaria, Croatia, Czech Republic, Lithuania, Poland, Romania, Russia, Ukraine, and US	Randomised, double-blind, parallel-group	Gemifloxacin 320 mg od oral	**Gemifloxacin 5 days** Gemifloxacin 7 days
Study 061	42 Centres: Central and S. America, Hong Kong, Hungary, SE Asia, Pakistan, Saudi Arabia, UK	Open-label	Gemifloxacin 320 mg od oral	Gemifloxacin 7 days
Study 287	45 Centres: Asia, US, Mexico, Philippines	Open-label	Gemifloxacin 320 mg od oral	Gemifloxacin 7 or 14 days

Results:
Pathogens at baseline (Screening Visit) reflect the expectations for mild to moderate CAP. The numbers of most of the pathogens are considered to sufficiently allow for pathogen specific assessment of efficacy, except legionella. In addition, there are some imbalances between the treatment groups regarding baseline pathogens.
Regarding the severity of the disease, the studies comparing gemifloxacin with different comparators are considered to appropriately cover mild and moderate disease. Contrarily, the comparison of gemifloxacin 7 days to gemifloxacin 5 days is mainly based on mild cases according to the classification of Fine, with 89.8% of the patients in the 5 day treatment arm showing mild CAP. Only 8.6% (22 patients) of the 5 day treatment group and 8.3% (21 patients) of the seven day treatment group were judged as moderate.

Consequently, the Applicant was asked to answer the following question (Part of Major Objection C1 in the Day 120 LoQ):

- Patient population and outcome according to Fine classification.

At present the indication for treatment of CAP of mild to moderate severity with treatment duration of 5 days cannot be supported by the data provided. In the three double blind, active controlled studies (011, 012, 049) the majority of patients (i.e. 71,4%) had CAP of mild severity (as retrospectively scored as Fine classes I-II) and only 17.4% of patients had CAP of moderate severity (Fine class III). Furthermore, the study of 5 days gemifloxacin versus 7 days gemifloxacin for CAP (OPC-634-001) is mainly based on mild cases, with 89.8% of the patients of the 5 day treatment arm classified as Fine class I or II. Only 8.6% (22 patients) of the 5 day group and 8.3% (21 patients) of the 7 day group were classified as Fine class III, showing moderate CAP. No analyses of outcome by Fine class were provided.

The Applicant provided the analyses of outcome by Fine class. According to these data, efficacy of gemifloxacin 7 day treatment compared to the pooled comparators is comparable between the treatment groups in both the ITT and PP populations.
In addition, the Applicant provided an efficacy analysis stratified by need for hospitalisation. According to this data, 59% of the patients in the gemifloxacin group and 58% of the comparator group required hospitalisation (ITT population). Regarding efficacy, gemifloxacin was comparable effective as the pooled comparators in both the in-patients and the out-patients. However, data analysis based on need for hospitalisation is somewhat subjective and the need for hospitalisation does not necessarily indicate the severity of the disease. Practises vary widely re threshold for hospitalisation according to the healthcare

system set-up. Hospitalisation in mild CAP is not commonly employed unless there are underlying factors that increase the overall risks of a lung infection. Thus the need for hospitalisation in about 60% of the patients studied does not necessarily indicate that these patients treated with gemifloxacin for 7 days had no mild CAP.

The percentage of patients with Fine class III disease was low in the CAP studies (17.2% and 19.3% for the gemifloxacin and the comparators, resp.). When looking at absolute numbers, 163 patients with moderate CAP were treated with gemifloxacin 7 days in all CAP studies. The efficacy results in this patient group are nevertheless considered to support the efficacy of gemifloxacin in moderate CAP for the following reason:
Applying Fine classification, 29% (271 patients) of the patients treated with gemifloxacin for 7 days had moderate to severe CAP. In the 108 patients classified as Fine class IV or V (severe CAP) efficacy of gemifloxacin 7 days again was similar compared to the pooled comparators. Although data in the patients with severe CAP were not measured in the sought indication, these data support the efficacy of gemifloxacin in CAP exceeding mild severity.

Outcomes:
The next table shows the clinical response at follow up in the controlled Phase III studies.

Clinical response at follow-up: controlled studies 011, 012, 049, 185, and OP-634-001 (follow-up clinical PP and clinical ITT populations)

	Study 011		**Study 012**		**Study 049**[1]		**Study 185**		**Study OP-634-001**	
	Gemifloxacin 320 mg od 7 day	**Amox/clav 1 g/125 mg tid 10 day**	**Gemifloxacin 320 mg od 7-14 day**[3]	**Cefuroxime + Clarithromycin 1-7 + 1-13 day**	**Gemifloxacin 320 mg od 7-14 day**[3]	**Trovafloxacin 200 mg od 7-14 day**[3]	**Gemifloxacin 320 mg od 7-14 day**[3]	**Ceftriaxone IV, Cefuroxime oral 7-14 day**[3]	**Gemifloxacin 320 mg od 7 day**	**Gemifloxacin 320 mg od 5 day**
Clinical PP Follow-up	N=115	N=113	N=251	N=257	N=215	N=207	N=116	N=121	N=227	N=242
Success, n (%)	102 (88.7)	99 (87.6)	220 (87.6)	238 (92.6)	202 (94.0)	186 (89.9)	107 (92.2)	113 (93.4)	209 (92.1)	230 (95.0)
Treatment Difference* (95% CI)	1.1 (-7.3, 9.5)		-5.0 (-10.1, 0.2)		4.1 (-1.1, 9.3)		-1.15 (-7.73, 5.43)		-2.97 (-7.42, 1.48)	
Clinical ITT	N=167	N=153	N=319	N=321	N=289	N=280	N=172	N=173	N=254	N=256
Success, n (%)	129 (77.2)	121 (79.1)	250 (78.4)	272 (84.7)	253 (87.5)	227 (81.1)	130 (75.6)	136 (78.6)	221 (87.0)	237 (92.6)
Treatment Difference* (95% CI)	-1.8 (-10.9, 7.2)		-6.4 (-12.4, -0.4)[2]		6.5 (0.5, 12.4)		-3.03 (-11.89, 5.83)		-5.57 (-10.81, -0.34)	

ITT = intent to treat; PP = per protocol; i.v. = intravenous; od = once daily; tid = three times daily; Amox/clav=amoxicillin/clavulanate

*Gemifloxacin 320 mg od success rate minus comparator success rate.

[1]Data refer to Abridged report of Study 049 (i.e. after exclusion of patients of GCP-failed site)

[2]Values in the multiple imputation (MI) analysis: treatment difference, -2,7; 95% CI, -7.6 to 2.2.

[3]Treatment was to be administered for a minimum of 7 days; however treatment could be extended to 14 days if the patient had a severe infection, if the pneumonia was confirmed or suspected to be due to an atypical pathogen, or otherwise at the investigators discretion.

Source: Report 100ZW1/1 (Study 011); Report 100ZW2/1 (Study 012); Report 100WPJ/1 and Report 101NMS/1 (Study 049); Report 1017ZS/1 (Study 185); Report OP-634-001 (Study OP-634-001)

Comparison of the 5 day to the 7 day treatment:
The study addressing the comparison of the 7 day treatment of CAP with the 5 day treatment showed at least non-inferiority of the 5 day treatment over the 7 day treatment. However, about 90% of the patients included suffered from mild CAP. Thus, the treatment duration of 5 days can not be accepted for the treatment of moderate CAP. (Major Objection 1)

The Applicant was asked to answer the following question (Part of Major Objection C1 in the Day 120 LoQ):

- Use of 5 days gemifloxacin for CAP.

Additionally, 5 day treatment with gemifloxacin was not compared to a licensed antibacterial agent. The lack of at least one study of 5 days gemifloxacin against an appropriate comparative regimen in a population relevant to the indication claimed cannot be accepted.

As expected, the Applicant does not provide new data. This argumentation is based on the fact that gemifloxacin is approved for 7 day treatment of CAP outside the EU which would make it a suitable comparator. According to the "Note for Guidance on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95/rev.1)" it is possible "that the comparator that is considered optimal may not be approved in some or all EU Member States for the indication under study". However, as long as the 7 day treatment is not accepted, it is not an appropriate comparator and to consider gemifloxacin "optimal" is not supported for the time being.
Besides this more formal reasoning, the question of acceptability of the 5 day treatment addresses the need for a study "in a population relevant to the indication claimed". As already stated in the first part of question C1, less than 10% (corresponding to about 20 patients in each treatment group) of the patients in study OPC-634-001 had moderate CAP. This number is not considered adequate to sufficiently address the question of efficacy of gemifloxacin 5 day treatment in moderate CAP. Reduced efficacy due to reduction of treatment duration is not considered to occur in the same frequency in mild and moderate CAP.

As the efficacy of gemifloxacin in treatment of CAP caused by legionella was seriously questioned in the Day 80 ARs of the Rapporteurs, the Applicant was asked to answer the following question (Part of Major Objection C1 in the Day 120 LoQ):

- Use of 5 days gemifloxacin to treat atypical pneumonia.

Across the studies that evaluated 7 days gemifloxacin with extension allowed to 14 days efficacy in infections ascribed to M. pneumoniae or C. pneumoniae appeared to be similar between gemifloxacin and comparators. Numbers of L. pneumophila treated are smaller and there is a suggestion that gemifloxacin might not be as good as comparators. For these cases the applicant should clarify the proportions that were diagnosed based solely on serology as opposed to culture, the proportions that received >7 days therapy and the outcomes by duration of therapy.
In the only study that evaluated 5 days gemifloxacin the numbers of M. pneumoniae or C. pneumoniae treated and assessed at follow-up were relatively small but suggested a possible advantage for 7 days over 5 days. In addition, there were no cases of L. pneumophila. Currently the use of 5 days gemifloxacin for such infections cannot be accepted.

