17 December 2015
EMA/CHMP/390341/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xegafri

International non-proprietary name: rociletinib

Procedure No. EMEA/H/C/004053/0000

Note

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

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List of abbreviations

AAG alpha-1 acid glycoprotein
AE adverse event
ALT alanine transaminase
AST aspartate transaminase
ATP adenosine triphosphate
AUC(0–inf) area under the concentration versus time curve from time zero extrapolated to infinity
AUC(0–24) area under the concentration versus time curve from time zero to 24 hours postdose
AUC50: half maximal effective area under the concentration versus time curve from time zero to 24 hours postdose
AUC90:90% maximal effective area under the concentration versus time curve from time zero to 24 hours postdose
AUCss area under the concentration-time curve at steady-state
BCRP breast cancer resistance protein
BID twice daily
CL clearance
CLcr creatinine clearance
CL/F apparent clearance
Cmax maximum observed plasma concentration
CR complete response
DCR disease control rate
DLT dose-limiting toxicity
ECOG Eastern Cooperative Oncology Group
EGFR epidermal growth factor receptor
FB free base
HBr hydrobromide
HER2 human epidermal growth factor receptor 2
ICH International Conference on Harmonisation
IGF-1R insulin-like growth factor 1 receptor
ILD interstitial lung disease
INSR insulin receptor
IRR independent radiological review
mRNA messenger RNA
MTD maximum tolerated dose
NSCLC non-small cell lung cancer
OAT organic anion transporter
OATP organic anion transporting polypeptide
OCT organic cation transporter
OGTT oral glucose tolerance test
ORR objective response rate
OS overall survival
P-gp p-glycoprotein
PFS progression-free survival
POPPK population pharmacokinetics
PPI proton pump inhibitor
PR partial response
PS performance status
QD once daily
QTc corrected QT interval
RECIST Response Evaluation Criteria in Solid Tumors
SAE serious adverse event
SD stable disease
SLD sum of the longest diameter
StD standard deviation
T1/2 elimination half-life
TDI time-dependent inhibition
TEAE treatment-emergent adverse event
TGI tumor growth inhibition
TK1 tyrosine kinase inhibitor
Tmax time from dosing at which Cmax occurs
wt wild-type

1. Recommendations

Based on the review of the data on quality, safety and efficacy, the CHMP considers that the application for Xegafri, in the treatment of adult patients with T790M positive mutant epidermal growth factor receptor(EGFR) non-small cell lung cancer (NSCLC) 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 MA pertain to the following principal deficiencies:

Clinical

- ***Efficacy***

Due to data immaturity, the benefit, especially in terms of duration of response, is non-evaluable.

- ***Safety***

QT prolongation and a number of serious cardiac events, including sudden death and ventricular tachyarrhythmias, constitute a major safety issue.

NB: Due to the complexity of the outstanding issues, an accelerated assessment is no longer an option.

Proposal for questions to be posed to additional experts

Not at this stage.

Proposal for inspection

GMP inspection(s)

No cause for inspection has been identified by the CHMP.

GCP inspection(s)

No for cause need for inspection has been identified by the CHMP.

New active substance status

Based on the review of the data the CHMP considers that the active substance rociletinib contained in the medicinal product Xegafri could be qualified as a new active substance in itself, provided that satisfactory responses are given to the concerns as detailed in the List of Questions.

2. Executive summary

2.1. Problem statement

Lung cancer is both the most common cancer and the leading cause of cancer-associated death worldwide. It is histologically classified into non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), and carcinoid. NSCLC accounts for 80-85 % of all lung cancers and is further subtyped into adenocarcinoma, squamous-cell carcinoma and large-cell carcinoma. Most cases of NSCLC are unresectable locally advanced / metastatic at presentation, thus entailing a poor prognosis. However, a substantial proportion of NSCLC depend on driver-mutations to fuel the malignant phenotype: EGFR, ALK, ROS1, BRAF, KRAS, HER2, c-MET, PIK3CA and the list continues to grow in the literature; these mutations are the object of targeted therapies, who offer significant, albeit transitory, tumor responses.

EGFR-activating mutations (most commonly including exon 19 deletions and/or exon 21 L858R missense mutations) occur in approximately 10-15% of NSCLC cases in Caucasians and 30-50% in East Asian patients; the cause of this differential ethnic prevalence remains unknown. Moreover, EGFR mutations are most frequently observed in women, light or never smokers and in patients with adenocarcinoma histology.

Most of EGFR-mutated patients respond to frontline first- or second-generation EGFR TKIs (gefitinib, erlotinib, afatinib), with response rates of 56 to 74% and PFS of 10 to 14 months; both outcomes are superior to traditional platinum-based chemotherapy. A minority achieve disease control for years on these drugs, however most patients develop acquired resistance within 10-12 months.

There are multiple mechanisms for acquired resistance, e.g.: amplification of the mesenchymal epithelial transition (MET) protooncogene, which activates an AKT-mediated signaling pathway, bypassing the EGFR; BRAF mutations; HER2 amplification; even histologic changes, i.e transformation to small-cell or epithelial-mesenchymal transition.

However, the most common cause of acquired resistance (50-60%) is the EGFR T790M point mutation. Initially thought to simply exclude binding of EGFR-TKI drugs by steric hindrance, the substitution of methionine for threonine at position 790 in exon 20 is suggested to cause resistance by restoring the EGFR affinity for ATP, thus decreasing the binding of the reversible ATP-competitive TKIs, gefitinib and erlotinib.

Several studies showed that patients who acquired the T790M mutation after EGFR TKI therapy had longer post-progression survival than those without it, associated with less metastatic sites and a better performance status. In this sense, the acquired T790M mutation may be indicative of a more indolent disease. There also is increasing evidence that a low level of the T790M mutation exists before treatment in many patients with EGFR-mutant NSCLC and may predict a worse PFS on e.g. erlotinib, compared to those without pre-treatment T790M.

The second-generation inhibitors afatinib and dacomitinib irreversibly inhibit both wild-type and mutant EGFR proteins, and to a lesser extent, T790M EGFR. In clinical trials designed to test activity in patients with acquired resistance, however, these drugs have not induced robust responses. The response rates were around 10% and PFS under 4 months in NSCLC previously treated with gefitinib or erlotinib, presumably due to the inability of afatinib or dacomitinib to inhibit *EGFR* T790M at clinically relevant doses. In addition, the inhibition of wild-type EGFR is associated with known anti-EGFR class effects (rash and diarrhea).

Currently there is no approved targeted therapy for the T790M 'gatekeeper' mutation. Platinum-based doublet chemotherapy post-EGFR TKIs offers an ORR of 25%, with mPFS of 5.4 months, according to the IMPRESS study. Beyond this point, the options are few: rechallenge with EFGR TKIs - due to re-senzitation, in absence of drug selection pressure that stimulates the growth of resistant clones, with response rates at approx. 10% and PFS similar to chemotherapy, about 4 months; combination of afatinib with cetuximab, with an ORR at 29% and PFS of <5 months; salvage chemotherapy (single agent usually); inclusion in a CT. As such, this is an area of unmet clinical need.

Several third-generation EGFR TKIs are under development: AZD9291, rociletinib and HM61713. Rociletinib is designed to covalently (hence irreversibly) bind to a specific site and inhibit the mutant forms of EGFR, while relatively sparing WT EGFR.

2.2. About the product

Xegafri (rociletinib, CO-1686) is a small molecule TKI that irreversibly binds and inhibits EGFR with the common activating (L858R, Del19) and the T790M resistance mutation to erlotinib and gefitinib, and less activity towards wild-type (WT) EGFR.

Xegafri is developed as a single agent for the treatment of adult patients with metastatic / unresectable locally-advanced, mutant-EGFR NSCLC, who have been previously treated with an EGFR-targeted therapy and have the T790M mutation.

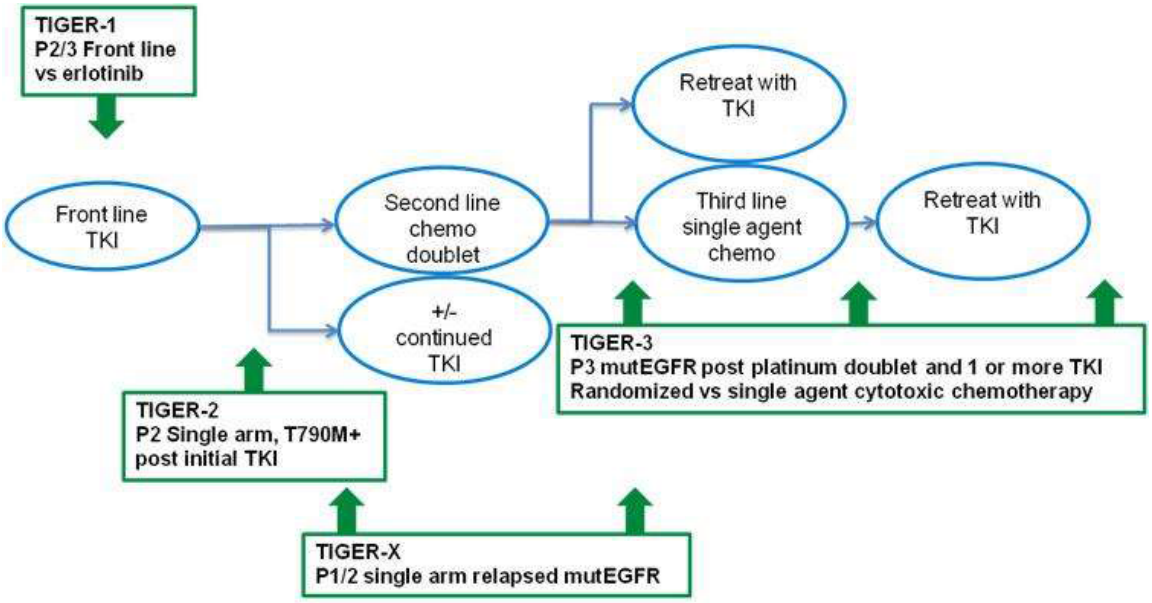
2.3. The development programme/compliance with CHMP guidance / scientific advice

Development program

1. The initial clinical development program focused on patients whose disease has progressed on existing EGFR-TKIs, where T790M is the dominant single driver of progression.

2. As rociletinib inhibits the common initial activating EGFR mutations, development is also ongoing in EGFR TKI-naïve patients with EGFR mutant NSCLC.

3. In addition, as responses have been observed in patients whose tumors centrally test negative for T790M, T790M-negative patients are included in the ongoing Phase 2 and 3 programs.



The Applicant has received both CHMP/EMA and FDA advice.

2.4. General comments on compliance with GMP, GLP, GCP

No concerns have been raised during the Quality assessment that would give cause of a GMP inspection prior to authorisation.

The pivotal toxicity studies were performed in accordance with GLP.

According to the Applicant, all studies in the rociletinib clinical development program were performed in concordance with current standards for the design, conduct, and analysis of clinical research, including the ICH GCP and all relevant region-specific requirements.

2.5. Type of application and other comments on the submitted dossier

- Legal basis: This is a centralized procedure, a full application (NCE) for a Marketing Authorisation (MAA) in accordance with Directive 2001/83/EC as amended and Regulation (EC) No 726/2004 as amended).
- Accelerated procedure: requested on 3rd July 2015, under Article 14(9) of regulation 426/2004 and granted on 23rd July 2015.
- Conditional approval: requested in accordance with the Article 14(7) of Regulation (EC) No 726/2004
- Exceptional circumstances: no
- Biosimilar application: no
- 1 year data exclusivity: no
- Significance of paediatric studies: class waiver (CW/1/2011) confirmed on 11 January 2013 (EMA/460326/2012)

3. Scientific overview and discussion

3.1. Quality aspects

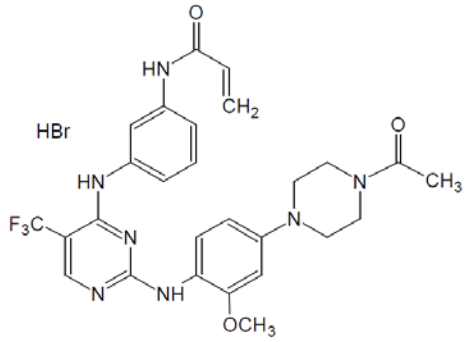
3.1.1. Introduction

The application concerns the medicinal product Xegafri in the form of film-coated tablets of the two strengths 125 mg and 250 mg. The active substance rociletinib hydrobromide is claimed to be a new active substance (NAS) and a separate NAS assessment report has been established.

3.1.2. Active Substance

General Information

The active substance rociletinib hydrobromide is pale to dark yellow and crystalline. It is slightly hygroscopic and its aqueous solubility is pH dependent. Several polymorphic forms exist and the anhydrous Form 1 is used in Xegafri. The chemical name of rociletinib hydrobromide is *N*-[3-({2-[4-(4-acetylpiperazin-1-yl)-2-methoxy-anilino]-5-(trifluoromethyl)pyrimidin-4-yl}amino)phenyl]prop-2-enamide hydrobromide and it has the following structure:



The molecular formula is $C_{27}H_{28}F_3N_7O_3$ • HBr.

Manufacture, characterisation and process controls

The active substance is manufactured by a five-step linear synthesis from three starting materials by one manufacturer. There are four isolated intermediates and the last step of the synthesis is the salt formation. The choice of starting materials was discussed in connection with CHMP Scientific Advice sought by the applicant and the definition of starting materials is considered acceptable. Characterisation has been performed by elemental analysis, IR spectroscopy, proton and carbon NMR spectroscopy and mass spectrometry.

Generally, the manufacturing process, its development and the control of starting materials, reagents, solvents and intermediates are sufficiently described but a number of concerns are raised. The process controls applied during the synthesis are considered adequate.

Potential and actual impurities have been discussed in detail. Four impurities are limited in the active substance specification. For one impurity, the structure has not been conclusively determined and further attempts to confirm its identity are requested. An acceptable discussion regarding potential genotoxicity of the active substance and related substances has been presented.

Specification

The active substance specification proposed includes tests for appearance, identity, assay, related substances, residual solvents, inorganic impurities, heavy metals, water content, bromide content, polymorphic form and particle size. The parameters included are adequate but questions are posed regarding the assay limits and discussions with respect to the potential carry-over of some reagents/solvents need to be presented. Further information also has to be provided regarding the test methods and validations of the same.

Extensive batch analyses data has been provided and results presented are well within the proposed specification limits.

Stability

The active substance is packaged in double polyethylene (LDPE) bags and secured with a cable tie. The filled bags are placed into a heat-sealed laminated aluminium bag and then into a lined steel or HDPE locking-ring drum.

Formal stability studies on three primary pilot scale batches are ongoing. The active substance is evaluated for appearance, assay, related substances, water content and polymorphic form. Storage conditions of 5ºC, 25°C/60% RH and 40ºC/75% RH are included in the evaluation. So far results from

12 months of storage at 5ºC and 25°C/60% RH and from 6 months of storage at 40ºC/75% RH have been presented.