The Applicant provided new analyses on the efficacy of gemifloxacin in the treatment of atypical pneumoniae based on treatment duration. Although the number of the pathogens causing atypical pneumonia is low in the CAP studies, and almost all were based solely on serology, the following conclusions can be drawn:
Chlamydophila pneumoniae:
For direct comparison of 5 day to 7 day treatment (study OP-634-001) only 20 patients are available in the 5 day treatment regimen and 33 in the 7 day regimen (Bacteriological ITT population). The small differences between the treatment groups are always in favour for the 7 day regimen but are hard to assess

due to the small numbers. However, efficacy in the 7 day regimen is at least 93.9% (Bacteriological ITT at FU).
Comparison of all CAP studies except study OP-634-001 reveals a numerical advantage of the > 7 day regimen compared to the ≤ 7 day regimen, especially in the bacteriological ITT population at EOT. Thus, there are some indications that the treatment duration is critical for the efficacy in atypical pneumonia due to *C. pneumophila*.
Mycoplasma pneumoniae:
For direct comparison of 5 day to 7 day treatment (study OP-634-001) the number of patients available in the 5 day treatment regimen (n=27) and in the 7 day regimen (n=21) is similar than with *C. pneumophila* (Bacteriological ITT population). Again, the small differences between the treatment groups are always in favour for the 7 day regimen but are hard to assess due to the small numbers. As with Chlamydia pneumoniae, 7 day treatment results in high efficacy rates (always 100% at EOT, 95% at FU).
Comparison of all CAP studies except study OP-634-001 reveals a clear numerical advantage of the 7 day regimen compared to the ≤ 7 day regimen, in the bacteriological ITT and PP population both at EOT and Follow up. As the numbers of patients with *Mycoplasma* infection is quite acceptable (98 patients ≤ 7 days, 54 patients > 7 days) these data clearly show that the treatment duration is important in the treatment of CAP due to *M. pneumoniae*.
Legionella pneumophila:
This pathogen was not included in study OP-634-001.
Comparison of all CAP studies except study OP-634-001 reveals a numerical advantage of the > 7 day regimen compared to the ≤ 7 day regimen, in the bacteriological ITT and PP population both at EOT and Follow up. Although data are hard to assess due to the very small numbers, the advantage of the > 7 day regimen is consistently found in all analyses.
Taken together, data available indicate that the efficacy of gemifloxacin in atypical pneumonia caused by *Legionella*, *Mycoplasma* or *Chlamydophila* depends on treatment duration.
For *Chlamydia pneumophila* and *Mycoplasma pneumoniae* data are considered to support a 7 day treatment regimen. This assessment is based on the current guideline (CPMP/EWP/558/95 rev. 1) which considers at least 20 treated cases due to a single species within any one indication to denote that efficacy has been demonstrated. Five days are not supported as the available data indicate inferiority compared to 7 days.

Regarding *Legionella pneumophila*, no data on 5 day treatment are available and data comparing ≤ 7 and > 7 days even indicate that 7 day treatment seems not be appropriate. This has to be adequately addressed in the SPC. Therefore, the following wording should be included in section 4.4 of the SPC:

The efficacy of gemifloxacin for 7 days treatment of pneumonia caused by legionella is unproven. Patients with evidence of legionella should not be treated with gemifloxacin. If legionella pneumonia is discovered after starting gemifloxacin treatment, therapy should be switched substances recommended for the treatment of legionella pneumonia.

Conclusion on the efficacy in CAP
Efficacy data in the population studied is considered to support the indication "Community acquired pneumonia, of mild to moderate severity (see section 4.2)". However, the available data do not support the efficacy of 5 day treatment due to the low number of patients with moderate CAP and the reduced efficacy of shorter treatment towards pathogens causing atypical pneumonia.
In consequence, the posology has to be changed to 7 days for standard treatment resulting in the need for a new benefit/risk assessment of the indication CAP due to the increased frequency of rash and severe rash associated with the 7 day treatment compared to the 5 day treatment.
In addition, the SPC must adequately warn against using gemifloxacin even at 7 days to treat suspected or proven legionella infections.

Acute exacerbation of chronical bronchitis (AECB):

Overall, a total of 11 clinical studies were conducted according with Good Clinical Practice (GCP) in more than 2500 patients to evaluate the efficacy and safety of gemifloxacin 320 mg administered once daily for 5 days in the treatment of AECB.

The clinical program consists of three pivotal double blind, randomised, active-controlled clinical studies (Studies 068, 070 and 212), two active controlled (one double blind and one open label) supportive studies (Studies 069 and 207) and six ancillary clinical studies (Studies 001, 008, 061, 105, 112, and 139). The definition of ancillary applied to studies meeting one or more of the following conditions: open label studies, non comparative studies, studies performed using different treatment regimen from gemifloxacin 320 mg od for 5 days, or studies with a different primary endpoint than the clinical response at follow-up.

A summary of the main features of the clinical studies in AECB is presented in the next table.

The inclusion criteria of the pivotal studies aimed at selecting a study population that was representative of patients with well-defined AECB, without serious complications and suitable for treatment with an oral antibiotic. Male or female patients aged ≥ 40 years were selected if they met standard clinical criteria for AECB including a history of chronic bronchitis characterized by cough and sputum production for more than two consecutive years and for most days in a consecutive three month period, and a current episode of AECB characterized by increased purulent sputum together with increased cough and increased dyspnoea.

A more severe patient population was selected in the supportive Study 207, which included hospitalised patients presenting with any one of the following conditions: age > 65 years, airflow limitation (FEV_1 < 50% of predicted normal), at least 4 episodes of AECB in the last year requiring antibacterial treatment, cardio-respiratory co-morbidity, or three co-morbidity markers among cardiovascular, musculoskeletal, central nervous system, endocrine, haematologic, or hepatic system organ. Similarly, Study 105 and Study 112 included patients presenting with any one of the following conditions: age ≥ 65 years, FEV_1 < 50% of predicted normal, at least 4 episodes of AECB per year requiring antibacterial treatment, or any other co-morbidity.

Generally, patients who had complicating infections, diseases, or concomitant therapy that would compromise evaluation of the study outcome, or pneumonia, were excluded from study participation. Other standard exclusion criteria included the presence of severe renal impairment, impaired liver function and (in female patients) pregnancy, lactation, or inadequate birth control method.

Table 1. Studies with gemifloxacin on AECB

Protocol No.	No. of Centres: Location	Study Design	Treatment Dose	Treatment Duration	Primary/secondary efficacy endpoints	Number Enrolled / ITT / Completed
Principal Controlled Studies						
Study 068*	91 Centres: Austria, Canada, France, Germany, Mexico, UK, US	Randomised, double-blind, double-dummy, parallel-group	Gemifloxacin 320 mg od oral or Clarithromycin 500 mg bid oral	Gemifloxacin 5 days Clarithromycin 7 days	Primary: clinical response at follow-up Secondary: clinical response at other time points; bacteriological response rates and eradication of *H. influenzae*	Gemifloxacin 340/340/303 Clarithromycin 351/348/309
Study 070	112 Centres: Belgium, UK, Denmark, Estonia, Finland, France, Germany, Ireland, Norway, Sweden	Randomised, double-blind, double-dummy, parallel-group	Gemifloxacin 320 mg od oral or Amoxicillin/clavulanate 500/125 mg tid oral	Gemifloxacin 5 days Amoxicillin/ clavulanate 7 days	Primary: clinical response at follow-up Secondary: clinical response at other time points; bacteriological response rates	Gemifloxacin 304/304/287 Amoxicillin/ clavulanate 296/296/275
Study 212	61 Centres: Germany, UK, US	Randomised, double-blind, double-dummy, parallel-group	Gemifloxacin 320 mg od oral or Levofloxacin 500 mg od oral	Gemifloxacin 5 days Levofloxacin 7 days	Primary: clinical response at follow-up Secondary: clinical response at other time points; bacteriological and therapeutical response rates	Gemifloxacin 182/182/175 Levofloxacin 179/178/160
Supportive studies						
Gemifloxacin 303/302/287 Trovafloxacin 314/314/283	100 Centres: Austria, Belgium, France, Germany, Nederlands, Poland, Switzerland, UK	Randomised, double-blind, double-dummy, parallel-group	Gemifloxacin 320 mg od oral or Trovafloxacin 200 mg od oral	Gemifloxacin 5 days Trovafloxacin 5 days	Primary: clinical response at follow-up Secondary: clinical response at other time points; bacteriological response rates	Gemifloxacin 303/302/287 Trovafloxacin 314/314/283
Study 207	112 Centres: Belgium, Hungary, Italy, Mexico, Nederland, Poland, South Africa, UK	Randomised, open-label	Gemifloxacin 320 mg od oral or Ceftriaxone 1g od i.v. followed by Cefuroxime 500mg bid oral	Gemifloxacin 5 days Ceftriaxone/ cefuroxime 1-3/7 days	Primary: clinical response at follow-up Secondary: clinical response at other time points; bacteriological response rates; time to discharge from hospital; quality of life; cost-efficacy; time to switch from i.v. to oral therapy	Gemifloxacin 138/138/130 Cefriaxone/ cefuroxime 136/136/120