The primary stability data is claimed to support an initial retest period of 12 months at 5°C. However, no retest period is granted at this stage as there are outstanding questions regarding the control of the active substance.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The medicinal product is a conventional immediate-release film-coated tablet manufactured by a dry granulation process, compression and coating. The tablets are provided in two dosage strengths of 125 mg and 250 mg with respect to rociletinib free base. The 125 mg strength tablet is a 9 mm round, yellow tablet debossed with “C11”. The 250 mg strength tablet is a 7.5 mm x 16 mm oval, yellow tablet debossed with “C77”.

Both tablet strengths are manufactured from a common blend and have the same film-coating. Hence, their compositions are proportional. The excipients used are commonly used in tablet formulations: silicified microcrystalline cellulose, copovidone, colloidal silicon dioxide, croscarmellose sodium and magnesium stearate in the tablet core and hypromellose, titanium dioxide, triacetin, iron oxide yellow and water in the film-coating blend.

The medicinal product is packaged in a clear triplex laminate blister (PVC/PCTFE (polychloro-trifluoroethylene)/PVC) with a multilayer lidding foil consisting of paper/PET/Alu/heat seal coating.

The pharmaceutical development has been thoroughly described as concerns both the formulation and the manufacturing process. In both cases a traditional approach has been used and no design space is claimed. In this part questions are raised regarding the pH dependent solubility of the active substance as well as the choice of in-vitro dissolution method.

Manufacture of the product and process controls

The film-coated tablets are manufactured by a standard process comprising blending, milling, roller compaction, granulation, tablet compression and film-coating. The tablets will be produced by one manufacturer.

The manufacturing process is sufficiently described and appropriate in-process controls are considered to be in place. Only a few minor issues need to be resolved.

Formal manufacturing process validation will be conducted following a prospective, traditional approach at commercial-scale blend batch size on a minimum of three consecutive batches of the blend and a minimum of three consecutive batches of each of the tablet strengths during the compression and coating steps. An adequate validation plan has been presented. This is acceptable as the manufacturing process has been sufficiently described and evaluated in the development part of the dossier.

Product specification

The specification of the tablets includes tests for colour, appearance, identity, assay, degradation products, dissolution, uniformity of dosage units, water content and microbial limits. The control of the film-coated tablets is found acceptable with the exception of the proposed limit of one of the specified

degradation product. Furthermore, the dissolution method is not accepted. A discriminatory method with relevant limits is expected. There are also questions regarding test method validation.

Extensive batch analyses data for the medicinal product has been provided, and among them results from 20 batches of the proposed formulation. All results presented are within the proposed specification limits.

Stability of the product

Formal stability studies on four pilot-scale batches of each of the strengths of the drug product have been initiated and these have been stored for up to 9 months at long-term conditions (25°C/60% RH) and for 6 months under accelerated conditions (40ºC/75% RH). Additionally, forced degradation and photostability studies have been performed. It has been demonstrated that the tablets are photostable.

The stability data provided is claimed to support a shelf life of 18 months with the temperature storage restriction “Store below 25°C”. However, no shelf life is accepted at this stage as there are questions regarding the control of the drug product which need to be addressed and only limited stability data has been provided. The post-authorization protocol and the stability commitment need to be amended. Furthermore, a holding time for the bulk product and supporting stability studies should be presented.

3.1.4. Discussion on chemical, pharmaceutical and biological aspects

The quality documentation presented on the active substance rociletinib hydrobromide and the medicinal product Xegafri 125 mg and 250 mg film-coated tablets is in general considered acceptable. The development as well as manufacture has been well described. However, additional information needs to be provided and the specifications are not yet accepted. No retest period or shelf life is granted at this stage.

3.1.5. Conclusions on the chemical, pharmaceutical and biological aspects

No major objections are raised but a number other concerns on the quality documentation for the active substance and the medicinal product should be addressed. These issues need to be resolved before the application can be approved from a quality perspective.

3.2. Non clinical aspects

3.2.1. Pharmacology

Rociletinib is a small molecule irreversible tyrosine kinase inhibitor that targets the most common EGFR activating (L858R, delE746-A750) and resistance mutations (T790M) observed in NSCLC, while relatively sparing WT EGFR. A number of biochemical, cellular and in vivo studies has been conducted to characterize rociletinib pharmacology activity.

Primary pharmacodynamics

In vitro studies

Enzyme biochemical studies showed rociletinib to be a potent and selective irreversible inhibitor of isolated mutant Epidermal Growth Factor Receptors (EGFRs) with a margin of selectivity against wild-type EGFR (apparent IC50s < 1 nM for double mutant L858R/T790M *vs.*6 nM for wild-type EGFR).

In in vitro cell proliferation studies, rociletinib demonstrated inhibition of single-activated mutant EGFR (DelE746-A750) and double mutant (EGFR L858R/T790M) assays with an apparent mean IC50s from 14 nM and 48 nM, respectively. In contrast, weaker inhibition towards wild-type EGFR was detected in cell proliferation assays (apparent IC50 544 nM). In EGFR phosphorylation assays, rociletinib showed inhibition of single-activated mutant EGFR (DelE746-A750, HCC827 cell) and double mutant (EGFR L858R/T790M, H1975 cells) assays with an apparent mean IC50s from 58 nM and 187 nM, whereas rociletinib displayed a potency against WT EGFR of apparent IC50 > 4331 nM (A431 cells). Thus, in vitro data indicate that in cellular context rociletinib has greater activity towards mutant EGFRs compared to wild-type EGFR.

In vivo studies

The efficacy of chronic once daily oral dosing of rociletinib across different subcutaneous cell line single mutant EGFR (HCC827, del19 EGFR) and double mutant EGFR (NCI H1975, L858R/T790M) and wild-type EGFR xenograft mice models was determined in vivo. Furthermore, efficacy was also evaluated long term study using a PC9 (Ex19del) xenograft model as well as in genetically engineered mouse (GEM) lung cancer models driven by WT or mutant EGFR. Finally, the efficacy of rociletinib was studied in a model with patient derived xenografts.

Rociletinib delivered as a single agent induced a dose-dependent and significant tumour growth inhibition (> 80%) across all mutant EGFR models tested at doses ≥ 30 mg/kg. Consistent with lower efficacy towards wild-type EGFR, analysis of p-EGFR signalling in normal lung and skin tissues revealed no significant inhibition of WT EGFR in vivo.

Rociletinib demonstrated dose- and time-dependent inhibition of phosphorylation of both EGFR and the downstream pathway marker AKT in xenografts with both activating and acquired resistance EGFR mutations.

At the same exposure levels, the tumor growth inhibition results with rociletinib HBr were comparable to those obtained with rociletinib FB in both HCC827 and NCI H1975 xenograft models.

PK/PD analysis revealed that time above the threshold of 200 ng/mL offered the best correlation with median tumor volume, whereas Cmax and Cmin demonstrated a poor association. In addition, the greatest reduction in tumor volumes were commonly observed when the time above the threshold of 200 ng/mL was ≥ 15 hours.

Secondary pharmacodynamics and safety pharmacology

The selectivity of rociletinib was profiled against 434 WT and mutant kinases using functional biochemical assays. The 4 clinically relevant mutant EGFR kinases (T790M, del19/T790M, and L858R/T790M, and L858R) were demonstrating the greatest inhibition at 100 nM. Additional kinases inhibited ≥ 70% when incubated with 100 nM rociletinib included 2 mutant leucine-rich repeat kinase 2 (LRRK2) kinases and 2 WT kinases, focal adhesion kinase (FAK/PTK2) and checkpoint kinase 2 (CHK2). Selectivity profiling data, thus, indicate a potential risk for off-target activity in patients given that the unbound Cmax concentration of rociletinib is 65 nM in human (at 500 mg BID).

The activity of rociletinib and the three active metabolites M460, M502, M544 was also examined in biochemical and cellular assays. In contrast to rociletinib, the metabolites M460, M502, and M544 demonstrated limited biochemical and cellular potency against single and double mutant EGFR (IC50s ≥ 700 nM in all assays). The metabolites showed also weak potency against WT EGFR in A431 cell line driven by WT EGFR, with IC50 > 1000 nM). In a kinome counter-screen panel of ~ 350 kinases, all three metabolites exhibited significant activity (>70% inhibition at 100 nM) against > 20 other kinases (including ALK, LRRK2, FER, FES/FPS, IRR/INSRR, FAK/PTK2). Since M460, M502 and M544 are all

present in human plasma at unbound Cmax concentrations ranging from ~ 80-500 nM, there is a potential for off-target activity of rociletinib metabolites in clinical settings**.**

Hyperglycemia has been observed in patients treated with rociletinib. However, rociletinib administration did not significantly elevate plasma glucose or insulin levels over vehicle treatment in rats or dogs in vivo. Therefore the activity of the metabolites against IGF1R and InsR was therefore further investigated using additional enzyme and cellular assays.

Cellular profiling indicated that metabolites M460 and M502 had 2- to 7 fold greater potency towards IGF1R and INSR as compared to rociletinib, respectively. Further characterisation showed that dosing of M502 resulted in a significant increase in glucose and insulin levels in rat and dog. Dosing of M460 also caused an apparent increase in glucose and insulin levels although the increases did not reach statistical significance. Given that the exposure to circulating M502 is approximately 8-fold higher than M460 in humans, these data suggest that M502 is likely to play a causal role, and M460 to a lesser extent, in the hyperglycemia observed in patients.

Rociletinib causes prolongation of QTc interval in some patients. However, rociletinib was weakly potent with an IC50 value of 13.2 µM in the human ether-a-go-go (hERG) assay which is 203-fold higher than the Cmax unbound plasma rociletinib concentration (65 nM) observed in patients at 500 mg BID. In vivo, no adverse cardiovascular effects were noted in a conscious dog study in which telemetry-instrumented dogs received rociletinib FB at doses of up to 500 mg/kg/dose BID or rociletinib HBr a dose of 600 mg/kg QD. In the repeat-dose toxicity studies in dog with rociletinib FB there were no treatment-related cardiovascular effects at doses up to 500 mg/kg/dose BID, which corresponded to a Cmax of 4000 ng/mL. This concentration was in the range and slightly (~1.4 fold) above the Cmax bound plasma rociletinib concentration (2800 ng/mL) observed in patients at 500 mg BID.

Characterisation of the metabolites demonstrated that the IC50 values for the inhibitory effects of M460, M502, and M544 on hERG potassium currents were 0.05 µM, 6.1 µM, and 18.1 µM, respectively which are 0.6, 12, and 203 fold higher than the Cmax unbound plasma M460, M502, and M544 concentrations (81 nM, 516 nM, and 89 nM, respectively) observed in patients at 500 mg BID. Based on the information currently available concerning these 3 metabolites, M460 may play a role in the development of QTc prolongation in patients.

3.2.2. Pharmacokinetics

Rociletinib has a pH-dependent aqueous solubility with a low solubility of 0.006 mg/mL seen at pH 7, whereas a solubility of ~7 mg/mL was stated at pH 1. As a consequence of the pH-dependent solubility the absorption of rociletinib was improved at low gastric pH or by the presence of food. The hydrobromide (HBr) salt of rociletinib displayed improved absorption and increased systemic exposure at a given dose as compared to rociletinib FB. At equivalent exposures, the nonclinical pharmacodynamics and the toxicity profiles are comparable for both forms of rociletinib.

Absorption

Plasma clearances were 0.53 and 0.64 L/h/kg in mice and rats and ~0.75 L/h/kg in the dog. A low volume of distribution of rociletinib as observed in the mouse (0.34 L/kg), rat (0.23 L/kg), and dog (1.01 L/kg) is consistent with the acidic nature of the compound, with an ionization equilibrium favouring plasma.

The combination of low clearance and low volume of distribution 0.23 to 1.0 L/kg in all non-clinical species examined results in half lives of 2.6-4.5 hours. The T1/2 following oral administration was

longer than that following intravenous dosing (0.5 to 1.6 hours), which can be due to absorption-rate limited elimination. Consistent with the elimination half-life of rociletinib, little accumulation in non-clinical species was observed after repeated oral dosing. Moreover, the exposure to rociletinib was comparable between sexes in the dog, while female rats had generally a higher exposure than male rats.

The oral bioavailability of rociletinib FB was < 5% in fasted dogs, but was increased to 27% in fed dogs. The oral bioavailability was moderate, 21% and 65% in the rat and mouse, respectively. With increasing oral dose of rociletinib FB, a less than dose-proportional increase in the exposure was seen at doses ≥300 mg/kg/dose BID. The exposure increased approximately in proportion to dose up to 250 mg/kg BID. In addition, the variability in exposure also increased with escalating doses. Since rociletinib exhibited good permeability in Caco 2 cells, the increase in PK variability is likely due to the pH-dependent solubility of rociletinib FB with low solubility at neutral pH.

Distribution

A whole body autoradiography (QWBA) study was performed to investigate the tissue distribution of radioactivity in albino Sprague-Dawley rats (male and female) as well as in pigmented Long-Evans rats (male). Following oral administration of [14C] rociletinib HBr at a dose of 150 mg/kg (~400 µCi/kg) the radioactivity was well distributed in rats and most tissues had concentrations that were similar to or higher than blood at all time-points. The Cmax of [14C] rociletinib HBr-derived radioactivity in most tissues were found at 6 h post-dose. The highest concentrations (> 20.0 µg equiv/g) at Cmax were found in tissues of the gastrointestinal tract (stomach, small intestine, cecum, and colon), the Harderian gland, liver, kidney medulla and cortex, and adrenal cortex where concentrations ranged from approximately 20.0 to 1100.0 µg equiv/g. The tissues having the lowest concentrations (< 1.0 µg equiv/g) at Cmax were: brain, spinal cord, eye lens, bone, and reproductive tissues (epididymis and testis).

The tissues with the longest terminal half-life were blood (351 h), lung (274 h), heart (202 h), adrenal cortex (143 h), kidney cortex (134 h), and salivary gland (129 h), whereas oral mucosa (34.5 h), colon (21.3 h) and cecum (8.0 h) showed the shortest t1/2.

In pigmented male rats, higher concentration of radioactivity was observed in the uveal pigment of the eyes and the pigmented skin as compared to albino rats, suggesting an association between radioactive drug-related material and melanin. At 1176 hours (i.e., 49 days) after dosing, radioactivity was still detectable in the uveal pigment of the eyes and the pigmented skin. However, rociletinib was not phototoxic (eye and skin evaluated) following 3-day repeat oral dose administration to pigmented rats at 500 mg/kg/dose BID.

Rociletinib exhibited concentration-independent protein binding in the plasma from mouse, rat, dog, and human, with 98.7%, 98.7%, 96.8%, and 98.7% bound, respectively. In contrast, a concentration-dependent protein binding was observed for rociletinib in rabbit plasma. The plasma protein binding of the metabolites M502 and M544 showed higher plasma protein binding (approximately 99% and 98.1% bound, respectively) in rat and a lower plasma protein binding (approximately 94.3% and 94.7% bound, respectively) in human. M460 was the least bound of the 3 metabolites tested with protein binding in human plasma ranging from 88.9% to 93.5%.

Metabolism

In vitro, rociletinib is not extensively metabolized by cytochrome P450 enzymes (CYPs). In vivo, rociletinib is extensively metabolized mainly by phase 2 reactions such as glutathione conjugation, acetylation and amide hydrolysis.

In vivo, unchanged rociletinib was the predominant radioactive component detected in rat and dog plasma and feces. While small amounts of rociletinib were detected in dog urine (0.01% dose), rociletinib was not detected in rat urine. The major circulating metabolite in rat was M10 (M544, N acetylated N desacryloyl rociletinib).

The entire circulating radioactivity in human plasma following [^{14}C] rociletinib administration consisted of unchanged rociletinib and metabolites M460, M502, and M544 through 24 hours postdose. The N-desacryloyl metabolite (M502) was the major circulating metabolite in human plasma due to a greater capacity for amide hydrolysis in humans.

Metabolite M502 was detectable in circulation in all nonclinical species; although the M502 AUC was at least 10-fold lower than in humans. M460 was at low or undetectable levels in all nonclinical species. M544 was not detectable in dog, whereas the AUC of M544 in rats was slightly higher (1.2-1.7-fold) (at STD 10 dosing) than in patients at 500 mg BID. Generally, human subjects have higher circulating levels of M460 and M502 compared to nonclinical species. In vitro kinase profiling revealed an increased potency of M460 and M502 (> 6-fold) against IGF1-R and insulin receptor compared to rociletinib. M460 is also potent on hERG potassium currents (IC50: 0.05 µM). Thus, the M502 and M460 metabolites could contribute to hyperglycemia and the development of QTc prolongation as observed in some patients.

Excretion

Excretion mass balance studies in the rat, dog, and human concluded that the primary route of elimination of radioactivity following an oral administration of [^{14}C] rociletinib HBr was in the feces, > 92% ≥ 94%, and > 85%, respectively. In BDC rats, > 23% of the administered dose was recovered in bile. Urinary elimination was a minor route of elimination (≤ 1.5% and 4.7% of administered dose in nonclinical species and humans, respectively). In rat and dog, the majority of the administered dose was excreted in 24 to 48 hours.

Rats and dogs are the species used in the pivotal repeated toxicology studies. The choice of nonclinical species can be considered acceptable. However, plasma exposure of the metabolites M502 and M460 was clearly below the human exposure in all toxicology studies. Further, the exposure of metabolite M544 at the rat STD10 or NOAEL was approximately equal or slightly above to the human exposure. Consequently there are no established exposure margins in the performed toxicology studies. This is still acceptable according to the ICH S9 guideline.

3.2.3. Toxicology

The toxicology program for rociletinib FB was designed to support the daily oral dose administration to advanced NSCLC patients. Rats and dogs were chosen as appropriate species for toxicology studies based on similar metabolic profiles across all species in *in vitro* assays. For rociletinib FB, nine toxicity studies were completed. In the rat, an acute toxicity study was followed by two repeat-dose studies that were 7 and 28 days in duration. In the dog, an escalating single dose study was followed by two repeat-dose studies that were 7 and 28 days in duration. Also conducted were an *in vitro* Ames assay, an *in vitro* chromosomal aberration assay, and an *in vivo* phototoxicity study in Long Evans pigmented rats. With the development of rociletinib HBr, additional safety and toxicology studies were performed in rat and dog to compare rociletinib FB and rociletinib HBr toxicity and TK profiles. Nine studies were also completed using rociletinib HBr: a single escalating dose study in dog, a 14-day dose range finding (DRF) study in rat, plus 28 day and 91-day repeat-dose studies in rat and dog, DRF and confirmatory embryo-fetal development studies in rat and rabbit and an *in vivo* micronucleus test in the rat.

Rociletinib was of low acute toxicity in non-GLP single dose studies performed with the FB formulation in the rat and the dog, and with the HBr formulation in the dog.

Rociletinib FB and HBr demonstrated qualitatively similar toxicity in a range of non-GLP and GLP repeated dose toxicity studies. However, the compound plasma concentrations in the rat toxicology study were highly variable. .

Repeat-dose toxicity studies in rat

In rats, consistent findings were abnormal feces and effects on body weight ranging from losses to significant decreases in body weight gain. Body weight changes correlated with decreases in food consumption. Body weight losses and severe decreases in body weight gain were most pronounced in the initial 2 weeks of drug administration at doses ≥ 500 mg/kg/day. Rociletinib did not induce acute lethality, but moribundity and deaths (moribund sacrifices) did occur after 2 weeks of dosing in the 28- and 91-day studies in the rat. Effects on reticulocyte counts, RBC mass indices, and bone marrow cellularity were primarily seen in moribund animals. In general, changes in clinical pathology parameters in animals that survived to study termination were minor, non-progressive and reversible. Gastrointestinal lesions were identified in the 28-day studies but not the 91-day study. Dermal changes were seen in the 14-day study and included thin/rough hair coat and sores. The skin lesions were principally inflammatory in nature and involved hair follicles and sebaceous glands at 400 mg/kg/day. Similar dermal changes were seen sporadically after 28 and 91 days of treatment but no pathologic lesions were detected in skin at the study termination. Squinting, attributed to meibomian atrophy (eyelid), was observed in rats treated for 28 days and also in moribund male rats in the 91-day study at doses ≥ 500 mg/kg/day. Glandular atrophy of multiple organs was present in all repeat-dose studies, and in each case these changes were fully reversible.

Repeat-dose toxicity studies in dog

There were no deaths in the dog studies. The common clinical presentation was abnormal feces. Decreased food consumption and body weight changes were evident in the dog although body weight changes did not occur in all studies and were much less severe than those seen in the rat. After 28 days of treatment (rociletinib FB), lesions in the oral mucosa (buccal mucosa, tongue, and hard palate) and esophagus were identified and characterized as chronic active inflammation. At the high dose of 1000 mg/kg/day, the finding was severe and established the HNSTD in that study. With chronic (91 days) rociletinib HBr administration, inflammatory changes in the hard palate and esophagus were insignificant components of the lesions that consisted of minimal squamous hyperplasia. All mucosal lesions were fully reversible. In general, changes in clinical pathology parameters were minor, non-progressive and reversible in each repeat-dose study. The only noteworthy exceptions were elevated total WBC, neutrophils, and monocytes in dogs with inflammatory lesions in the oral mucosa or skin. The dermal changes were detected after 4 weeks of rociletinib administration and included: red discoloration of skin, thin hair coat, broken skin, and sores at doses of 150 mg/kg/day. The skin lesions were characterized as chronic active inflammation involving hair follicles, and thus bore morphologic similarity to skin lesions seen in rats after 14 days of treatment. Skin lesions in dogs were considered severe and in some instances required veterinary treatment. Thus, the clinical dermal findings established the HNSTD as 200 mg/kg/day in this study. Microscopic findings in dogs treated for 91 days were fully reversible.

In summary, the main observed findings included effects on the gastrointestinal system (GI), hematopoietic system, glands, and skin. The majority of the target effects reversed following 28 days recovery periods.

Toxicokinetics and metabolites

The highest human plasma concentrations observed at the dose of 500 mg BID were used in exposure margin calculations. The exposure to rociletinib was approximately equal to the human exposure at the rat STD10 and the dog HSTND. Consequently, there are no exposure margins to the observed toxicity. The exposure to the metabolites M502 and M460 was clearly below the human exposure in all toxicology studies. The exposure to metabolite M544 at the rat STD10 or NOAEL was approximately equal to the human exposure and clearly below the exposure at the highest dose (NOEL) in the pregnant rabbit. The complete toxicologic profiles of these metabolites have not been established and consequently there are no established exposure margins.

In fact, two (or possible 3) metabolites have been implicated to be the cause of unexpected AEs observed in the clinic. In patients treated with rociletinib hyperglycemia is one of the most common AEs. This was not observed in dogs or rats treated for up to 3 months in toxicology studies. Increased glucose and insulin levels were also not observed in an OGTT performed with rociletinib where the plasma levels achieved were approximately 3 to 5-fold higher than the mean C_{max} of rociletinib (2800 ng/mL) in patients dosed at 500 mg BID, suggesting that the parent molecule is unlikely to play a role in the hyperglycemia observed in patients. Taken together, these results suggested that the parent molecule was unlikely causative for hyperglycemia and indirectly implicated metabolite(s) that occurred in greater abundance in humans than in rats or dogs. Cellular profiling demonstrated that M460 and M502 have 2- to 3-fold and 3- to 7-fold greater potency against the INSR and IGF1R, respectively, than rociletinib, while M544 showed a similar *in vitro* inhibitory potency for INSR and IGF1R as rociletinib. Dosing rats with M502 and M460 in an OGTT resulted in increased glucose and insulin excursion, consistent with the increased glucose levels observed in patients dosed at 500 mg rociletinib BID. Given that the exposure to circulating M502 is approximately 8-fold higher than M460 in humans and that M502 and M460 have comparable potency for IGF1R and INSR, these data suggest that inhibition of IGF1R and IR by M502 causes dose dependent hyperglycemia due to reversible insulin resistance.

In addition, prolongation of QTc interval has been observed in some patients. Cardiac safety of rociletinib was thoroughly evaluated in *in vitro* assays for hERG activity and hERG trafficking and *in vivo* safety pharmacology studies using conscious telemetry-instrumented dogs and monitoring of ECGs in the 28 and 91-day repeat-dose study in dog. No significant nonclinical cardiac safety data was observed with rociletinib. Given these results and the levels of human metabolites observed in patients, hERG assays were conducted on M502, M544, and M460. It was found that the IC_{50} for the inhibitory effect of M460 on hERG potassium currents was 0.05 µM, which is 0.6-fold lower than the C_{max} unbound plasma M460 concentration (81 nM) observed in patients at 500 mg BID. Collectively, these data suggest that the human metabolite, M460, may play a contributory role in the development of QTc prolongation.

Based on the lack of exposure margins also for the parent compound, the pharmacological mode of action described for the parent and the metabolites, the patient population and the nature of the adverse effects the lack of further toxicity studies for the metabolites are accepted.

Reproductive and developmental toxicity

Rociletinib did cause maternal toxicity in rats and rabbits at high doses. Clinical signs and significant decrease in body weight gain and food consumption were noted in pregnant rats at 300 mg/kg/day. At the same dose, a statistically significant reduction in total fetal body weights was noted that was correlated with the decrease maternal body weight. In pregnant rabbits, 2 mortalities, adverse clinical signs, body weight loss, and significantly reduced food consumption were observed at 80 mg/kg/day in the DRF study. At the same dose, there was a 19% reduction in total fetal body weights that was correlated to the rociletinib-related effects on maternal body weights. In the GLP study, no changes in

body weight or food consumption were noted at the high dose of 40 mg/kg/day. No additional rociletinib-related effects or teratogenic effects were observed in rats or rabbits. The NOAEL values for maternal toxicity in the rat and rabbit were 70 mg/kg/day and 40 mg/kg/day, respectively, which corresponded to AUCs of 18700 and 21200 ng·hr/mL, respectively for rociletinib. These were 0.7 fold and 0.8 fold lower than the mean AUC in patients at 500 mg BID for rat and rabbit, respectively. Importantly, the exposure to the measured metabolites M502 and M544 in both the rat and the rabbit were clearly below the anticipated clinical exposure. In addition, there were no detectable levels of M460 in pregnant rabbits or rats. Therefore the embryofetal toxicity of the metabolites cannot be considered sufficiently characterized in the performed studies. It is recognized that administration of higher doses of rociletinib in order to achieve higher exposure of the metabolites would not be feasible.

Genotoxicity

Rociletinib was not genotoxic in *Salmonella typhimurium* and *Escherichia coli* strains and did not induce chromosomal aberrations in cultured human lymphocytes, with or without metabolic activation. In addition, it was not clastogenic in the *in vivo* micronucleus test in rats.

Phototoxicity

In the tissue distribution study in Long-Evans pigmented male rats given [^{14}C]-rociletinib, radioactivity was present after 1176 hours of initial exposure in melanin-containing tissues such as pigmented skin. These results suggest that rociletinib and/or its metabolites have an affinity for melanin. Rociletinib FB was not phototoxic when evaluated in a phototoxicity study with Long Evans pigmented rats using a study design aligned with ICH S10. In addition, there have been no clinical signs of phototoxicity in patients treated with rociletinib HBr.

3.2.4. Ecotoxicity/environmental risk assessment

The initial $PEC_{SURFACEWATER}$ is above the trigger value. The Fpen was refined in order to take into account the prevalence of advanced stage NSCLC patients with EGFR+/T790M+ mutations. The refined $PEC_{SURFACEWATER}$ is 9 ng/L and a Phase II assessment was not undertaken. The calculation of the refined Fpen is adequately supported by published literature and is accepted. It can be concluded that the action limit is not exceeded and the assessment can stop in Phase I.

The predicted Log Kow is 2.6375. No conclusion regarding the need for a PBT assessment can be made at this point. .

It is not possible to conclude on the ERA at this point.

3.2.5. Discussion on non-clinical aspects

Pharmacology and pharmacokinetics

In vivo efficacy studies demonstrated anti-tumor efficacy of rociletinib FB and rociletinib HBr in various mice tumor models, including cancer cell line models with activating and resistance mutations of EGFR, patient-derived xenografts and genetically engineered mouse (GEM) lung cancer models. Selectivity profiling indicates that rociletinib and its active metabolites M460, M502, and M544 has potential for off-target activity with a likely clinical relevance for M502 and M460 in the development of hyperglycaemia and generation of QTc prolongation, respectively, in some patients. Overall, the non-clinical pharmacokinetic and toxicokinetic studies provided are considered sufficient and are conducted according to the ICH S9 for anticancer pharmaceuticals.

Toxicology

The exposure to the metabolites M502 and M460 was clearly below the human exposure in all toxicology studies. The exposure to metabolite M544 at the rat STD10 or NOAEL was approximately equal to the human exposure and clearly below the exposure at the highest dose (NOEL) in the pregnant rabbit. The complete toxicologic profiles of these metabolites have not been established and consequently there are no established exposure margins. In addition, these metabolites have shown pharmacological activity in vitro and in vivo.

Concerning the environmental risk assessment (ERA), it is not possible to conclude on the need for a PBT assessment since there is no experimental Log Kow available yet.

3.2.6. Conclusion on non-clinical aspects

There are no major objections on the non-clinical parts precluding a marketing authorisation of rociletinib, however, a number of OCs that need to be addressed have been identified.