Protocol No.	No. of Centres: Location	Study Design	Treatment Dose	Treatment Duration	Primary/secondary efficacy endpoints	Number Enrolled / ITT / Completed
Ancillary Studies						
Study 008**	53 Centres: Canada, US	Randomised, double-blind, double-dummy, parallel-group	Gemifloxacin 320 mg od oral or Levofloxacin 500 mg od oral	Gemifloxacin 7 days Levofloxacin 7 days	Primary: clinical response at follow-up Secondary: clinical response at other time points; bacteriological response rates	Gemifloxacin 280/280/247 Levofloxacin 281/281/254
Study 061	42 Centres: Argentina, Chile, Colombia, Costa Rica, Ecuador, Guatemala, Hong Kong, Hungary, Indonesia, Malaysia, Mexico, Pakistan, Peru, Philippines, Saudi Arabia, Singapore, Taiwan, Thailand, UK	Open, non-comparative	Gemifloxacin 320 mg od oral	Gemifloxacin 7 days	Primary: clinical response at follow-up Secondary: clinical response at other time points; bacteriological response rates	Gemifloxacin 477/477/419
Study 112	256 Centres: Australia, Brazil, Canada, Germany, Ireland, Mexico, Nederlands, Poland, UK, US	Randomised, double-blind, double-dummy, parallel-group	Gemifloxacin 320 mg od oral or Clarithromycin 500 mg bid oral	Gemifloxacin 5 days Clarithromycin 7 days	Primary: time to next exacerbation of chronic bronchitis Secondary: clinical response; time to resolution; quality of life; health-economic assessment	Gemifloxacin 908/903/820 Clarithromycin 897/896/791
Study 105	15 Centres: Austria, Czech Republic, Poland, Sweden, UK, US	Randomised, double-blind, double-dummy, parallel-group	Gemifloxacin 320 mg od oral or Clarithromycin 500 mg bid oral	Gemifloxacin 5 days Clarithromycin 7 days	Primary: none Secondary: clinical and bacteriological response; time from follow-up to the next AECB episode; rates of eradication; signs and symptoms; quality of life; lung function; inflammatory parameters; sputum cytology	Gemifloxacin 83/83/73 Clarithromycin 80/80/73

Study 139	56 Centres: Canada, US	Double-blind, observational, parallel follow-up of Study 068	Gemifloxacin 320 mg od oral or Clarithromycin 500 mg bid oral	Gemifloxacin 5 days Clarithromycin 7 days	Primary: rates of resolution of the AECB episode with no recurrence; Secondary: quality of life; health-economic assessment	Gemifloxacin 83/83/73 Clarithromycin 80/80/73
Study 001***	43 Centres: Belgium, Canada, France, Germany, Ireland, Nederlands, UK, US	Randomised, double-blind, double-dummy, parallel-group	Gemifloxacin 80, 160 or 320 mg od oral or Ofloxacin 400 mg bid oral	Gemifloxacin 80, 160 or 320 mg 10 days Ofloxacin 10 days	Primary: clinical response at follow-up Secondary: clinical response at other time points; bacteriological response rates	Gemifloxacin 80mg 66/66/55 Gemifloxacin 160mg 64/63/55 Gemifloxacin 320mg 61/61/46 Ofloxacin 68/67/56

ITT = intent-to-treat; UK=United Kingdom; US = United States; yr = year; i.v.= intravenous; od = once daily; bid = twice daily; tid = three times daily

*The patient data listed for this study exclude data from a total of 21 patients (11 gemifloxacin, 10 clarithromycin) enrolled by two disqualified investigators (Dr. DeAbate/Dr. Sokol).

**The patient data listed for this study exclude data from a total of 25 patients (13 gemifloxacin, 12 levofloxacin) enrolled by one disqualified investigator (Dr. Mathew).

*** The patient data listed for this study exclude data from a total of 10 patients (3, 4, and 1 patients randomly assigned to treatment with gemifloxacin 320 mg, 160 mg and 80 mg, respectively) enrolled by one disqualified investigator (Dr. DeAbate)

Results:
Baseline:
In the principal controlled AECB studies, treatment groups were generally well matched with respect to demographic and disease related baseline characteristics (Table 4). As usually observed in AECB studies, patients were generally elderly and had suffered from chronic bronchitis for several years (average of 12-14 years).
Pathogens at baseline as reported by the Applicant are quite balanced. Most obvious differences in the number of baseline pathogens are *H. influenzae* and *S. aureus* in study 070. These differences are considered not assessable due to the low number of pathogens. In study 212 there is a remarkable difference in the total number of pathogens recovered between the two treatment arms (24.2% gemifloxacin versus 33.5% levofloxacin).
The low number of pathogens recovered is most prominent in studies 068 and 070 (pathogens recovered in about 15% of patients), whereas in study 212 in 24.2% of the patients in the gemifloxacin arm and in 33.5% of patients in the levofloxacin arm pathogens were recovered. These data raises the question about the study population and the need for antibiotic therapy in the study population especially in studies 068 and 070. In all pivotal AECB studies, no data on the frequency of atypical pathogens or viruses were found in the study protocols. Additionally, no data on the number of patients requiring hospitalisation, showed an increased dyspnoea or needed ventilation were given.

Outcomes:
The next table shows the clinical response at follow up in the pivotal Phase III studies.
Table 10. Clinical response at follow-up (test of cure): pivotal AECB studies 068, 070, 212

	Clinical success rate		
	Gemifloxacin % (n/N)	**Comparator % (n/N)**	**Treatment difference % (95% CI)**
Clinical PP Population			
068	86.0 (239/278)	84.8 (240/283)	1.2 (-4.7, 7.0)
070	93.6 (247/264)	93.2 (248/266)	0.3 (-3.9, 4.6)
212	88.2 (134/152)	85.1 (126/148)	3.0 (-4.7, 10.7)
ITT Population			
068	80.0 (272/340)	78.2 (272/348)	1.8 (-4.2, 7.9)
070	88.5 (269/304)	88.9 (263/296)	-0.4 (-5.4, 4.7)
212	85.2 (155/182)	78.1 (139/178)	7.1 (-0.9, 15.1)

Source: Report 100WPL/1 and Abridged Report 101NN1/1 (Study 068); Report 100ZW7/1 (Study 070); Report 101LP2/1 (Study 212)

Analysis across studies:
Pathogen specific efficacy analysis across the studies revealed a activity of gemifloxacin against the main pathogens causing AECB in the patient population studied comparable to the activity of the pooled comparators. In this pooled analysis, the number of pathogens is considered adequate to assess the efficacy of gemifloxacin regarding eradication of the pathogens. Overall, the eradication rate which is 84.7% in the Bacteriology ITT at the EOT decreases to 71.7% at Follow up (i.e. 10 to 15 days after EOT).

The deficiencies of the AECB studies were addressed in the Major Objection 2 of the Day 120 LoQ:

The sponsor chose to classify patients with AECB according to a 1998 publication. The majority of patients were classified as having Stage 2 AECB with only a small proportion of patients meeting the definition of severe Stage 3 AECB. The applicant has not discussed how these categories might relate to the very many published opinions regarding selection of patients who might actually derive a benefit from antibacterial therapy. In addition, with no placebo controlled studies it is not possible to determine from

the overall body of data whether gemifloxacin or comparators were exerting a clinically important effect on outcomes.
The lack of a clear demonstration of benefit associated with gemifloxacin therapy in patients with AECB and the fact that even 5 days of treatment is associated with an excess risk of rash (regardless of gender and age group) over comparators means that the risk-benefit relationship cannot be considered to be favourable for this indication.

The Applicant provided new analyses based on reclassification of the severity of AECB by applying the Anthonisen criteria. According to the data of the Applicant, the vast majority of patients exhibited clinical signs of acute exacerbation which are in line with Type I in the Anthonisen classification. This type is considered the most severe type. In 76% of the patients acute exacerbation set on moderate to severe COLD according to the GOLD criteria. However, severity of the disease of the patients included is still questioned, as only one supportive study included hospitalised patients (Study 207). To proof the possible benefit of antibiotics in the patient population included in the pivotal studies requires superiority studies either to placebo or an approved antibiotic.
According to the analyses and recommendations of the recent systematic review of the Cochrane Centre quoted by the Applicant (Ram FSJ et all., First published 19.04.06) "in exacerbations of COPD associated with increased cough and sputum purulence, antibiotic therapy, regardless of choice, significantly decreases short-term mortality, treatment failure and sputum purulence". However, this conclusion is further restricted by the authors. "Analyses restricted to community-based studies did not find differences between antibiotic and placebo." Of note, only 4 of the 11 studies included in this Cochrane review came to the conclusion that the patients benefit from antibiotics. Thus, based on this review, antibiotic treatment of AECB outside the hospital is not established.
All pivotal studies conducted were community-based except the supportive study 207 which included hospitalised patients only. This study, however, is not considered to support the indication as it is not a pivotal study and has some important deficiencies (e.g. inconsistency of clinical and bacteriological results).
Not to conduct a placebo-controlled study for ethical reasons is not supported except for very severely ill patients (i.e. patients requiring mechanic ventilation). This is in line with the recent draft of the FDA guidance for industry on AECB/COPD which clearly recommends superiority studies in this indication and the FDA draft guidance on non-inferiority studies, which proposed that such a design would not be considered acceptable for AECB. The "Note for Guidance on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections (CPMP/EWP/558/95/rev.1)" currently states "If a placebo-controlled study is possible, this would be desirable and applicants should discuss the provision of such a study as part of the clinical development programme with EU Regulators." In the patient population studied, placebo-controlled or comparator-controlled superiority studies are possible and necessary.

Conclusion on the efficacy of gemifloxacin in the sought indication AECB:
The indication AECB is not a suitable indication for gemifloxacin due to the lack of superiority studies which are considered absolutely necessary in the patient population included in the pivotal studies.

Clinical safety

Gemifloxacin mesilate is an antibiotic related to the fluoroquinolone class currently on the market under the name of Factive® tablets in the US (where it was launched in September 2004) and in Korea, South Africa, Jordan, Russia and Canada. Approved indications include the treatment of community acquired pneumonia (CAP) and acute bacterial exacerbation of chronic bronchitis (AECB) both with a 5 days treatment regimen.

The safety profile of gemifloxacin has been extensively characterised by means of:

- A large clinical development program where more than 8000 patients mainly with respiratory tract infections received oral administrations of gemifloxacin 320 mg once daily up to 14 days of treatment.
- A large clinical pharmacology development program that included studies conducted in approximately 1300 healthy volunteers and in special populations including a landmark clinical study (Study 344) carried out to further characterize the nature of gemifloxacin-associated rash.
- A phase IV study (FORCE STUDY) designed to fulfil a post-marketing commitment to FDA where more than 5000 patients were treated with gemifloxacin 320 mg once daily for 5 or 7 days.
- Post marketing experience deriving from the first three years of marketing in the US on more than 1.2 million patients exposed.

The pooled safety population includes all patients receiving at least one dose of Gemifloxacin 320 mg (8119 patients) or the relevant comparator (5248 patients) from the following Phase II/III clinical studies:

- twenty-one studies conducted in patients with respiratory tract infections (CAP, AECB and ABS indications) in support of the present application;
- four studies conducted in patients with complicated or uncomplicated urinary tract infections (UTI);
- one study conducted in patients with skin and skin structure infections (SSSIs);
- one study conducted in patients with non-gonococcal urethritis (NGU).

One hundred and thirty (130) patients were excluded from the safety population based on the findings of failed GCP audits conducted by the sponsor or FDA. The lack of impact on the safety or efficacy outcomes derived from the exclusion of these patients has been assessed in individual abridged study reports (see Module 5.3).

In addition to the analysis of the pooled safety population, the following sources of safety data were analysed:

Study 344 [Report 101N7W/1]

This study was conducted in 1011 healthy female subjects to further characterise the nature of the rash occasionally observed after gemifloxacin administration and the potential for cross-sensitisation to other quinolones or sub-clinical sensitization. A trained dermatologist assessed the dermatologic findings using a standard Questionnaire assessment and by means of skin biopsy examinations.

Study OS-001 (FORCE)

This post-marketing study, (Module 5.3.6) which enrolled more than 7500 patients was designed to fulfil a post-marketing commitment to the FDA, to further evaluate the overall safety profile of gemifloxacin particularly related to rash and potential for QT prolongation. The study enrolled patients with mild-to-moderate CAP treated with gemifloxacin 320 mg od for 7 days versus clarithromycin XL 1000 mg od per 7 days, and patients with AECB treated with gemifloxacin 320 mg od for 5 days versus amoxicillin/clavulanate 875 mg bid per 7 days.

Post-marketing surveillance (PMS) data in US

Gemifloxacin is currently undergoing a post-marketing surveillance (PMS) program in US, which started from the date of first launch in September 2004. Periodic updated safety reports (PSURs) have been issued to document all post-marketing individual case safety reports.

The following safety variables were measured in the clinical studies included in the pooled analysis: adverse events (AEs), vital signs (sitting blood pressure, heart rate, temperature and respiration rate), electrocardiogram (ECG) and clinical laboratory tests (haematology, clinical chemistry and urinalysis).

The patients' demographic characteristics in the overall safety population are presented in the next Table.

Table 4. Demographic profile (age and gender) in the overall safety population

Demographic characteristic	Gemifloxacin 320 mg	All Comparators
Age (years)		
N	8119	5248
Mean (SD)	51.7 (18.04)	55.1 (17.19)
Median	53.0	57.0
Range	16-98	16-99
≥ 16 to <18, N (%)	22 (0.27)	8 (0.15)
≥ 18 to <40, N (%)	2207 (27.18)	1029 (19.61)
≥ 40 to <65, N (%)	3576 (44.04)	2398 (45.69)
≥ 65 to <75, N (%)	1449 (17.85)	1126 (21.46)
≥ 75, N (%)	865 (10.65)	687 (13.09)
Weight (kg)		
N	8112	5247
Mean (SD)	74.1 (18.52)	75.8 (18.64)
Median	72.0	74.0
Range	23.3-184.0	31.0-204.0
Height (cm)		
N	8096	5230
Mean (SD)	168.0 (9.87)	168.3 (9.83)
Median	168.0	168.0
Range	102.4- 207.0	106.7-205.7
Gender		
Male, N (%)	3948 (48.63)	2511 (47.85)
Female, N (%)	4170 (51.37)	2737 (52.15)
Missing	1(0.01%)	0
Race		
Caucasian, N (%)	6792 (83.66%)	4825 (91.94%)
Black, N (%)	380 (4.68%)	192 (3.66%)
Asian, N (%)	463 (5.70%)	43 (0.82%)
Other, N (%)	484 (5.96%)	188 (3.58%)

Source: Section 2.7.4.7, Tables 5-6. Listing 04

Overall, the rate of patients with at least one AE was lower in patients assigned to the overall gemifloxacin group (43.64%) than in the all comparators group (47.48%). The rate of patients with at least one AE was further reduced in the subgroup of patients assigned to the 5-day regimen of gemifloxacin (37.31%). Similarly, less patients in the overall gemifloxacin group than in the all comparators group reported drug-related AEs (17.34% versus 19.95%) or SAEs of any cause (3.60% versus 4.34%) and these rates were further reduced in patients assigned to 5-day gemifloxacin (drug-related AEs: 14.12%; SAEs of any cause: 2.35%). Drug-related SAEs were rare and occurred in 0.43% of the patients in the overall gemifloxacin group, 0.36%, of the patients in the all comparators group, and 0.08% of the patients in the 5-day gemifloxacin group. The rate of patients that discontinued the study due to AEs was 3.57% in the overall gemifloxacin group, 4.31% in the all comparators group and 1.68% in the 5-day gemifloxacin group. The rate of patients with fatal events was low in all groups (below 0.5%). Table 6 shows the most frequently reported drug-related AEs (reported in at least 0.1% of the patients) ordered by decreasing frequency in the gemifloxacin overall group.

Table 5. Summary of adverse events in the overall safety population

	Gemifloxacin 320 mg overall N=8119		**Gemifloxacin 320 mg 5 Days N=3696**		**All Comparators N=5248**	
	N	**(%)**	**N**	**(%)**	**N**	**(%)**
Number of AEs	6858		2547		5136	
Number of patients with at least one AEs	3543	(43.64%)	1379	(37.31%)	2492	(47.48%)
Number of drug related AEs	2007		759		1565	
Number of patients with at least one drug related AEs	1408	(17.34%)	522	(14.12%)	1047	(19.95%)
Number of SAEs	376		114		295	
Number of patients with SAEs	292	(3.60%)	87	(2.35%)	228	(4.34%)
Number of related SAE	37		3		24	
Number of patients with at least one related SAE	35	(0.43%)	3	(0.08%)	19	(0.36%)
Number of AEs leading to withdrawal	367		80		311	
Number of patients with at least one AEs leading to withdrawal	290	(3.57%)	62	(1.68%)	226	(4.31%)
Number of related AEs leading to withdrawal	206		42		171	
Number of patients with at least one related AEs leading to withdrawal	165	(2.03%)	34	(0.92%)	109	(2.08%)
Number of patients with Deaths due to an AE	40	(0.49%)	9	(0.24%)	30	(0.57%)

Source: Section 2.7.4.7 Table 8; Listing 08-11

Diarrhoea, rash, nausea and headache were among the most common drug-related AEs reported in clinical studies, with the highest incidence of diarrhoea (4.61%), nausea (3.20%) and headache (1.52%) being observed in the all comparator group, while rash was reported more frequently in the overall gemifloxacin group (2.80%). Within the central nervous system side effects, dizziness occurred in 0.81% of all gemifloxacin-treated patients versus 1.52% in the all comparators group. The risk of dizziness in the 5-day gemifloxacin group was lower (0.70%) than in the overall gemifloxacin and all comparators groups. The same trend was observed for vertigo (5-day gemifloxacin: 0.11%; overall gemifloxacin: 0.14%; all comparators 0.59%).
Photosensitivity reactions (events reported with the use of some fluoroquinolones), occurred in only 4 patients (0.05%) treated with gemifloxacin (2 of them, 0.05%, assigned to the 5-day regimen) and in 1 patient (0.02%) treated with a comparator.
Potential alterations in hepatic function (i.e. AEs of increased hepatic enzymes) were reported in a small and similar percentage of patients in the overall gemifloxacin and comparator group (hepatic enzymes increase 0.32% gemifloxacin vs. 0.32% comparators; ALT increased: 0.83% gemifloxacin vs. 0.61% comparators; AST increased: 0.62% gemifloxacin vs. 0.44% comparators; alkaline phosphatase increased: 0.25% gemifloxacin vs. 0.08% comparators). Also in this case, the corresponding AEs rates observed in the 5-day gemifloxacin group were slightly lower than those reported in the overall gemifloxacin group.
Most of the AEs in both the overall gemifloxacin and the all comparators group were of mild to moderate intensity. In the overall gemifloxacin group, AEs of mild intensity were reported in 8.72% of patients, while 6.60% and only 2.02% of patients reported AEs of moderate or severe intensity, respectively. The corresponding rates of patients with mild, moderate or severe AEs in the all comparators group were 9.74%, 8.06% and 2.15%, respectively.