3.3. Clinical aspects

- ***Tabular overview of clinical studies***

Rociletinib clinical development program

Study No.	Description	Study Status (29 April 2015)
CO-1686-008 (TIGER-X)	A Phase 1/2, Open-label, Safety, PK and Preliminary Efficacy Study of Oral Rociletinib in Patients with Previously Treated Mutant EGFR NSCLC	Phase 1 Completed Phase 2 Ongoing
CO-1686-019 (TIGER-2)	A Phase 2, Open-label, Multicenter, Safety and Efficacy Study of Oral Rociletinib as Second-line EGFR-Directed TKI in Patients with Mutant EGFR NSCLC	Cohort A Ongoing Cohort B Ongoing
CO-1686-018 (TIGER-J)	A Phase 1, Open-label, Safety, PK, and Preliminary Efficacy Study of Rociletinib in Patients with Previously Treated Mutant EGFR NSCLC	Enrollment completed/study ongoing
CO-1686-022 (TIGER-1)	A Randomized, Open-label, Phase 2 Study of Rociletinib or Erlotinib as First-line Treatment of Patients with Mutant EGFR Advanced NSCLC	Enrollment/study ongoing
CO-1686-020 (TIGER-3)	A Phase 3, Open-label, Multicenter, Randomized Study of Oral Rociletinib Monotherapy Versus Single-agent Cytotoxic Chemotherapy in Patients with Mutant EGFR NSCLC after Failure of at Least 1 Previous EGFR-directed TKI and Platinum-doublet Chemotherapy	Enrollment/study ongoing
CO-1686-016	A Phase 1, 3-part, Open-label Study to Assess the PK of Single and Multiple Doses of Oral Rociletinib Hydrobromide Salt in Healthy Subjects	Completed
CO-1686-027	A Phase 1, Open-label, Single-center, Parallel Group Study of the Effect of Rociletinib on the PK of Omeprazole and Digoxin and the Effect of Paroxetine or Omeprazole on the PK of Rociletinib in Healthy Adult Subjects	Completed
CO-1686-028	A Single-dose Study of the Disposition of ^{14}C Radiolabeled Rociletinib in Healthy Male Subjects	Completed
CO-1686-029	A Phase 1, Randomized, Single Dose, Crossover Study of the Effect of Food on the PK of Rociletinib	Completed
CO-1686-030	A Phase 1, Open-label, Single-center, Parallel Group, Fixed Sequence Study to Assess the Effect of Multiple Dose Administration of Rociletinib on Single Dose PK of Oral Rosiglitazone, Celecoxib, and Midazolam in Healthy Male Adult Subjects	Completed

3.3.1. Pharmacokinetics

Rociletinib is a new chemical entity and full pharmacokinetic characterization is required. The evaluation should aim at describing the absorption and disposition of the compound in order to support dosing recommendations and predict situations and subgroups where exposure may be different than in the average clinical study patient.

The clinical pharmacology package for this application includes seven clinical studies. Furthermore, population PK and exposure-response analyses were performed resulting in two reports. In addition, 13 in vitro studies using human biomaterials were submitted.

Analytical methods

Fully validated methods have been applied for the analysis of rociletinib, M544, M502 and M460 in human plasma. A liquid chromatography method with tandem mass spectrometry and deuterium labelled rociletinib as internal standard was used. Sample preparation was based on protein precipitation. The methods appeared to be accurate and precise.

Bioequivalence

The HBr salt formulation C has been used in the patient studies and DDI studies, and no formal bioequivalence study is needed as this is the intended commercial formulation.

Absorption

Aqueous solubility of the HBr salt was stated to be 1 mg/mL at room temperature and < 0.1 mg/mL at pH > 2. Co-administration of rociletinib and omeprazole decreased the exposure of rociletinib with ca. 70%. The permeability of rociletinib was indicated to be high in Caco2 cells. Rociletinib is relatively rapidly absorbed, with a median tmax of 2.5 h (range 1-8 h) after twice daily repeated oral dosing of 500 mg of the tablet formulation at steady state in patients. The obtained mean C_{max} was 2330 ng/mL and AUC was 23700 ng/mL. According to in vitro studies, rociletinib is a substrate of P-gp and BCRP transport proteins.

The absolute bioavailability of rociletinib has not been determined. At least 4.4% is absorbed after a 625 mg oral dose in fed state, based on radioactivity recovered in urine in the mass balance study in healthy volunteers. Exposure to rociletinib is increased when administered with food; A high fat meal 30 min prior to rociletinib dosing, increased AUC by 54%.

Distribution

Based on the population PK analysis, the apparent volume of distribution (V/F) in patients was determined to be 41 L (94%) (mean (CV%)), indicating restricted distribution to tissues. The blood-plasma ratio was approximately 0.6, indicating that rociletinib is not widely distributed to blood cells.

Plasma protein binding of rociletinib and its metabolites are high (rociletinib 98-99%, metabolites 93-95%) and appears independent of concentration in the therapeutic range based on in vitro data. In vitro, alpha-1 acid glycoprotein and albumin were shown to be important binding proteins of rociletinib. The unbound concentrations were not determined in renal and hepatic impaired patients.

Elimination

In the mass balance study in healthy volunteers in the fed state, the plasma clearance (CL/F) of rociletinib was 51±17 L/h. In the PopPK analysis the estimated CL/F for a typical patient was 55 L/hr (41%) (mean (CV%)). The terminal half-life was 2.7 h and 2.6 h after single dose of rociletinib in patients and healthy volunteers, respectively.

<u>Excretion</u>

In the human mass balance study the total mean recovery of the administered radioactive dose was ca. 90% of dose over the 10-day collection period. The majority of radioactivity was excreted into feces (85% of the dose), with a smaller percentage excreted into urine (4.4% of the dose). Parent compound accounted for ca. 65% in feces and 0.4% in urine. In feces, metabolites M502 and M544

accounted for approximately 6% and 3% of the administered dose, respectively. In urine, M502 and M544, accounted for approximately 3% and 1%, respectively. Renal clearance of total radioactivity was low at ca. 0.23 L/h.

Metabolism

The primary metabolic pathways included an amide hydrolysis followed by oxidation and *N*-acetylation (Figure 1). Metabolite M544 is formed through N-acetylation of M502 and M460 is eliminated via N-acetylation. The Applicant suggests that N-acetyltransferase is the responsible enzyme. N-acetyltransferases (NATs) are polymorphic drug metabolizing enzymes, and the activity in humans can be classified as rapid or slow. CYP enzymes appear to have a minor role in the metabolism of rociletinib.

The plasma profiles of total radioactivity, parent and metabolites is shown in Figure 2. Rociletinib and the metabolites M502, M544 and M460 accounted for approximately 10%, 52%, 17% and 5% of AUC after a single dose of 625 mg to healthy volunteers. The half-life for the metabolites M502, M544 and M460 was reported to be 20, 20 and 51 h. Metabolites M502, M544 and M460 are not considered to be active on EGFR or WT EGFR (See Non clinical pharmacology). However, M460 and M502 are associated with adverse reactions (See Pharmacodynamic section below).

Figure 1 Proposed biotransformation pathway of rociletinib in humans

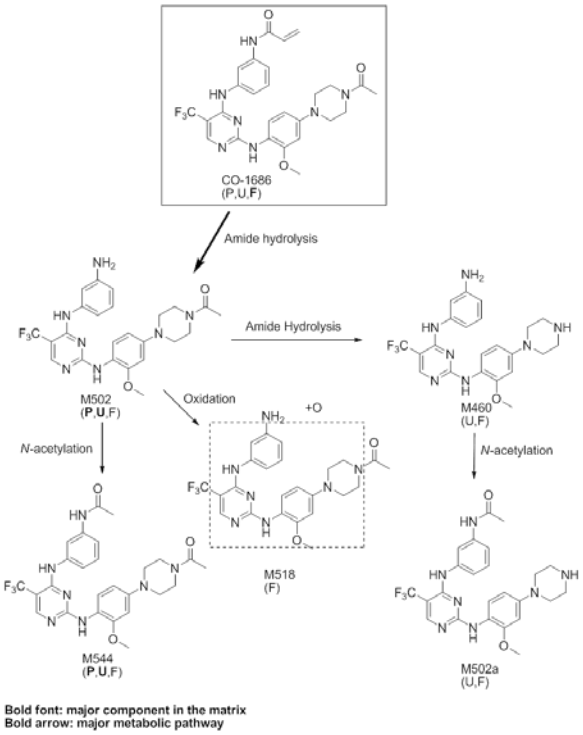
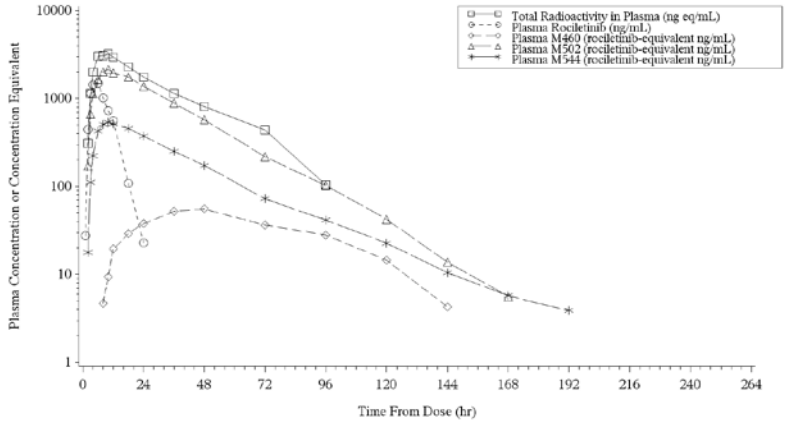


Figure 2 Mean plasma total radioactivity, rociletinib and metabolites, concentration[a] vs. time



[a]presented as rociletinib-equivalent conc., calculated as; metabolite conc. x (molecular weight $[MW]_{parent}/MW_{metabolite}$)

Dose proportionality and time dependency

In healthy volunteers, the increase in exposure of rociletinib (Cmax and AUC(0-inf)) was dose proportional between 50 and 125 mg rociletinib, and thereafter (250–1000 mg) it was less than dose proportional. In patients, the increase of rociletinib exposure was less than dose proportional in the 500 mg to 1000 mg range. Most likely the nonlinearity is due to the limited the solubility, especially at the increased pH in the intestine.

Although very few healthy volunteers completed day 4 of the repeat dose study (n=3), there seem to be a time-dependency when comparing the exposure of rociletinib at day 1 and 4 (AUC decreased ca. 20-25%, Cmax ca. 45%, t½ and C_{trough} were unchanged). The time-dependency in rociletinib exposure was also evident in the Phase II data.

At steady state in patients, the accumulation of metabolites M502 and M544 was approx. 2-fold and 6 to 11 fold for M460. This is in line with dosing interval (BID) and the half-lives for the metabolites (20, 20 and 51 h, respectively).

Intra- and inter-individual variability

Based on the preliminary popPk analysis in patients, the inter-individual variability (IIV CV%) for rociletinib was 41% for CL/F and 94% for V/F. The intra-individual variability (inter-occasion variability, IOV) was 55% for the relative bioavailability.

Pharmacokinetics in target population

The exposure in patients was approx. 2-fold for $AUC_{(0-24)}$ and 1.3-fold for C_{max} compared to healthy volunteers in the fed state using the same formulation at 625 mg BID.

Special populations

Formal studies to investigate the impact of renal and hepatic impairment on the rociletinib and metabolites exposure have not been performed. Based on the preliminary popPK results of 132 patients with mild renal impairment (60 ≤ CLcr < 90 mL/min), 53 patients with moderate renal impairment (30 ≤ CLcr < 60 mL/min) and 204 patients with normal renal function (CLcr ≥ 90 mL/min), rociletinib and metabolite exposures were similar in patients with mild and moderate renal impairment

and normal renal function. Patients with severe renal impairment (CLcr < 30 mL/min) or on dialysis were not included in clinical studies and an appropriate dose has not been established for these patients.

Based on the preliminary popPK analysis of 65 patients with mild hepatic impairment (total bilirubin ≤ ULN and AST > ULN or total bilirubin > 1.0 to 1.5 x ULN and any AST) and 323 patients with normal hepatic function (total bilirubin ≤ ULN and AST ≤ ULN), rociletinib and metabolite exposures were similar in patients with mild hepatic impairment and normal hepatic function. The number of patients with moderate hepatic impairment was too small (n=5) to analyse. Patients with severe hepatic impairment were excluded from clinical studies. An appropriate dose has not been established for patients with moderate or severe hepatic impairment.

There appears to be no impact on exposure of rociletinib and metabolites based on gender, weight, BMI or age. Children were not included in the clinical studies. The popPK analysis indicated that there was no influence of race on the exposure of rociletinib and metabolites. However, only Caucasian and Asian race were included in sufficient number. Only seven were Black subjects, which limits the interpretation regarding race. ***Interactions***

Effect of other medical products on the PK of rociletinib

The absolute bioavailability is not known and therefore the relative contribution of metabolism and biliary excretion to the overall clearance is unknown and as a consequence the interaction effects by other drugs are not possible to fully assess. Rociletinib was shown to be substrate of P-gp and BCRP, but not of OATP1B1 or OATP1B3. In vitro data indicate that rociletinib is not metabolized via CYP enzymes, rather an initial amide hydrolysis step followed by N-acetylation.

When rociletinib was co-administered with paroxetine (CYP2D6 inhibitor) the rociletinib exposure was reduced (mean point estimates, Cmax by 15% and AUC(0-24) by 26%). This result is unexpected, since an increase in exposure was anticipated if rociletinib is metabolised via CYP2D6. However, even though the decrease was statistically significant, the decrease is not considered to be clinically relevant. Administration of omeprazole (40 mg during 6 days) and co-administered with rociletinib reduced Cmax of rociletinib by 72% and AUC(0-24) by 69%. The decrease is likely due to the effect of increasing gastric pH on rociletinib PK as the solubility decreases with increasing pH. The concomitant administration of proton pump inhibitors should be avoided.

Effect of rociletinib on PK of other medical products

The potential for rociletinib to inhibit or induce CYPs has been investigated in vitro and based on this, the risk of clinically relevant DDIs due to inhibition of CYP1A2, CYP2B6, CYP2C19 and CYP2D6, caused by rociletinib is considered to be low. However, from in vitro data inhibition of CYP2C8, CYP2C9 and intestinal CYP3A4 cannot be excluded. A time dependent (+NADPH) inhibition was indicated for CYP3A4, but not for any of the other CYPs investigated. Rociletinib was shown to be an in vitro inducer of CYP1A2, CYP2B6 and CYP3A4. In vitro, rociletinib did not inhibit OAT1, OAT3, and systemic P-gp or BCRP to any clinically relevant extent. However, rociletinib did inhibit P-gp (intestinal), BCRP (intestinal), OATP1B1, OATP1B3, OCT1, and OCT2 in vitro.

In vivo studies using digoxin (P-gp probe), rosiglitazone (CYP2C8 probe), celecoxib (CYP2C9 probe), omeprazole (CYP2C19 probe) and midazolam (CYP3A4 probe) were performed.

Administration of rociletinib with digoxin increased Cmax of digoxin by 44% and AUC(0-inf) by 29%. However, even though digoxin is a good probe to investigate potential interactions with P-gp primarily in the kidneys, it is not a suitable probe for intestinal P-gp. Therefore, firm conclusions cannot be drawn regarding interactions caused by rociletinib on intestinal P-gp from this study.

Co-administration of rociletinib (625 mg BID in fed state for 10 days) with rosiglitazone (CYP2C8 probe) increased the Cmax, AUC0-t and AUC0-inf of rosiglitazone by 7%, 28% and 30% (point estimates). There is a large discrepancy between the planned number of subjects (n=20) and the evaluated DDI population (n=5), which is reflected in the wide confidence intervals presented (see Figure 4). The results need to be interpreted with caution.