Rash:
Within the most common AEs observed in the clinical program, the only AE with a higher incidence in the gemifloxacin group versus the comparator group was rash. In most cases the rash appeared as a typical exanthematous drug eruption of mild to moderate severity and rarely required discontinuation from the study. Data from the pooled clinical studies regarding this cutaneous adverse event are summarised in Table 7.

Table 7. Summary of adverse events of rash (irrespective of treatment-relationship) in clinical studies

	Gemifloxacin 320 mg overall (N=8119)		**Gemifloxacin 320 mg 5 days (N=3696)**		**All Comparators (N=5248)**	
	N	**(%)**	**N**	**(%)**	**N**	**(%)**
Number of patients with rash	283	(3.49%)	56	(1.52%)	59	(1.12%)
Number of patients with rash as SAE	6	(0.07%)	0	(0.00%)	1	(0.02%)
Number of patients with rash leading to withdrawal	66	(0.81%)	6	(0.16%)	15	(0.29%)

Rash included the following PTs: rash, rash erythematous, rash maculo-papular, rash pustular
SAE=serious adverse event
Source: Section 2.7.4.7, Table 13; Listing 8-10

As the posology has to be changed to 7 days for standard treatment there is a need for a new benefit/risk assessment of the indication CAP due to the increased frequency of rash and severe rash associated with the 7 day treatment compared to the 5 day treatment.

The incidence of SAEs was low in the overall gemifloxacin group (3.60%) and the all comparators group (4.34%).

The next table shows the most frequently reported SAEs (observed in at least 0.5% of patients in any group) by preferred term (PT) and ordered by decreasing frequencies in the gemifloxacin overall group.

Table: Number of patients with SAEs in the overall safety population by PT, observed in at least 0.5% of patients in any group

	Gemifloxacin 320 mg overall (N=8119)		Gemifloxacin 320 mg 5 Days (N=3696)		All Comparators (N=5248)	
Preferred Term	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Number of Patients With At Least One SAE	292	(3.60%)	87	(2.35%)	228	(4.34%)
Pneumonia	30	(0.37%)	7	(0.19%)	25	(0.48%)
Pulmonary Carcinoma	15	(0.18%)	4	(0.11%)	8	(0.15%)
Dyspnoea	15	(0.18%)	9	(0.24%)	10	(0.19%)
Chronic Obstructive Pulmonary Disease	14	(0.17%)	6	(0.16%)	17	(0.32%)
Respiratory Insufficiency	14	(0.17%)	3	(0.08%)	10	(0.19%)
Bronchitis	13	(0.16%)	8	(0.22%)	16	(0.30%)
Therapeutic Response Increased	11	(0.14%)	4	(0.11%)	5	(0.10%)
Injury	10	(0.12%)	4	(0.11%)	3	(0.06%)
Respiratory Disorder	8	(0.10%)	2	(0.05%)	8	(0.15%)
Cardiac Failure	7	(0.09%)	3	(0.08%)	8	(0.15%)
Cardiac Arrest	7	(0.09%)	5	(0.14%)	5	(0.10%)
Chest Pain	6	(0.07%)	4	(0.11%)	2	(0.04%)
Myocardial Infarction	6	(0.07%)	0	(0.0%)	10	(0.19%)
Pleural Effusion	6	(0.07%)	0	(0.0%)	1	(0.02%)
Pleurisy	6	(0.07%)	1	(0.03%)	1	(0.02%)
Neoplasm NOS	5	(0.06%)	0	(0.0%)	1	(0.02%)
Rash*	6	(0.07%)	0	(0.0%)	1	(0.02%)
Pyelonephritis	5	(0.06%)	0	(0.0%)	2	(0.04%)
Renal Failure Acute	5	(0.06%)	1	(0.03%)	2	(0.04%)
Fever	4	(0.05%)	2	(0.05%)	2	(0.04%)
GI Haemorrhage	4	(0.05%)	0	(0.0%)	2	(0.04%)
Fibrillation Atrial	4	(0.05%)	0	(0.0%)	2	(0.04%)
Cerebrovascular Disorder	4	(0.05%)	2	(0.05%)	3	(0.06%)
Dehydration	3	(0.04%)	1	(0.03%)	3	(0.06%)
Suicide Attempt	3	(0.04%)	2	(0.05%)	3	(0.06%)
Abscess	3	(0.04%)	1	(0.03%)	6	(0.11%)
Infection TBC	3	(0.04%)	1	(0.03%)	5	(0.10%)
Sepsis	2	(0.02%)	0	(0.0%)	4	(0.08%)
Asthma	2	(0.02%)	2	(0.05%)	4	(0.08%)
Haemoptysis	2	(0.02%)	0	(0.0%)	3	(0.06%)
Abdominal Pain	1	(0.01%)	1	(0.03%)	5	(0.10%)
Angina Pectoris Aggravated	1	(0.01%)	0	(0.0%)	3	(0.06%)
Myelomatosis Multiple	1	(0.01%)	0	(0.0%)	3	(0.06%)
Embolism Pulmonary	1	(0.01%)	0	(0.0%)	3	(0.06%)
Diarrhoea	0	(0.00%)	0	(0.0%)	4	(0.08%)

AE=adverse event; NOS=non-otherwise specified; GI=gastrointestinal; TBC=tuberculosis
*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular and rash pustular

Source: Section 2.7.4.7, Table 22, Listing 10

Due to the consideration of the Rapporteurs that AECB is not acceptable without superiority studies and that CAP requires 7 day treatment, the adverse event rate with the 5 day treatment is no longer adequate for benefit/risk assessment. Instead, the Applicant should provide a benefit/risk assessment for the indication CAP based on the adverse event rates of the 7 day treatment. (Major Objection C1)

Hepatotoxicity:
Elevation in liver function enzymes was reported as an AE in a very small amount of patients, with no relevant differences in the distribution between treatment groups. In detail, 0.60% of patients under gemifloxacin reported the AE “hepatic enzyme increased” compared to 0.48 % of patients in the all comparator group. The AEs “AST increase” and “ALT increase” were reported by 1.02 % and 1.47 %, respectively, under gemifloxacin, and 0.69 % and 0.93 % in the all comparators group. The incidence of drug-related AEs concerning hepatic function shows a very similar picture. Similarly,

serious adverse events concerning hepatic enzyme elevations were very rare with gemifloxacin as well as with comparators. With the exception of the one case of "hepatic failure" in the gemifloxacin-group, all serious adverse events in either treatment group were considered related to study medication.

Serious adverse events related to liver function

Preferred Term	**Gemifloxacin 320 mg overall (N=8119)**		**All Comparators (N=5248)**	
	N	**(%)**	**N**	**(%)**
Hepatic enzymes increased	3	0.04	0	0.00
Hepatic failure	1	0.01	1	0.01
Hepatic function abnormal	1	0.01	0	0.00
SGOT (AST) increased	0	0.00	1	0.01
SGPT (ALT) increased	0	0.00	1	0.01

Source: Section 2.7.4.7, Table 22, Listing 08 and 09

The hepatic failure events occurred in the gemifloxacin and comparator (clarithromycin) group resulted in the death of the patient which in the gemifloxacin case was due, according to the investigator, to respiratory insufficiency, renal and hepatic failure probably associated to sepsis. The narrative of these two events is reported in the clinical study reports 070 (ID:070.093.0440) and 112 (ID:112.122.38697) respectively.

The fatal case is considered unlikely to be related to the treatment with gemifloxacin mainly due to the fact that the hepatic failure occurred more than one week after the last study medication. The case more likely seems to be associated with an early relapse of AECB after end of treatment with gemifloxacin. The investigator came to the same conclusion.

The cases of liver enzyme increases are considered to be associated with gemifloxacin. However, frequency of these events is hard to estimate due to the overall low numbers. This issue should be addressed by RMP measures.

Cardiac toxicity:

Treatment with some fluoroquinolones has been associated with prolongation of the ECG QT interval [Iannini et al., 2006; Lode, 2001]. Non-clinical studies, while not quantitatively predictive of clinical effect, can help to assess the potential for QT interval changes in man. As described in Module 2.6, comparative in vitro assays showed a low potential of gemifloxacin in prolonging APD 90 in Purkinje fibres or inhibiting the hERG channel compared to other quinolones. In animal studies, reversible QT interval prolongation was observed only in dogs dosed intravenously, but not orally, at multiples of clinical exposure.

Gemifloxacin's potential to alter the QTc interval in humans was evaluated in approximately 650 healthy volunteers in clinical pharmacology studies and in approximately 800 patients in clinical studies. In addition, the effect of gemifloxacin on QTc interval was further assessed in the FORCE Study (refer to Section 2.7.4.6.1). From the results of ECG tracings in clinical pharmacology studies, there is no evidence of mean QTc prolongation with the use of the 320 mg gemifloxacin dose. Furthermore, there was no apparent dose-relationship for mean changes in QTc in single-dose studies testing different doses of gemifloxacin up to 800 mg.

In the phase II and III clinical studies, patients were not excluded because of risk factors for QT prolongation, therefore the population studied can be considered to be broadly representative of that expected in clinical use of gemifloxacin. The analysis of the distribution of drug-related AEs relative to the cardiovascular system showed only few cases of rhythm disorders, reported in both the gemifloxacin- or comparators-treated patients.

Upon request in the Day 120 LoQ an analysis of safety in Phase II/III studies that is separated according to the class of comparator was provided by the Applicant. QTc-changes with gemifloxacin were more frequent compared to other fluoroquinolones (namely trovafloxacin and levofloxacin), and penicillins, while macrolides show a higher frequency of QTc-prolongation than gemifloxacin. This assessment is based on the analysis of patients with an QTc-prolongation of $\geq$ 30msec. Regarding cephalosporins only few data are available.

In addition, the QRS-prolonging properties of gemifloxacin which have been described in the nonclinical overview had to be addressed by the Applicant based to the QRS-prolonging properties of gemifloxacin which have been described in the nonclinical overview.
The clinical data provided by the Applicant revealed no increased overall risk for QRS-prolongation compared to all pooled comparators but a comparison against pooled comparators is anyway not appropriate here due to the variety of risks associated with the different agents. However, in the case of the five fatal cases due to cardiac events it can not be excluded that these cases were due to gemifloxacin. T

In conclusion, a clinical study on cardiac conduction according to the ICH E14 guideline is absolutely required and timelines must be provided for this.

Discontinuation due to AES:
The lowest rate of patients with adverse events leading to withdrawal was observed in patients assigned to 5-day gemifloxacin (1.68% of patients in this group) compared to the overall gemifloxacin group (3.57%) and to the all-comparators treatment group (4.31%). The rate of discontinuations due to drug-related AEs was also lower in the 5-day gemifloxacin group (0.92%) than in the overall gemifloxacin group (2.03%) and all comparators group (2.08%). As seen in Table 13, rash (reported as rash, rash erythematous and rash maculo-papular) was the cause of study discontinuation in only 0.16% of patients assigned to gemifloxacin 5-day, in 0.81% of those assigned to gemifloxacin (any duration) and in 0.29% of those assigned to any comparators. Discontinuation from studies due to gastrointestinal symptoms (diarrhoea, nausea, vomiting and abdominal pain) was more frequent in patients treated with comparators than with gemifloxacin overall and gemifloxacin 5-day.

Number of patients with AEs that caused early study discontinuation in the overall safety population by PT, observed in at least 0.1% of patients in any group

	Gemifloxacin 320mg overall (N=8119)		**Gemifloxacin 320mg 5 Days (N=3696)**		**All Comparators (N=5248)**	
Preferred Term	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**
Number of patients with at least one AE leading to withdrawal	290	(3.57%)	62	(1.68%)	226	(4.31%)
Rash*	66	(0.81%)	6	(0.16%)	15	(0.29%)
Diarrhoea	25	(0.31%)	11	(0.30%)	25	(0.48%)
Nausea	24	(0.30%)	9	(0.24%)	20	(0.38%)
Urticaria	16	(0.20%)	4	(0.11%)	4	(0.08%)
Vomiting	15	(0.18%)	5	(0.14%)	16	(0.30%)
Pneumonia	14	(0.17%)	4	(0.11%)	12	(0.23%)
Dyspnoea	10	(0.12%)	4	(0.11%)	7	(0.13%)
Respiratory insufficiency	7	(0.09%)	1	(0.03%)	6	(0.11%)
Cardiac arrest	6	(0.07%)	4	(0.11%)	5	(0.10%)
Dizziness	5	(0.06%)	1	(0.03%)	8	(0.15%)
Abdominal pain	5	(0.06%)	2	(0.05%)	15	(0.29%)
Chronic obstructive airways disease	4	(0.05%)	1	(0.03%)	8	(0.15%)
Bronchitis	3	(0.04%)	2	(0.05%)	6	(0.11%)
Respiratory disorder	2	(0.02%)	1	(0.03%)	10	(0.19%)
Sinusitis	2	(0.02%)	0	(0.0%)	5	(0.10%)
Cardiac failure	2	(0.02%)	0	(0.0%)	5	(0.10%)
Vertigo	1	(0.01%)	0	(0.0%)	9	(0.17%)
Creatinine clearance decreased	1	(0.01%)	0	(0.0%)	5	(0.10%)

*Rash includes the preferred terms rash, rash erythematous, rash maculo-papular and rash pustular
Source: Section 2.7.4.7, Table 24, Listing 08 and 09.

Again, based on the requirement for 7 day treatment in CAP, the analyses of the benefit/risk with gemifloxacin must be based on the 7 day data.

Post marketing experience:
The FORCE Study (Module 5.3.6) was designed to fulfil a post-marketing commitment to the FDA, to conduct a prospective, randomised study comparing gemifloxacin mesylate (5,000 patients) to an active control approved antibiotic (2,500 patients) in patients with mild-to-moderate CAP or AECB. The primary objective of this study was to evaluate and compare the overall safety in CAP patients treated with gemifloxacin 320 mg od for 7 days versus clarithromycin XL 1000 mg od per 7 days, and patients with AECB treated with gemifloxacin 320 mg od for 5 days versus amoxicillin/clavulanate 875 mg bid per 7 days. The secondary objectives of this study included the evaluation of the incidence of rash and effect on QTc.
Following the screening visit, during which patients started the assigned drug regimen, all patients were to return to the clinic 5 to 7 days after initiation of therapy. Patients were instructed to contact the study investigator/staff if they experienced any adverse event (AE) from the period starting with the first dose of study medication through 30 days after initiation of study medication. Patients were seen for evaluation of reported AEs as clinically indicated. A follow-up contact was completed by the patient, either by telephone or by patient-initiated interactive voice response system (IVRS), on Day 28, Day 29, or Day 30 after the initiation of therapy. The purpose of this follow-up was to capture any AEs not previously reported to the investigator. The total duration of the patient's study participation was to be 28 to 30 days. The ITT population (i.e. the reference population for the safety analyses) included all randomized patients who had been given study drug or given a prescription for the study drug.
A total of 7495 patients were randomised to either gemifloxacin (N=5027) or a control agent (N=2464) and 7458 patients (5016 gemifloxacin patients and 2442 control patients), were found eligible for the ITT/Safety population. In the CAP indication, 1409 patients were randomised to gemifloxacin and 696 to clarithromycin XL. In the AECB indication, 3617 patients were randomised to gemifloxacin and 1764 to amoxicillin/clavulanate.
While the incidence of rash was higher in each of the gemifloxacin group compared to the respective control group, only a minority of patients discontinued the study due to this event. Most occurrences of rash in each treatment group were rated as mild in intensity, and there were a total of four occurrences of severe rash in gemifloxacin patients (two in CAP patients and two in AECB patients). Only one of the four severe rashes in gemifloxacin-treated patients was reported as an SAE.
There were no significant treatment group differences for the incidence of SAEs for all indications.
ECG data were available for 300 CAP patients (196 gemifloxacin and 104 clarithromycin XL). Both gemifloxacin and clarithromycin XL had minimal effects on QTc using either the Bazett's correction (QTcB) and the Fridericia's correction formula (QTcF). Similar percentages of patients in each treatment group had an absolute change from baseline in QTcB or QTcF of 30 msec or 60 msec with no statistically significant differences between the two treatment groups. It should also be noted that no patients in the FORCE study were found to have QTc values in excess of 500 msec. Moreover, in the total ECG population, there were no statistically significant differences in absolute or percentage change from baseline for QTcB or QTcF between treatment groups. There were also no statistically significant treatment group differences in absolute or percentage change from baseline for QTcB or QTcF for the following subgroups of the ECG population: male patients, female patients, patients <65 years old, patients ≥ 65 years old, male patients <65 years old, female patients <65 years old, male patients ≥ 65 years old, female patients ≥ 65 years old, patients with comorbidities, including hypertension (70 patients with ECGs), hypothyroidism (14 patients with ECGs), and atrial fibrillation (2 patients with ECGs).
The results from this study related to rash are consistent with the observations in the clinical development program and indicate that the rate of rash with the intended treatment regimen (5 days) is only slightly higher than the one observed with the comparators tested. Most rashes in the gemifloxacin group were mild to moderate in intensity and of short duration and rarely required discontinuation from the study. With the exception of the rash the overall incidence of AEs and discontinuation of study medication due to AEs was significantly higher in the combined comparator groups compared to the gemifloxacin group: patients who received clarithromycin XL had a higher incidence of diarrhoea and dysgeusia and patients who received amoxicillin/clavulanate had a higher incidence of diarrhoea compared to gemifloxacin-treated patients.