Co-administration of rociletinib (500 mg BID in fed state for 10 days) with celecoxib (CYP2C9 probe), an increase in median t1/2 (from 5.3 to 7.6 h) and tmax (from 2.5 to 4 h) was observed. In addition, a decrease in Cmax of celecoxib by 30%, while the reduction of AUC0-t and AUC0-inf was less than 10% was found. Celecoxib is also eliminated via CYP3A4 as a minor pathway. Rociletinib is a CYP3A4 inducer (see midazolam below) and furthermore, CYP2C9 is like CYP3A4 regulated via PXR, which may explain the decrease in exposure of celecoxib after rociletinib repeated dosing.

Administration of rociletinib (625 mg x 2 during 1 day) with omeprazole increased Cmax of omeprazole by 44% and AUC(0-24) by 39%. The results show that rociletinib is a mild inhibitor of CYP2C19.

Co-administration of rociletinib (500 mg BID fed state for 10 days) decreased the plasma exposure of midazolam (CYP3A4 probe) by 39% and 35% for Cmax and AUC(0-inf), respectively. However, only 3 subjects were evaluated, which is reflected in the wide confidence intervals presented (See Figure 4). The results need to be interpreted with caution.

Figure 3 Geometric Mean Ratios and 90% CI for DDI in Study CO-1686-027

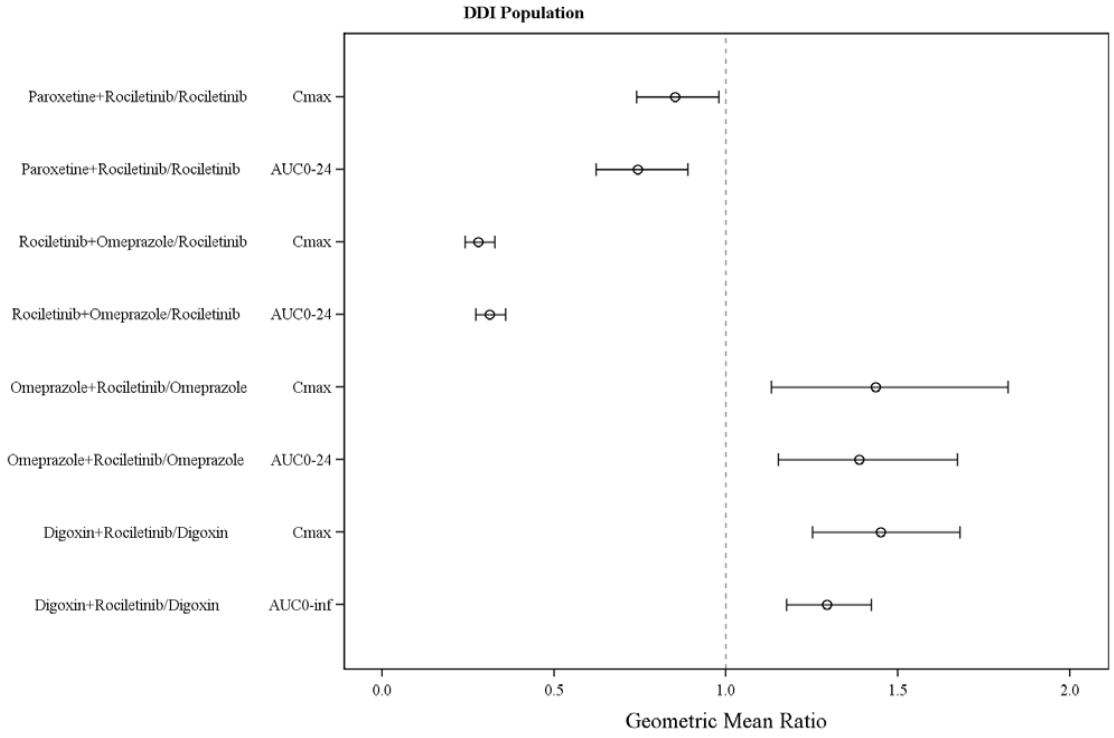
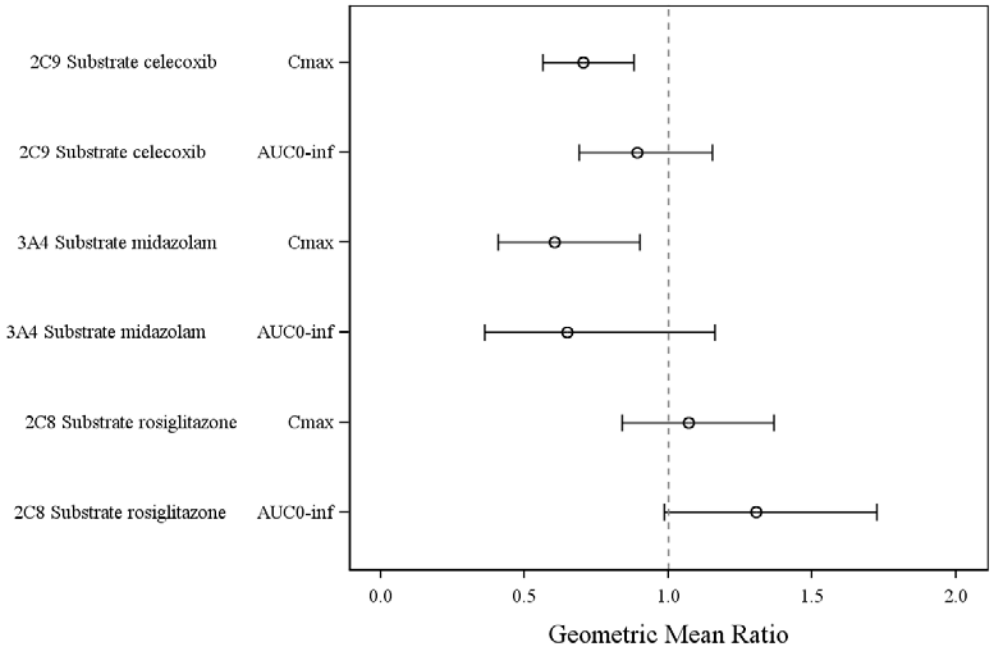


Figure 4 Geometric Mean Ratios and 90% CI for DDI in Study CO-1686-030



3.3.2. Pharmacodynamics

Mechanism of action

Rociletinib is an inhibitor of EGFR with the common activating (L858R, Del19) and T790M resistance mutations and with reduced activity towards WT EGFR. At clinical achievable concentrations rociletinib and its metabolites also inhibits a number of other kinases, the full clinical consequences of which are currently unknown (see non-clinical above and hyperglycaemia and QT below).

Rociletinib covalently binds and irreversibly inhibits the kinase activity of mutant EGFR, resulting in sustained EGFR pathway blockade in tumour cells. Selectivity profiling demonstrated that rociletinib has the greatest potency against clinically relevant mEGFR kinases, including T790M.

At concentrations that inhibited tumour growth, dose-dependent decreases in phosphorylated EGFR (p-EGFR) levels were observed in tumour tissues expressing mEGFR, but not in normal lung and skin tissue expressing WT EGFR. The strongest inhibition of p-EGFR was observed after 4 to 6 hours, and the signal started to recover 12 hours postdose. These data indicate that BID dosing is likely to result in more durable EGFR pathway inhibition than QD dosing. Administration of rociletinib BID was well-tolerated and resulted in significant tumour growth inhibition (TGI) in 6 mEGFR xenograft models whereas limited activity was observed in a tumour model dependent on WT EGFR signalling for growth.

Secondary pharmacology

Metabolites of rociletinib inhibit the insulin like growth factor 1 receptor 1 (IGF1R) and the insulin receptor (INSR) in biochemical and cellular assays at clinically relevant concentrations. This likely explains the observed hyperglycaemia. Similar to EGFR, IGF1R is a transmembrane receptor tyrosine kinase responsible for activating the PI3K and MAPK pathways that promote cell growth, transformation, migration, and survival. Preclinical studies in NSCLC models have demonstrated a role for IGF1R signalling in mediating resistance to EGFR inhibitors, and sensitivity could be restored with dual inhibition of mutant EGFR and IGF1R.

Hyperglycemia

Hyperglycemia is one of the most common AEs in patients treated with rociletinib. Metabolites M460 and M502 were directly tested in an OGTT to achieve plasma exposures comparable to those observed in patients at 500 mg HBr BID. Dosing of M502 resulted in significant elevations in postprandial glucose and insulin levels, while dosing of M460 caused an apparent increase in postprandial glucose and insulin levels, which did not reach statistical significance. Given that the exposure to circulating M502 is approximately 8-fold higher than M460 in humans and that M502 and M460 have comparable *in vitro* potency towards IGF1R and INSR, these data suggest that M502 is likely to play a causal role, and that M460 may contribute to a lesser extent, in the hyperglycemia observed in some patients during treatment with rociletinib.

QTc Prolongation

QTc prolongation has been observed in some patients during treatment with rociletinib. Based on the level of these metabolites in humans and the absence of a significant nonclinical cardiac safety signal with rociletinib, hERG assays were conducted on the metabolites. The IC50 values for the inhibitory effects of M460, M502, and M544 on hERG potassium currents were 0.05, 6.1, and 18.1 µM, respectively, which are 0.6-, 12-, and 203-fold higher than the Cmax unbound plasma M460, M502, and M544 concentrations (81, 516, and 89 nM, respectively) observed in patients at 500 mg rociletinib BID. Collectively, these data suggest that the human metabolite M460 plays a contributory role in the development of QTc prolongation in some patients during treatment with rociletinib.

Evaluation of QT/QTc Interval Effect and Proarrhythmic Potential of Rociletinib (data from CO-1686-008 and CO-1686-019)

A central tendency analysis of the QTc data at average steady-state concentrations demonstrated that the maximum mean change from baseline was 36 msec for rociletinib 500 mg twice daily, occurring at week 2. QTcF increased by > 60 ms post-baseline occurs in 22.2% of patients at 500 mg BI. Of 90 patients treated with rociletinib at 500 mg twice daily, 8 had QTc > 500 ms.

Recommendations that will be made in the prescribing information, in accordance with published guidance from the ICH (ICH Topic E 14, The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, 2005), will minimize the risk of cardiac events related to QT prolongation during rociletinib therapy, including the following:

1. Avoidance of prescribing rociletinib in patients at increased risk for QT prolongation-related complications, including patients with pre-existing QTc > 450 ms, bradycardia, personal or family history of long QT syndrome, or inability to measure QT interval.

2. Performance of serial routine ECG monitoring, more frequently in the initial cycles, to assess QTc interval.

3. Avoidance of concomitant medications that have the potential to prolong the QT interval.

4. Serial monitoring for, and prompt correction of, electrolyte disturbances that may exacerbate the risk for prolongation of the QT interval.

5. Dose modification guidance for instances of QTc > 500 ms.

Experience from clinical trials (Study CO-1686-008 and Study CO-1686-019) was used to establish the dose modification guidance:

- *For QTc > 500 ms*

Events of QT prolongation to greater than 500 ms (i.e. Grade 3 QT prolongation) have been managed successfully with a brief dose hold (approximately 2 - 4 days) to allow QTc to fall to Grade 1 or better,

followed by rociletinib rechallenge at a reduced dose. In individual cases of QT prolongation, dose reduction results in resolution of the event, which provides evidence of an exposure-response relationship at the patient level. The reversibility of QT prolongation once rociletinib therapy is stopped is consistent with the half-life (approximately 50 hours) of the causative metabolite, M460.

- *Torsade de Pointes and ventricular tachyarrhythmia*

Ventricular arrhythmias in patients receiving rociletinib are rare and dose-related. The serious events of Torsade de Pointes and ventricular tachyarrhythmia, each in 1 patient in the rociletinib 625 mg BID dose group, were successfully managed medically. Both patients recovered without sequelae upon permanent discontinuation of rociletinib. No cardiac events associated with prolonged QTc or ventricular arrhythmias have been observed in patients treated at the recommended rociletinib dose of 500 mg BID.

Relationship between exposure-effect

The relationship between exposure and effect was evaluated in study QS-CL-002 to quantify the relationship between rociletinib and objective response rate (ORR) and best tumor response (sum of the longest diameter of the target lesions) (best SLD) and to assess the impact of T790M status on the efficacy of rociletinib. Moreover the relationship between exposure and effect on glycemic levels and QTc was also evaluated.

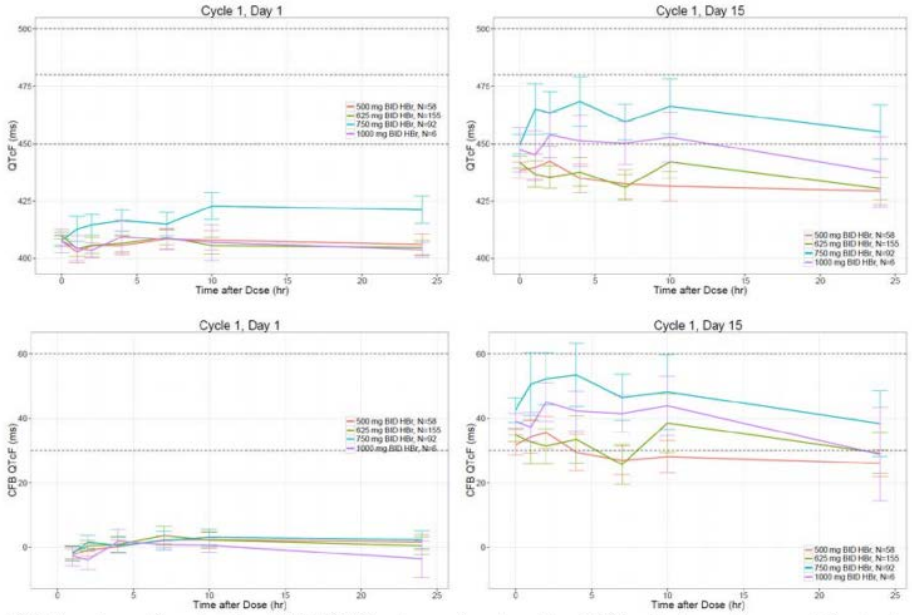
Study CO-1686-008 and Study CO-1686-019 were used in the primary analyses of the 2 safety and 2 efficacy endpoints presented. Study CO1686-030 data were included in an exploratory analysis to assess the profile of ΔQTcF between the 1st and 15th days of the first treatment cycle.

QT prolongation

A concentration-ΔQTcF relationship was presented to describe the effect of M460 and M502 on ΔQTcF.

According to figure below the effect observed on C1D1 and after C1D1 was different.

Figure 2. Mean (±SE) QTcF and QTcF change from baseline (CFB) vs. time following rociletinib administration on Cycle 1 Day 1 (left panel) and Cycle 1 Day 15 (right panel)



ΔQTcF = change from baseline QTcF, CFB = change from baseline, ECG = electrocardiogram, SE = standard error
Note: Mean (±SE) QTcF and QTcF CFB on C1D1 (left) and Day 15 (right) are shown. 12-lead ECG recordings were taken (in triplicate) at predose, and 1, 2, 4, 7, 10, and 24 hr after the morning doses on Day 1 and Day 15. Horizontal dashed lines are at 450, 480, and 500 ms for the QTcF plots (upper panels) and at 30 and 60 ms for the QTcF CFB plots (bottom panels).

The final model describes prolongation due to a unit increase in M460 approximately 20 times larger than the prolongation due to a unit increase in M502 concentration (see table below)." *in vitro"* hERG results showing the IC 50 for the inhibitory effect on hERG potassium currents was 6.1 µM and 0.05 µM, respectively, for M502 and M460.

Table 4. Final model parameter estimates for the ΔQTcF model

Parameter	Value	Std. Error	95% CI	p-value
Intercept (ms)	-2.33	0.92	(-4.12 - -0.535)	2.42E-03
>C1D1 on intercept, additive (ms)	15.1	1.25	(12.7 - 17.6)	8.29E-34
Baseline QTcF on intercept, additive	-0.210	3.86E-02	(-0.286 - -0.134)	1.21E-08
Slope of the M460 relationship (ms per ng/mL)	0.0327	3.60E-03	(0.0256 - 0.0397)	1.31E-16
Baseline HR effect on M460 slope (ms per ng/mL per bpm)	-0.000670	1.67E-04	(-0.00100 - -0.000343)	1.15E-04
Slope of the M502 relationship (ms per ng/mL)	1.56E-03	3.55E-04	(0.000868 - 0.00226)	2.39E-06
IIV intercept (sd)	6.86	0.801	(5.47 - 8.61)	--
IIV M460 slope (sd)	0.0279	0.00237	(0.0236 - 0.0329)	--
IIV M502 slope (sd)	0.00173	0.000341	(0.00118 - 0.00252)	--
Sigma, >C1D1(ms)	2.53	0.13	(2.29 - 2.8)	--
Sigma (ms)	6.3	0.282	(5.77 - 6.87)	--

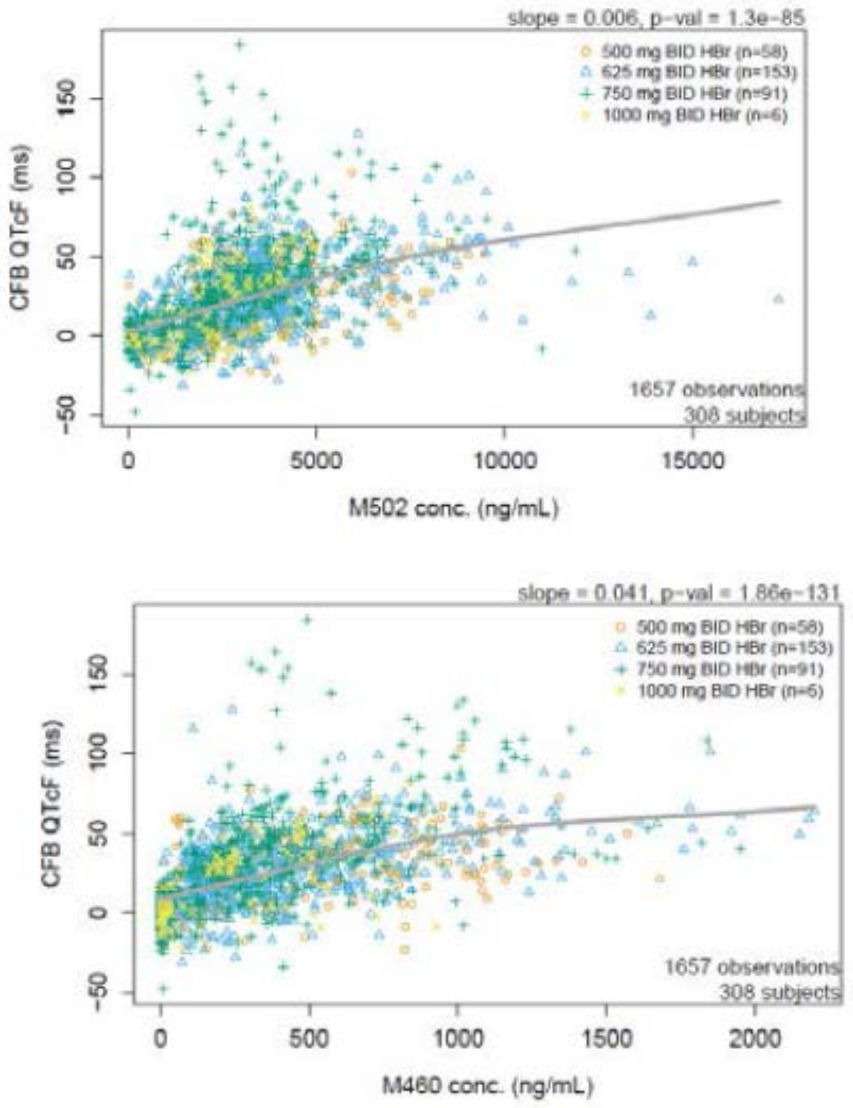
>C1D1 = after Cycle 1 Day 1, CI = confidence interval, HR = heart rate, IIV = inter-individual variability, QTcF = Fridericia corrected QT interval, sd = standard deviation, Std. Error = standard error
Note: Covariate effects on the intercept and M460 slope are for median-centered baseline QTcF and median-centered HR. Linear relationships between ΔQTcF and M460 or M502 are not median-centered.

Higher baseline QTcF was correlated with smaller ΔQTcF. For every 10% decrease in heart rate from the median (76 bpm), the slope of the relationship between M460 and ΔQTcF increased 16%.
A significant effect of study day (Day 1 vs. after Day 1) on the intercept of the relationship was identified, with the typical value of the intercept of -2.33 ms (95% confidence interval [CI], -4.12 to -

0.535 ms) on C1D1, and 12.8 ms (95% CI, 8.57 to 17.1 ms) after C1D1. The applicant is asked to provide an explanation for such effect and the implications in the QTc.

The predicted mean ΔQTcF on C1D15 was 34.0 ms (90% CI, 25.4 to 42.6 ms) at the mean observed M460 Cmax of 457 ng/mL and M502 Cmax,ss of 3993 ng/mL for the 500 mg.

ΔQTcF (CFB QTcF) relationship with plasma concentrations of metabolites M502 (upper graph) and M460 (lower graph).



A study day effect was observed with no dose dependency detected at C1D1, but a dose dependent increase of both QTcF and change from baseline QTcF at C1D15. This time delay also supports that metabolites are associated with the QTc prolongation, as the time to steady state for metabolite M502 and M460 was 4 and 7 days, respectively.

Collectively, these data suggest that the human metabolite M460 plays an important role in the development of QTc prolongation during treatment with rociletinib.

No statistically significant covariate relationships were identified with age, weight, gender, race, T790M status, or history of hyperglycemia.

Hyperglycemia

Of note, the rociletinib population PK model does not appear to capture the trends of the data and are currently not suitable to predict steady state exposures.

Logistic regression analyses identified M502 AUCss as the best predictor of the probability of a Grade 3 or 4 event, with a mean value of the intercept of -83 and the AUCss slope of 2.58E-5. At the population median M502 AUCss, the predicted incidence (95% CI) for the 500 mg, 625 mg, and 750 mg BID cohorts were 27.0% (20.9 to 33.1%), 30.5% (24.6 to 36.4%), and 31.2% (25.3 to 37.0%), respectively.

No statistically significant covariate relationships for age, weight, BMI, gender, race, T790M status, or history of hyperglycemia remained in the final model.

ORR

Of note, the rociletinib population PK model is currently not suitable to predict steady state exposures.

Objective response rate was best predicted by the model-predicted rociletinib C min,ss.

No statistically significant covariate relationships for age, weight, BMI, gender, race, T790M status, or history of hyperglycemia remained in the final model. There were few patients T790M-negative (9.6%) which may have precluded detecting a difference in ORR between the 2 populations.

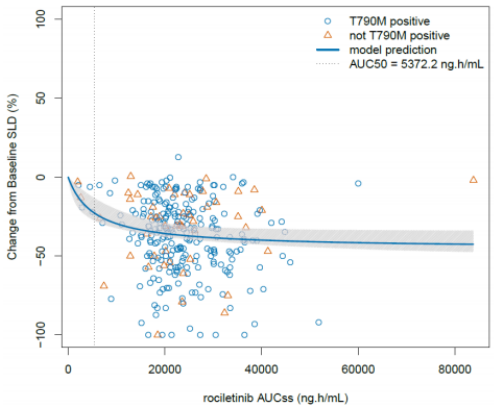
The predicted ORRs (95% CI) for the 500 mg, 625 mg, and 750 mg BID HBr cohorts were 47.2% (41.2 to 53.2%), 46.2% (40.5 to 52.0%), and 45.7% (40.0 to 51.3%), respectively.

Best tumor response

Best tumor response was described as a saturable relationship with rociletinib AUC ss. The maximal CFB SLD was 45.2% (95% CI, 33.0 to 57.4%) with an AUC50 of 5372 ng.h/mL (95% CI, 1462 to 19737 ng.h/mL). The analysis dataset for Best SLD may have included too few T790M-negative subjects (8%) to detect a difference between the 2 populations.

According to figure below the maximal effect is predicted for the majority of the concentrations with no differences between doses.

Figure 11. Predicted best tumor response from the final model



AUC_{ss} = area under the curve at steady state, AUC50 = half maximal AUC, SLD = sum of the longest diameter of the target lesions

Note: The shaded region represents the 95% prediction interval for the final model. The dashed vertical line represents the predicted AUC50. The symbols represent individual observations. The y-axis of the figure is truncated to exclude a single subject with a CFB SLD of 208%.

The 500 mg BID regimen provides a similar efficacy to higher doses according to the exposure-response models; however, the relationship between exposure and ΔQTcF and Grade 3 or 4 hyperglycemia suggest a better safety profile when compared to 625 mg and 750 mg BID regimens.

3.3.3. Discussion on clinical pharmacology

Analytical methods

Overall, the analysis methods seem to be adequately described and validated and show acceptable performance. However, further data should be provided to allow a full assessment.

ADME

There is a lack of data on absolute bioavailability and the feasibility to conduct a study to determined absolute bioavailability should be discussed. The uncertainty in the fraction absorbed after oral dosing has consequences for the PK assessment of rociletinib. Nearly all administered radioactivity was found in feces and of this, parent compound was predominant (65%). Therefore the relative contribution of metabolism and bilary excretion to the overall clearance is difficult to determine. As a consequence it is not possible to fully assess the potential effect of other drugs on rociletinib exposure. Approximately 4.4% of radioactive dose was found in urine, i.e. only this fraction can with certainty be considered as absorbed. In the mass balance study, in essence no radioactivity was found in the 0-24 h feces collection interval and in addition the excreted radioactivity was found in rather late fractions (~65% of the fecal excretion was observed >48 hrs post-dose). It is unexpected that radioactivity is found in feces in such late collection intervals considering that the median t_{max} was 6 h and plasma half-life was 3 h. A possible explanation could be enterohepatic circulation of rociletinib. The permeability is indicated to be high. Taken together, these data may indicate that the fraction absorbed is large.

The Applicant has reported different values for the apparent volume of distribution. Non-compartmental (healthy volunteers) results ranged from 194 to 231 L in fed state and PopPK (NSCLC patients) resulted in 41 L. Moreover, Vss/F in study CO-1686-008 has not been located.

Time dependency

A time dependency was indicated in when rociletinib was administered 500 mg BID in healthy volunteers although there were only few subjects (n=3) completing the four day repeated dosing. Since rociletinib is an in vitro PXR inducer and also a P-gp substrate, auto-induction of P-gp at intestinal level is a possible hypothesis. The patient data also indicated a time dependency, which is not captured in the current popPK model as it appears to underestimate the exposure following to first dose.

Pharmacokinetics in target population

The exposure in patients was higher compared to healthy volunteers. The reason for this is unknown. The magnitude of interactions when investigating the effect of rociletinib on other medical products might be underestimated as the DDI studies is performed in healthy volunteers. The dose level of rociletinib in the DDI studies when investigating the effect on other medical products was in several cases 625 mg BID instead of the therapeutic 500 mg BID.

Special populations

All conclusions in special populations are based on popPK analysis and as there issues related to the model, the results and SmPC wording may be updated for the special populations.

Based on the preliminary popPK analysis only patients with mild hepatic impairment was included with a sufficient number (n=65) resulting in similar rociletinib and metabolite exposures compared to normal hepatic function. The number of patients with moderate hepatic impairment was too small (n=5) to analyse. Patients with severe hepatic impairment were excluded from clinical studies. Thus, an appropriate dose has not been established for patients with moderate or severe hepatic impairment.

Interactions

Effect of other medical products on the PK of rociletinib

Rociletinib was shown to be a substrate of P-gp and BCRP, but not of OATP1B1 or OATP1B3. No in vivo study has been performed to address whether rociletinib is a sensitive in vivo substrate of P-gp. The Applicant should perform an in vivo DDI study with a strong P-pg inhibitor (consider itraconazole), meanwhile wording need to be included in the SmPC reflecting the lack of information in vivo and also including a list of examples of strong P-gp inhibitors. In addition, the Applicant should discuss the risk of underexposure of rociletinib, and thus risk of lack of efficacy, if co-medicated with medical products that are inducers of drug transporters and enzymes (e.g. rifampicin, phenytoin, St. John's wort). Possible effect on rociletinib exposure by inhibition of BCRP can be handled with SmPC wording as there are not many known in vivo inhibitors. In vitro data indicate that rociletinib is not metabolized via CYP enzymes, rather an initial amide hydrolysis step and further N-acetylation, which is mediated via NAT2 as proposed by the Applicant. The applicant has not presented any convincing evidence for the involvement of NAT2.

Effect of rociletinib on PK of other medical products

The potential for rociletinib to inhibit CYPs has been investigated in vitro using relevant enzymes. However, the metabolites M502 and M544 are major metabolites and should also be investigated for potential CYP450 inhibitory effect according to Guideline on the investigation of drug interactions (CPMP/EWP/560/95). Any in vivo effect on CYP2C8, CYP2C9 and CYP3A4 by M502 and M544 was investigated simultaneously with rociletinib in the repeat dose DDI study, since steady state concentrations of M502 and M544 were obtained.

The potential for rociletinib to induce CYPs has been investigated in vitro using in general relevant enzymes. Rociletinib was shown to be an in vitro inducer of CYP1A2, CYP2B6 and CYP3A4. CYP3A4 was investigated in vivo as described in Section 3.3.1 and as only few narrow therapeutic substrates are known for CYP2B6 (e.g. efavirenz), this can be handled with SmPC wording. The results for CYP1A2 in the CYP induction study in not correctly interpreted by the Applicant. A positive response is ≥100% increase in mRNA in a concentration dependent fashion. A negative result can only be claimed when <100% increase of mRNA is observed and if the increase is <20% of the response of the positive control, according to the EMA Interaction guideline (CPMP/EWP/560/95/Rev. 1, 2012). Thus, the Applicant's conclusion that rociletinib is not a CYP1A2 inducer is incorrect since the increase was ≥2-fold in all three donors.