Post-marketing surveillance:

It is estimated that approximately 1,268,562 patients have been exposed to gemifloxacin in the United States with a global exposure of 1.6 million patients around the world.
This significant exposure with commercial product allows for a comparison with the safety profile observed in the clinical trials and an assessment of the potential onset for rare adverse events.
Overall, there were spontaneous reports from 1.411 patients that included a total of 1.982 AEs of which 169 (8.53% of total AEs) were SAEs.
The most frequently involved SOC was the skin and subcutaneous tissue, which accounted for 1181 AEs (59.6% of total events). Among these events, 51/1181 (4.3%) were serious. Of the1181 events categorised as disorders of skin and subcutaneous tissue 979 consisted of rash, which was reported in the form of rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash morbilliform, rash popular, rash pruritic, or rash rubelliform. Among all the events of rash, 33/979 (3.3%) were SAEs
The second most frequently involved SOC was the gastrointestinal system, with 189 AEs (9.5% of total events), 10 of them being SAEs (5.9% of total SAEs). Nausea (46 AEs, 1 SAE), diarrhoea (33 AEs, all non-SAEs) and abdominal pain (27 AEs, all non SAEs) were the most common GI disorders.
Other frequently involved SOCs were: general disorders and administration site conditions (163 AEs, 8.2% of total AEs; 16 SAEs, 9.4% of total SAEs), among which lack of efficacy was the most common event (n = 49); nervous system disorders (105 AEs, 5.3% of total AEs; 12 SAEs, 7.1% of total SAEs), among which dizziness (n = 24) and headache (n = 18) were the most common event; and respiratory, thoracic and mediastinal disorders (66 AEs, 3.3% of total AEs; 9 SAEs, 5.3% of total SAEs), among which dyspnoea (presumably due to worsening of the underlying disease) was the most common event (n = 30).
In general, the post-marketing experience with gemifloxacin has not revealed any new safety signal compared the safety profile observed in the clinical trial database. Some quinolone class effects have been reported (e.g. 11 cases of anaphylaxis, 4 cases of increased International Normalized Ratio (INR), 1 case of decreased prothrombin time (PT), and 2 cases of haemorrhage). Importantly, to date there have been also no spontaneous reports of torsades des pointes, which may be the result of QTc interval prolongation (event reported in only one case).
Up to October 2007 (cut off used for the reporting of PSUR for this submission), there were 5 spontaneous reports of cutaneous adverse reactions where SJS was initially suspected but not confirmed (events were coded as “rash”, “rash generalised”, “rash pruritic”, or “urticaria”).
However, after the last PSUR (no. 18, covering the period from 05 Jul 2007 - 04 Oct 2007) one spontaneous report was received on Feb 13, 2008 via the U.S. MEDWATCH surveillance system which was coded as “Stevens-Johnson syndrome”.

Conclusion on clinical safety:
Clinical safety of gemifloxacin has been established in more than 8,000 patients included in clinical studies and globally about 1,6 million patients have been treated with gemifloxacin.
Data analysis from the clinical studies and the post-marketing data revealed an adverse event pattern similar to other antibiotics and fluoroquinolones with gastrointestinal symptoms accounting for the majority of adverse events.
Some class-specific adverse events such as photosensibility or QTc-prolongation were observed with gemifloxacin, too. However, severity and frequency of these adverse events is lower compared to the fluoroquinolones with most prominent problems regarding photosensibility and QTc prolongation. These adverse events are addressed in the SPC but a clinical study on cardiac conduction according to the ICH E14 guideline is absolutely required. Gemifloxacin does not interfere with glucose haemostasis in a clinical relevant extent, and no further – especially no further severe – adverse events have been observed which are not known to be observed with nearly every antibiotic (e.g. pseudomembraneous colitis, severe skin reactions). Regarding pseudomembraneous colitis, a respective question has been raised in the PK/PD section.
The most prominent, i.e. the most unusual adverse event for this class of antibiotics, are rashes. These rashes occur more often with gemifloxacin than with comparators and the frequency depends on the duration of therapy. The pathophysiology of the rashes has been intensively studied and from the current knowledge these rashes are considered to be no safety concern as they are mostly mild to moderate and reversible. The most important impact of this adverse event is triggering of withdrawals which are more frequently reported in the 7 day treatment compared to the 5 day

treatment. Thus, from a safety point of view, 5 day treatment would be the preferred treatment. However, based on the efficacy results, 7 day treatment is required in CAP and thus benefit/risk assessment must be based on the 7 day safety profile.

Pharmacovigilance System

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance (Version 7 dated 15 December 2008). A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.
However, the Rapporteurs consider that the Pharmacovigilance system as described by the applicant had some deficiencies. The applicant must ensure that the system of Pharmacovigilance is in place and functioning before the product is placed on the market.

Risk Management plan

The Risk Management Plan (RMP) reviewed in this report is version 2 with data lock point being 04/04/2008.

This version of the RMP has much improved in comparison to the previous version. However, some information from non-clinical and clinical experience is still missing and therefore this RMP has to be further modified.

Safety Specification

Non-clinical:

The applicant has addressed the following non-clinical safety concerns:
Carcinogenesis (not studied)
Cardiac (ECG) toxicity
Cytotoxicity
CNS toxicity (excl. ocular toxicity)
Genetic toxicity/ clastogenicity
Hepatotoxicity
Immunotoxicity
Nephrotoxicity
Ocular toxicity
Phototoxicity
Respiratory and gastrointestinal toxicity
Pregnancy/developmental toxicity
Paediatric use/ arthropathy and osteochondrosis

More detailed information/discussion on prolongation of the QRS complex and requested data from drug interaction studies are still missing (see LoOI).

Clinical:

A large patient safety database on gemifloxacin is available which includes data from 8119 patients who received a once daily 320 mg oral dose of gemifloxacin for 3-14 days in 27 Phase II/III clinical trials and from 5016 patients in Phase IV Post-marketing study (FORCE Study). Therefore, a total of 13,135 patients were included in the full safety database.

Post authorisation experience:

Gemifloxacin has been approved and is currently marketed in 11 countries (South Korea, United States, Canada, South Africa, Jordan, Russia, Mexico, China, Brazil, Saudi Arabia, and Taiwan). Gemifloxacin is not approved in any country of the European Union.

As of April, 2008, approximately 2 million patients worldwide have been exposed to gemifloxacin. Most of these patient exposures (~1.5 million) are from use in the United States and are described below. Detailed information on patient exposure data outside of the United States is not available.

United States Post-Marketing Exposure: Demographics

The US sponsor has conducted a study requested by the FDA to assess the prescribing patterns and use of FACTIVE® in the US ("Prescribing Use Study"). This study obtains prescription data from a large US health plan, United Healthcare. The underlying medical information from this health plan is geographically diverse across the US and is expected to reflect the real-life patterns of use of gemifloxacin in the US. This study is a three year commitment and the final report encompassing all three years was presented with version 2.0 of the RMP.

Estimation of treated population

The applicant used prescription data for moxifloxacin to estimate off-label use and the relative portions of indications to estimate the treated population during the next 3 years.

Regarding estimation of treatment population, the applicant provided data over 5 years for the 5 major EU countries estimating a cumulative exposure of about 23,000 sample units (5 tablets) accounting for approximately 5.5 % of total fluoroquinolone market.

Populations not studied:

The exclusion criteria in pre- and post-approval clinical studies included:

- Pregnant or breast feeding women
- Hypersensitivity to quinolone antibacterials
- History of fluoroquinolone-associated tendonitis
- Cystic fibrosis, active tuberculosis, bronchiectasis, or active pulmonary malignancies (CAP+AECB)
- Immunocompromised patients and HIV positive patients
- Known or suspected renal impairment
- Aspiration pneumonia or known bronchial obstruction (CAP studies)
- Concomitant treatment with systemic steroids (CAP studies)
- Hepatobiliary disease or known elevated liver function tests and/or elevated bilirubin levels
- History of haemolytic crisis or known glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Patients with a history, or currently receiving medications for epilepsy, convulsions or myasthenia gravis
- Concomitant treatment with sucralfate

The applicant further specifically addresses Children (contraindicated), Elderly, Pregnant and lactating woman, patients with renal and hepatic impairment, patients of different racial and/or ethic origins and other patient groups due to known class effects of fluoroquinolones.

All exclusions due to fluoroquinolone class effects (e.g. a statement on tendonitis is missing) should be discussed. In general this section should discuss the need for contraindications or warning statements regarding populations not studied in the trial program or even excluded from trials.

Adverse events/Adverse reactions:

References are given to clinical modules for a review of adverse events together with a table on frequencies of drug-related AEs during clinical trials. This table should be updated to include adverse reactions seen in $\geq$ 0.01% in any treatment group. The applicant should also calculate confidence intervals and statistically significance of differences in liver function tests vs. comparators based on the data presented in table 25, 26 and 30.

Details of important identified and potential risks:

Only rash is mentioned as identified risk. Differences especially regarding QT/QRS prolongation should be addressed in the section on class effects and results of the requested ICH-study should be included. QT/QRS prolongation should be mentioned as an important identified risk.

Identified and potential interactions with other medicinal products, food and other substances:
Interaction with di- and trivalent cations (e.g. aluminium and magnesium containing antacids) and probenecid are described.

Epidemiology of the indication(s) and important adverse events:
Epidemiology has been adequately addressed in this section.

Potential for off-label use:
For all antibiotics, the potential exists for off-label treatment of non-indicated infectious disease (ID). Prescription data from the US are given showing a significant amount of off-label usage. Measures to monitor and minimise the off-label use in the EU are presented.