Rociletinib did not inhibit OAT1, OAT3, and systemic P-gp or BCRP in vitro to any clinically relevant extent. However, rociletinib did inhibit P-gp (intestinal), BCRP (intestinal) OATP1B1, OATP1B3, OCT1, and OCT2 in vitro and according to EMA Interaction guideline (CPMP/EWP/560/95/Rev.1, 2012) in vivo DDI data is needed. In vivo DDI studies have not been conducted for BCRP (gut), OATP1B1, OATP1B3, OCT1 and OCT2. Therefore, further justification should be provided about the lack of the in vivo data, particularly for potential inhibition of sensitive OATP1B substrates like certain statins.

Two in vivo studies using digoxin (P-gp probe), rosiglitazone (CYP2C8 probe), celecoxib (CYP2C9 probe), omeprazole (CYP2C19 probe) and midazolam (CYP3A4 probe) and were performed.

Administration of rociletinib with digoxin increased Cmax of digoxin by 44% and AUC(0-inf) by 29%. Even though rociletinib was given BID when co-medicated with digoxin, the short half-life of rociletinib (~3h) compared to digoxin (~36 h) most likely lead to that digoxin transport was not inhibited during the time course of digoxin elimination and possibly leading to an underestimation of the magnitude of the interaction. Although, digoxin is a good probe to investigate potential interactions with P-gp primarily in the kidneys, it is not a suitable probe for investigating intestinal P-gp transport. The resulting effect on digoxin exposure cannot with certainty be extrapolated to other P-gp substrates as there are more sensitive substrates for intestinal P-gp such as dabigatran etexilate. Thus the inhibition of dabigatran would be expected to be larger. These findings suggest that co-administration of rociletinib with a P-gp substrate with narrow therapeutic index (i. e. digoxin, dabigatran etexilate) may require dose adjustment.

At co-administration of rociletinib (500 mg BID fed state for 10 days) with celecoxib (CYP2C9 probe), a decrease in Cmax and AUC was observed (10-30%). The effect on celecoxib exposure is likely a combination of CYP2C9 and CYP3A4 induction after repeated dosing with rociletinib.

A complicating factor is that rociletinib is a CYP inhibitor, both direct and time dependent, and also a CYP inducer. Thus at steady state, which mostly is the clinically relevant situation, there is a mix of mechanisms. However, the magnitude of the initial CYP2C8, CYP2C9 or CYP3A4 inhibition is not known. For studying the inhibition part, a single day dosing of rociletinib co-administered with the affected probe substrate should have been performed.

Population PK model

Population pharmacokinetic models were developed to describe the data from studies (CO-1686-008 and CO-1686-019) aiming at gaining knowledge of the covariates affecting the PK of rociletinib and at predicting individual parameters of Cmin, Cmax and AUC at steady state for all the participants to be further used in the study to determine the PK/PD relationships. The popPK analysis in this application is used for claims regarding influence of HI, RI, gender, weight, race and age in the SmPC.

Rociletinib PK following oral administration was described by a one-compartment model with first-order elimination and lagged first-order plus lagged zero-order absorption. See table below for the estimates. The shrinkage in the final base model was high, ranging from 42% for CL/F to 67% on F1.

Population PK parameters for rociletinib

Description	Estimate	RSE	%CV	Shrinkage
Ka (1/hr)	0.196	3.95	24.3	--
CL/F (L/hr)	54.8	5.31	41.0	--
V (L)	41.2	11.8	93.6	--
F1 (assumed)	1	--	--	--
Formulation on F1, (1+th*(1-FORM))	-0.391	-19.6	--	--
Lag time (hr)	0.436	2.05	--	--
Duration of 0-order process	2.44	5.80	--	--
F2 (fraction absorbed by 0-order process)	0.132	17.4	--	--
Difference in lag-time for 0-order, (1+th)	1.72	17.8	--	--
Dose on F1, (1+th*(dose-625))	-0.00143	-16.5	--	--
AAG on CL/F (1+th*[AAGi-79])	-0.00350	-11.9	--	--
IIV on Ka	0.059	27.1	--	56.9
IIV on CL/F	0.168	20.0	--	37.0
IIV on V	0.877	17.0	--	43.9
IOV on F1, C1D1	0.308	11.5	55.5	47.2
IOV on F1, C1D15	0.308	--	--	50.2
IOV on F1, SS	0.308	--	--	45.8

ADDERR, intensive	120540	10.0	--	--
ADDERR, sparse	14163	36.2	--	--
PROPERR, sparse	0.277	15.6	--	--

ADDERR = additive residual error, C1D1 = Cycle 1 Day 1, C1C15 = Cycle 1 Day 15, CL/F = apparent clearance, F1 = relative bioavailability in the central compartment, F2 = fraction of dose available to the zero-order absorption, FORM, formulation (0=FB, 1=HBr), IIV = inter-individual variability, IOV = inter-occasion variability, Ka = absorption rate constant, PROPERR = proportional residual error, RSE = relative standard error (%), SS = steady state (after C1D15) Not: Dose is the actual dose; Relative bioavailability (F1) is assumed to be 1 for the reference population, i.e., 625 mg BID HBr.

The resulting residual additive error for the rociletinib/metabolite results seems implausible. The magnitude is not understood and also the reason for a larger error for the intensive sampling compared to sparse sampling.

There seem to be a time-dependency comparing day 1 and at steady state exposure. The Applicant should evaluate this time-dependency with an appropriate model and once the most likely time-dependent parameter has been identified (F or CL) discuss the mechanistic background for this. The median observations are under-predicted at day 1, but seem to be captured in the steady state predictions.

It appears that relevant covariates have been included. However, it is not clear whether the popPK model supports conclusions regarding effects of age, weight, hepatic and renal function, due to that the covariate distribution has not been clearly presented.

Population PK models for rociletinib, M502, and M544 were developed independently, with the metabolite concentrations modelled as absorption of some unknown fraction of a rociletinib dose. The Applicant has not discussed whether a joint model for parent and metabolites has been considered, which would use all the data more efficiently.

M502 PK following oral administration of rociletinib was described by a 2-compartment model with first-order elimination and lagged first-order absorption. Both residual plots and VPCs for M502 are indicating a misspecification in the structural model. The steady state model predictions differ in shape compared to the median observed data.

M460 PK following oral administration of rociletinib, was described by a model which assumed 100% conversion of M502 to M460 with a delay compartment and single M460 compartment in sequence with the M502 model. For M460 >25% of the data points were BLQ and it seems from the model file that these were excluded. This is not according to analysis plan and best practice. In addition the covariate “slope” was missing for >10% and was imputed as population median which is not optimal.

In summary, the rociletinib and metabolite models do not appear to capture the trends of the data and are currently not suitable for covariate evaluation or to predict steady state exposures. VPCs and GOF plot suggest model misspecification. The Applicant needs to address the issues identified in LoQ Section 6.3.

3.3.4. Conclusions on clinical pharmacology

In general, the clinical pharmacology data for rociletinib and metabolites is acceptable. However, there are uncertainties, for example, regarding the interaction potential for rociletinib, both as affected by and effect on other medical products. Also, issues identified for the population PK model needs to be addressed to allow the use of the model. In addition, there are a number of other concerns that should be adequately addressed.

The formation of M460, the metabolite causally related to QT prolongation, appears to be governed by the enzyme N-acetyltransferase. This is a polymorphic enzyme; the consequences of this from a cardiac safety perspective constitute a major concern.

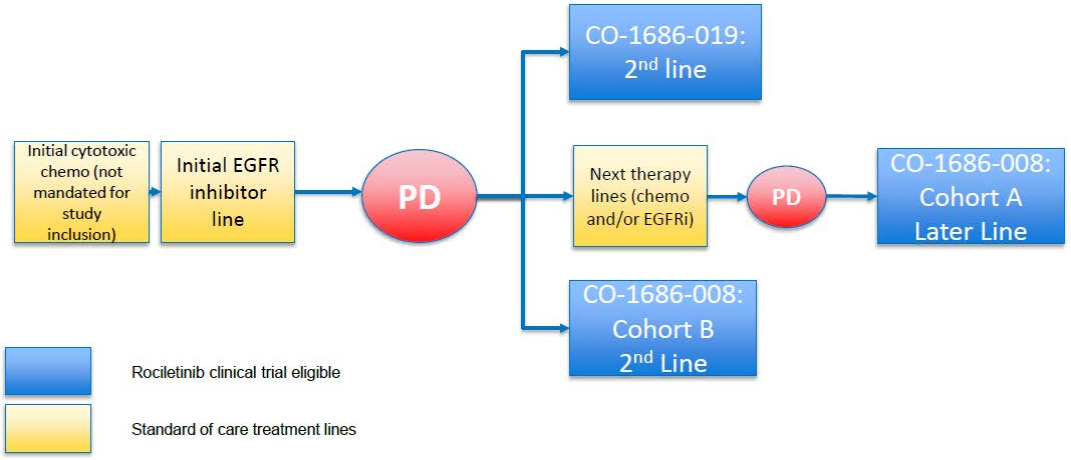
3.3.5. Clinical efficacy

The clinical program in support of the efficacy and safety of rociletinib for the treatment of patients with mutant EGFR NSCLC after failure of prior EGFR directed therapy and who have T790M-mediated resistant NSCLC is at the moment based on 2 ongoing clinical studies:

1. **Study CO-1686-008 (TIGER-X)** - A Phase 1/2, open-label, safety, pharmacokinetic and preliminary efficacy study of oral rociletinib in patients with previously treated, mutant EGFR NSCLC.

2. **Study CO-1686-019 (TIGER-2)** - A Phase 2 open-label, multicenter, safety and efficacy study of oral rociletinib as second-line EGFR-directed TKI in patients with mutant EGFR NSCLC.

Both studies are expected to be completed by late 2016.



Cut-off dates

Dose Group	N	Patients enrolled by	Includes All Visits Prior to
500 mg HBr BID All (Centrally confirmed T790M-positive patients)	 90 79	20 March 2015	29 April 2015
625 mg HBr BID All (Centrally confirmed T790M-positive patients)	 209 167	31 December 2014	
All other patients	158	31 December 2014	31 December 2014

Summary of main efficacy results

- **Summary of efficacy for trial CO-1686-008 (TIGER-X)**

A Phase 1/2, open-label, safety, pharmacokinetic and preliminary efficacy study of oral rociletinib in patients with previously treated mutant EGFR NSCLC.		
Study identifier	CO-1686-008 (TIGER-X)	
Design	Single arm, open-label	
	Phase 1: dose-escalation period with 21-day cycles; optional treatment extension starting on Day 22	completed

	Phase 2: Evaluation of activity and safety in patients with the T790M EGFR mutation who have: -Cohort A: Progressed on EGFR directed therapy (irrespective of the number and order of previous lines of NSCLC therapy) (750 mg BID, 625 mg BID and 500 mg BID) -Cohort B: progression on the first single agent EGFR directed therapy received and also had no more than one previous line of chemotherapy (750 mg BID, 625 mg BID and 500 mg BID) -Cohort C: discordance between local (T790M positive) and central (T790M negative) T790M results, or no central test result due to inadequacy of the tissue specimen and known to be T790M positive by local test (625 mg BID only)	ongoing

Treatments groups	Phase 1 EGFR-mutated (excluding exon 20 insertion) advanced NSCLC; prior EGFR-directed therapy; measurable disease per RECIST v1.1; available biopsy of primary or metastatic tumor tissue; life expectancy ≥ 3 months; ECOG 0-1		n=111 Until PD or unacceptable toxicity Continuous treatment
	Phase 2 T790M-positive (cohorts A and B only)		n=304 (Cohort A: 173; Cohort B: 97; Cohort C: 34) Until PD or unacceptable toxicity Continuous treatment
Endpoints and definitions	Primary	Phase 1 Phase 2	Incidence of DLTs; PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $T_{1/2}$, k_{el}, V_{ss}/F, Cl/F) ORR and DOR (investigator assessment)
	Secondary	Phase 2	-ORR, DOR, PFS by IRR - incidence of AEs, clinical laboratory abnormalities, and ECG abnormalities -OS, DCR and PFS by investigator assessment -plasma PK parameters for CO-1686 at Cycle 1 Day 1 and Cycle 1 Day 15 for a subset of patients; metabolite profile in the Day 15 plasma samples for a subset of patients; Plasma PK parameters for CO-1686 based on sparse sampling of all patients -change from baseline in PRO -change from baseline in QT/QTc interval
	Exploratory	Phase 2	-TTF -concordance of the presence of T790M mutation in blood and tumor tissue samples
Database lock	Start: March 2012 Different cut-off dates for different dose levels, see above		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Efficacy evaluable population, i.e. all patients who received at least one dose of IMP, had at least one measurable tumor lesion at baseline and at least 1 post-baseline tumor assessment by IRR.		
Descriptive statistics and estimate variability	Dose level	500 mg BID	625 mg BID
	Number of subjects	76	121

	Primary efficacy: ORR by inv.	42.1% (95% CI 30.9-54)	48.8% (95% CI 39.6-58)
	DOR (median, d.)	140	148
Analysis description	**Secondary analysis**		
	ORR by IRR	n=55 38.2% (95% CI 25.4-52.3)	n=87 52.9% (95% CI 41.9-63.7)
	confirmed ORR by inv	n=48 31.3% (95% CI 18.7-46.3)	n=103 45.6% (95% CI 35.8-54.7)
	confirmed ORR by IRR*	23.5%	41.2%
	DOR (median)	Not reached	151

*If 2 successive scans 28 days apart show CR/PR

A set of 40 T790M negative patients was treated at different dose levels in TIGER-X. An ORR effect (as PR) was observed in one of the five patients enrolled in the 500 mg BID group and in 7 of the 18 patients of the 625 mg BID group. These patients should be characterised in terms of both common EGFR sensitizing- and other mutations:

ORR in centrally-confirmed T790M negative patients, investigator efficacy evaluable population

	< 900 mg FB BID N = 5	900 mg FB BID N = 3	500 mg HBr BID N = 5	625 mg HBr BID N = 18	750 mg HBr BID N = 9	1000 mg HBr BID N = 0	Overall N = 40
Best Objective Single Response (n [%])							
CR	0	0	0	0	0	-	0
PR	0	1 (33.3)	1 (20.0)	7 (38.9)	2 (22.2)	-	11 (27.5)
SD	1 (20.0)	2 (66.7)	0	6 (33.3)	3 (33.3)	-	12 (30.0)
PD	3 (60.0)	0	4 (80.0)	5 (27.8)	3 (33.3)	-	15 (37.5)
Not evaluable[a]	1 (20.0)	0	0	0	1 (11.1)	-	2 (5.0)
ORR (CR + PR)	0	1 (33.3)	1 (20.0)	7 (38.9)	2 (22.2)	-	11 (27.5)
95% CI (%)	0.0, 52.2	0.8, 90.6	0.5, 71.6	17.3, 64.3	2.8, 60.0	-	14.6, 43.9