Evaluation of the need for a Risk minimisation plan

Table 41: Summary of the planned pharmacovigilance actions

Safety concern	**Planned action(s)**
Important identified risks	
Rash	***Routine pharmacovigilance*** - Analysis of adverse reactions in PSURs. - Follow-up of reports and signal detection. ***Additional Pharmacovigilance*** The Post-Marketing incidence and clinical features of the gemifloxacin-associated severe cutaneous ADRs will be evaluated in a European Survey performed by a qualified European Study Group of Dermatologists.
Important potential risks	
Pharmacological Class Effect: - QT Effects - Peripheral Neuropathy - Tendon Effects - CNS Effects - *Clostridium difficile* Associated Diarrhoea - Hepatic Effects - Photosensitisation	***Routine pharmacovigilance*** - Analysis of adverse reaction in PSURs. - Follow-up of reports and signal detection. ***Additional Pharmacovigilance*** Post-authorisation observational study to evaluate the safety of gemifloxacin in a large number of patients, in a real world setting.
Development of drug resistant strains	***Routine pharmacovigilance*** None. ***Additional Pharmacovigilance*** Involvement of a Pan-European Board of Microbiologists to assess periodically the comparative *in vitro* activity of Gemifloxacin against clinical isolated of *Streptococcus pneumoniae* and *Haemophilus Influenzae*.
Important missing information	None

Risk minimisation plan

Table 44: Summary of Risk Minimisation Activities

Safety concern	**Rash**
Routine risk minimisation activities	- Special warning included in section 4.4 of the SmPC and in the relevant section of the PIL. - Single commercial pack of 5 tablets. No larger hospital pack foreseen.
Additional risk minimisation activity	*Objective and rationale* To minimise the frequency of the rash.
	Proposed actions - Training on the medical representatives aimed to sensitize them to recall the risk of rash to the physicians. - Provision of educational and informative materials to healthcare professionals to recall the risk of rash due to gemifloxacin. - Appropriate information made by Independent Experts during congresses and official meeting. Key messages of the educational plan are included in Annex 8.
	Criteria to be used to verify the success of proposed risk minimisation activity Gemifloxacin-associated rash awareness in prescribing physicians.
	Action to verify the success of proposed risk minimisation activity - Indirect information regarding the gemifloxacin prescription will be obtained from the periodic IMS data. In particular data regarding the length of therapy will be considered. - Independent research on the awareness of gemifloxacin-associated rash in prescribing physicians: single countries focus groups will be performed in order to evaluate the awareness of prescribing physicians on the gemifloxacin-associated rash and relevant risk factors. An independent agency will involve physicians (mainly GP's) reflecting different geographic area. A specific questionnaire will be administered to verify the correct use of the drug together with the awareness of the identified and potential risks, including the related warnings and contraindications reported in the SmPC.
	Proposed review period 1 year from the first launch in the first country.
Safety concern	**Pharmacological class effect**
Routine risk minimisation activities	Special warning included in section 4.4 of the SmPC and in the relevant section of the PIL.
Additional risk minimisation activity	*Objective and rationale* To minimise the risks of the known class effects.
	Proposed actions A complete and balanced medical information is the core of the risk minimization strategy.

	Criteria to be used to verify the success of proposed risk minimisation activity Awareness in prescribing physicians about the FQ's pharmacological class effects that can be reported using gemifloxacin.
	Action to verify the success of proposed risk minimisation activity Independent research on FQ's pharmacological class effects awareness in prescribing physicians. Single countries focus groups will be performed in order to evaluate the awareness of prescribing physicians on the gemifloxacin-associated rash and relevant risk factors. An independent agency will involve physicians (mainly GP's) reflecting different geographic area. A specific questionnaire will be administered to verify the correct use of the drug together with the awareness of the identified risks including the related warnings and contraindications reported in the SmPC.
	Proposed review period 1 year from the first launch in the first country.
Safety concern	**<u>Selection of drug resistant strains</u>**
Routine risk minimisation activities	To reduce the selection of drug resistant strains it is important that the product is used only in the infections studied in the clinical trials. The approved therapeutic scheme, in the relevant sections of the SmPC and PIL, clearly reports the type of infections and duration of treatment which should be applied.
Additional risk minimisation activity	None

Table 45: Summary of Risk Management Plan

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
Rash	***Routine pharmacovigilance activities*** - Analysis of adverse reaction in PSURs. - Follow-up of reports and signal detection. ***Additional pharmacovigilance activities*** European Post-Marketing Surveillance Study on serious cutaneous ADRs associated with gemifloxacin use (two modules). **First Module**. The purpose is to rule out an increased risk of more severe skin reactions associated with gemifloxacin (Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, Acute Generalised	***Routine risk minimisation activities*** - Special warning included in section 4.4 of the SmPC and in the relevant section of the PIL. - Single commercial pack of 5 tablets. No larger hospital pack foreseen ***Additional risk minimisation activities*** - Training on the medical representatives aimed to sensitise them to recall the risk of rash to the physicians. - Provision of educational and informative materials to health care professionals to recall the risk of rash due to gemifloxacin - Appropriate information made by Independent Experts during congresses and official meeting. *Action to verify the success of proposed risk minimisation activity* - Indirect information regarding the

	Exanthematic Pustulosis and Drug Reactions with Eosinophilia and Systemic Symptoms) within the RegiSCAR network. **Second Module.** Monitoring of all the patients admitted to Dermatology Units for suspected fluoroquinolone-associated ADRs. The proportion of cases attributable to Gemifloxacin and other quinolones will be specifically analysed and characterised. The study will be performed in at least two major metropolitan areas in two different European countries. This Module will be coordinated by the Italian branch of the RegiSCAR group (Centro Studi GISED – www.gised.it),	gemifloxacin prescription will be obtained from the periodic IMS data. - Independent research on the awareness of gemifloxacin-associated rash in prescribing physicians: single countries focus groups will be performed in order to evaluate the awareness of prescribing physicians on the gemifloxacin-associated rash and relevant risk factors. An independent agency will involve physicians (mainly GP's) reflecting different geographic area. A specific questionnaire will be administered to verify the correct use of the drug together with the awareness of the identified and potential risks, including the related warnings and contraindications reported in the SmPC.
Pharmacological Class Effect: - QT Effects - Peripheral Neuropathy - Tendon Effects - CNS Effects - *Clostridium difficile* Associated Diarrhoea - Hepatic Effects - Photosensitisation	***Routine pharmacovigilance activities*** - Analysis of adverse reaction in PSURs. - Follow-up of reports and signal detection. ***Additional pharmacovigilance activities*** Post-authorisation observational study to evaluate the safety of gemifloxacin in a large number of patients, in a real world setting, specifically focused on Pharmacological Class Effect associated with the use of gemifloxacin.	***Routine Risk minimisation activities*** - Special warning included in section 4.4 of the SmPC and in the relevant section of the PIL ***Additional risk minimisation activities*** A complete and balanced medical information is the core of the risk minimization strategy. *Action to verify the success of proposed risk minimisation activity* Independent research on FQ's pharmacological class effects awareness in prescribing physicians. Single countries focus groups will be performed in order to evaluate the awareness of prescribing physicians on the gemifloxacin-associated rash and relevant risk factors. An independent agency will involve physicians (mainly GP's) reflecting different geographic area. A specific questionnaire will be administered to verify the correct use of the drug together with the awareness of the identified risks including the related warnings and contraindications reported in the SmPC.

Selection of drug resistant strains	***Routine pharmacovigilance activities*** None. ***Additional Pharmacovigilance activities*** A multi-centre, multi-country surveillance of the in vitro activity of gemifloxacin and other antimicrobial agents against clinical isolates of *Streptococcus pneumoniae* and *Haemophilus Influenzae*.	***Routine risk minimisation activities*** Therapeutic indications and posology scheme detailed in the relevant sections of the SmPC and PIL. ***Additional risk minimisation activities*** None.

The sufficiency of the Pharmacovigilance Plan and Risk minimisation Plan cannot be fully assessed for time being. The applicant should further update the RMP also in accordance with issues raised in the non-clinical and clinical AR.
Annex 8 should give more details on the proposed educational material.

IV. ORPHAN MEDICINAL PRODUCTS

N/A

V. BENEFIT RISK ASSESSMENT

Benefits

Gemifloxacin showed a good *in vitro* activity against most of the important bacteria causing community acquired respiratory infections.

Community acquired pneumonia:
The data provided by the Applicant are accepted to demonstrate that patients with mild to moderate CAP were included in the clinical studies.
Five day treatment however is not supported because the only study addressing 5 day treatment included less than 10% of patients with moderate CAP (predominately mild cases) and the comparator in this study was 7 day gemifloxacin still not approved in the EU.
Seven days treatment is needed for mild to moderate CAP. Even then, gemifloxacin is not considered to be an appropriate treatment for CAP due to legionella.

Acute exacerbation of chronic bronchitis:
This indication cannot be approved without a demonstration of superiority of gemifloxacin over placebo or over an active comparator.

Risks

The most common adverse effect of gemifloxacin is rash. Rash is less common with 5 days treatment than with 7 days treatment but the rate of rash even with 5 days is higher than observed with comparator regimens. Since five days gemifloxacin is considered to be inadequate for treatment of CAP, the frequency of rashes and of other AEs associated with seven days therapy must be used to assess benefit/risk.

Gemifloxacin is a more potent clastogen than other fluoroquinolones and appears to provide only a lower margin of safety than cipro- or moxifloxacin for therapeutic treatment. The margin of safety for therapeutic treatment based on exposure levels clastogenic in vivo in rat is relatively low.

Balance

The risk-benefit relationship for use of 7 days gemifloxacin to treat mild to moderate CAP is not considered to be favourable.

The risk-benefit relationship for 5 days gemifloxacin to treat AECB cannot be considered favourable without a demonstration of superiority against placebo or against an active comparator.

Conclusion

Currently none of the sought indications is approvable.