- Several factors could explain the observed activity in the T790M-negative subgroup. Firstly, heterogeneous T790M expression within tumors could produce a negative result when T790M clones that are present elsewhere drive tumor growth. Alternatively, inadequate testing sensitivity may be the cause; however, this is unlikely considering that central testing has identified T790M mutations in samples with a tumor content as low as 5% in Clovis clinical studies. Finally, activity driven by a non-T790M-mediated mechanism of action for rociletinib may be a factor. Nonclinical studies in NSCLC models have demonstrated a role for IGF1R signaling in mediating resistance to EGFR inhibitors, thus dual mutant EGFR and IGF1R pathway suppression may contribute to the anti-tumor activity of rociletinib observed in T790M-negative patients. **Summary of efficacy for trial CO-1686-019 (TIGER-2)**

A Phase 2 open-label, multicenter, safety and efficacy study of oral rociletinib as second-line EGFR-directed TKI in patients with mutant EGFR NSCLC.	
Study identifier	CO-1686-019 (TIGER-2)
Design	Single arm, open-label

	Status	ongoing
Treatments groups	Cohort A: EGFR-mutated (excluding exon 20 insertion) advanced NSCLC; progression on 1 previous EGFR-directed TKI; measurable disease per RECIST v1.1; available biopsy of primary or metastatic tumor tissue; life expectancy ≥ 3 months; ECOG 0-1. Patients with centrally-confirmed T790M-positive NSCLC Dose level: 625 mg BID	n=42 Until PD or unacceptable toxicity. Optional extension post-progression.
	Cohort B: Same as above, but patients with centrally-confirmed presence or absence of T790M-positive NSCLC. Patients with CNS metastases are excluded. Dose level: 500 mg BID	Opened in May 2015. No data. Until PD or unacceptable toxicity
	A and B: Patients with disease progression confirmed by radiologic assessment while receiving treatment with the first single-agent EGFR TKI (eg, erlotinib, gefitinib, afatinib, or dacomitinib) - EGFR TKI treatment discontinued ≤ 30 days prior to planned initiation of rociletinib (the washout period for an EGFR inhibitor is a minimum of 3 days) - No intervening treatment between cessation of single-agent EGFR TKI and planned initiation of rociletinib - Previous treatment with ≤ 1 prior chemotherapy (excluding prior neo-adjuvant or adjuvant chemotherapy or chemoradiotherapy with curative intent) - Any toxicity related to prior EGFR inhibitor treatment must have resolved to Grade 1 or less Measureable disease according to RECIST Version 1.1 Dose level: 500 mg BID (presumably)	No data

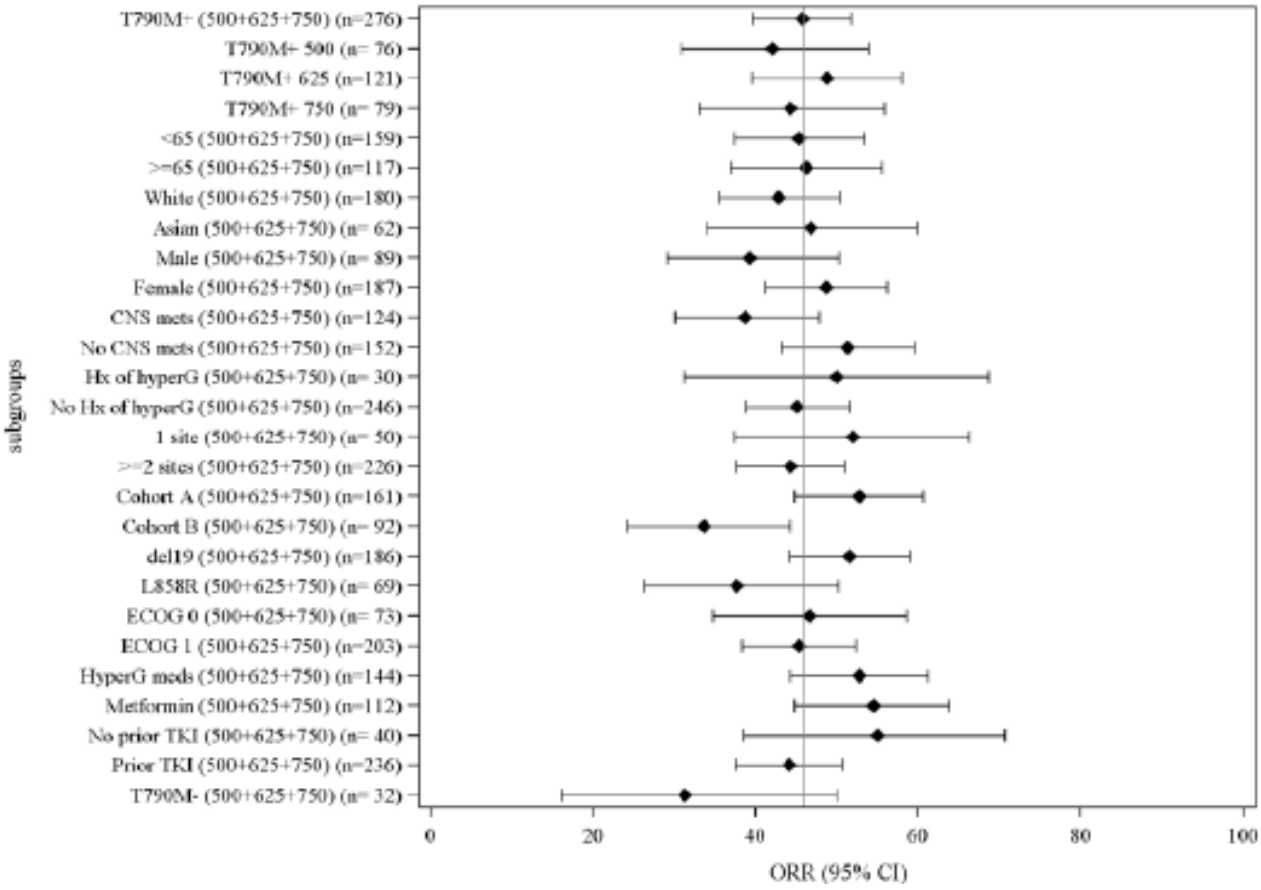
Endpoints and definitions	Primary	Cohort A: ORR (by IRR) in patients with T790M-positive NSCLC Cohort B: ORR (by IRR) in patients with T790M-positive or T790M-negative NSCLC
	Secondary	Investigator-assessed ORR, DCR, DOR, PFS, OS, QoL by PRO, popPK, safety.
	Exploratory	TTF, extra-cranial PFS, change from baseline in mutant EGFR levels in ctDNA obtained from plasma, positive and negative percent agreement between blood and tissue results for T790M, biomarkers associated with response or resistance to CO-1686
Database lock	Start: June 2014 Different cutoff dates for different dose levels, see above	

<u>Results and Analysis</u>

Analysis description	**Primary Analysis**		
Analysis population and time point description	Efficacy evaluable population		
Descriptive statistics and estimate variability	Treatment group	500 mg BID	625 mg BID
	Number of subject	-	39
	ORR by IRR	-	46.2% (95% CI 30.1-62.8)

	Confirmed ORR by IRR	-	n=37 35.1% (95% CI 20.2-52.5)
Effect estimate per comparison	NA. Single-arm study		
Analysis description	**Secondary analysis**		
	None available		

Subgroup analyses for TIGER-X and TIGER-2 combined have been performed:



The ORR subgroup analyses by investigator assessment (grouped 500, 625 and 750 mg doses, for both trials) show that rociletinib may be 'less effective' in the L858R mutation.

The results in earlier-line patients, i.e. cohort B in TIGER-X (who had radiologic progression on only 1 prior EGFR TKI agent for advanced/metastatic NSCLC, and who had not since received any intervening chemotherapy) plus the patients enrolled in TIGER-2, appear less "promising" than the rest. This preliminary result should be discussed in the context of the updated data at day 120.

So far, there are no data in patients >75 years. Clinical studies in special populations

Please refer to the pharmacokinetics section. No special population analyses in addition to subgroup analyses have been submitted.

Note the definition of "mild liver impairment". Patients with different degrees of cirrhosis appear were not studied.

3.3.6. Discussion on clinical efficacy

Rociletinib is a small molecule TKI, inhibitor of EGFR with common activating (L858R, Del19) and T790M resistance mutations, and low activity towards wild-type EGFR. Rociletinib covalently binds and irreversibly inhibits the kinase activity of mutant EGFR. Rociletinib and its metabolites at clinically achievable concentrations also inhibit a number of other kinases.

Rociletinib is developed as a single agent for the treatment of adult patients with mutant-EGFR NSCLC who have been previously treated with an EGFR-targeted therapy (mainly first generation, i.e. gefitinib and erlotinib) and have acquired the T790M resistance mutation.

The development program focused initially on patients whose disease has progressed on existing EGFR-TKIs, and where T790M is the dominant driver of progression, i.e. the patient population with the highest unmet clinical need. Development however is ongoing in EGFR TKI-naïve patients with EGFR mutant NSCLC and in T790M negative patients (in which rociletinib activity has been observed).

As of data cut-off dates, 457 patients across all dose ranges and formulations have been treated with rociletinib in two open-label, single-arm, ongoing studies, both with ORR as primary efficacy endpoint:

- CO-1686-008 (TIGER-X) - A Phase 1/2, open-label, safety, pharmacokinetic and preliminary efficacy study of oral rociletinib in patients with previously treated mutant EGFR NSCLC.

- CO-1686-019 (TIGER-2) - A Phase 2 open-label, multicenter, safety and efficacy study of oral rociletinib as second-line EGFR-directed TKI in patients with mutant EGFR NSCLC.

The patient population in study TIGER-2 recalls the cohort B of the TIGER X, comprised of earlier-line patients who had radiologic progression on only 1 prior EGFR TKI agent for advanced/metastatic NSCLC, and who had not since received any intervening chemotherapy. Thus the patients enrolled are similar to the real population to be treated in the clinical practice, i.e. patients treated with a previous line of TKI in the presence of T790M mutation. In addition, there was a maximum time lag from discontinuation of EGFR TKI treatment (≤ 30 days) to enter TIGER-2, with no intervening treatment allowed.

The patients largely represent the target population (predominantly younger and non-smoker females). Patients were in majority Caucasian/Asian.

In TIGER-X, the median: age at diagnosis was 62 years; time from initial NSCLC diagnosis was 27.5 months; median number of prior therapy line was 2, with 53% of patients having ≥3 lines of previous treatment; number of previous TKI therapies was 1, with 41% of patients having ≥2 prior TKI treatments. In 82.5% of patients the last previous therapy was a TKI. The majority of patients, 82%, had ≥2 metastatic sites at baseline, and 46% had prior CNS metastasis. Central testing showed that the primary EGFR activating mutations were exon 19 deletions (51.6%), L858R mutations (19.5%) and others, at 2.2% (excluding exon 20 insertion).

In TIGER-2, 78.6% of patients had Stage IV NSCLC and a median age of 65 years at initial diagnosis, with a median of 18.4 months since diagnosis. The majority of patients (69.0%) had ≥2 sites of disease at baseline. CNS metastases were present at baseline in 45.2% of patients, while 11.9% had a history of hyperglycemia. All patients, except one treated with 2 TKI lines, had received 1 prior EGFR TKI. All patients were T790M-positive using the central test. Activating mutations were mainly exon 19 deletions (76.2%), with L858R mutations reported for 19.0% of patients.

Based on the results from the phase 1 part of TIGER-X, the initially selected dose level for the phase 2 part was 750 mg, later to be complemented with 625 and 500 mg. The formal phase 2 TIGER-2 was initially planned as a randomised 500 vs. 625 mg study, but was redesigned so that the first cohort enrolled patients in a 625 mg cohort; later, 500 mg BID regimen was selected for further development

based on safety concerns. The intended treatment duration is until clinical benefit is no longer observed or unacceptable toxicity.

For patients initiating treatment at the 500 mg BID therapeutic dose, the mean relative dose intensity was 0.90, and for 625 mg BID, 0.87. There is some evidence of a dose-response relationship with regards to efficacy, with apparent higher response rates at 625 mg BID dose level than at 500 mg BID, of note the date of cut-off may to an underestimate of ORR on the 500 mg dose as there are some late responses. Duration of response and other time-related outcome measures are still immature, but there is a concern that a putatively suboptimal dose of rociletinib from an efficacy perspective might be related to the early evolution to resistance.

No informative analysis are available for the secondary (PFS, DCR, OS, QoL) and the exploratory endpoints, since data are immature and patients are still ongoing/enrolling in the phase 2 study and the phase 3 trials. ORR data from the intended recommended dose, 500 mg BID cohort B in study TIGER-2, were thus not presented in the current submission.

From the total 40 T790M negative patients enrolled across all dose ranges in TIGER-X, 1 of the 5 patients in the 500 mg BID group had a PR as best response; in the 625 mg BID dose level, 7 out of 18 patients had a PR as best response. These T790M negative patients should be further characterised in terms of common EGFR-sensitizing mutations and other, rarer, mutations.
In TIGER-X, and in T790M positive tumours 2/3 of ORR were reported at the end of cycle 2 and 97% at the end of cycle 4 for the 500 mg BID group (a cycle consisted of 21 days of treatment; cycle 2 began on day 22 and so on).

The subgroup analyses available so far show that rociletinib tends to be ‘less active’ against the L858R background missense mutation compared with del19, i.e. as for other EGFR-TK inhibitors. Results in earlier-line patients (who had radiologic progression on only 1 prior EGFR TKI agent for advanced / metastatic NSCLC, and who had not since received any intervening chemotherapy) appear less “promising” than the rest at this time.

The ongoing confirmatory studies whose results are expected (with the caveats already signalled by the CHMP regarding the difference in the studied populations in the confirmatory trials in comparison with the submission dossier) are as follows:

- CO-1686-020, TIGER-3: an open-label, randomized study of rociletinib monotherapy vs single-agent chemotherapy in patients with mutant EGFR NSCLC after failure of at least one previous EGFR-directed TKI and platinum-doublet chemotherapy. N=600. Primary endpoint is invPFS; secondary endpoints are invORR and invDR; OS.
- CO-1686-022, TIGER-1: an open-label, randomized, study of rociletinib or erlotinib as first-line treatment of EGFR-mutant advanced/metastatic NSCLC. N=1200. Primary endpoint: invPFS. Secondary endpoints: invORR and invDR; OS.

Acquired resistance to rociletinib has been evaluated in a cohort of 12 patients, and was attributed to histological transformation in 2 cases and increased EGFR amplification in 3 cases. Mutations in C797 or any other novel EGFR mutations have not been detected in any patients with acquired resistance to rociletinib. Although it seems premature to establish differences in resistance to T790M drugs, it would be of value that those would display different mechanisms of resistance.

3.3.7. Conclusions on clinical efficacy

The activity of rociletinib in the T790M positive metastatic/unresectable locally advanced EGFR mutated NSCLC is promising compared with historical chemotherapy studies, but cannot yet be properly assessed. The most appropriate analysis of ORR (RECIST), confirmed ORR by IRR - places the ORR for the 625 mg BID dose level between 35.1 and 41.2%, and for 500 mg BID at 23.5%, in comparison with approximately 10% of traditional chemotherapy.

Duration of response and other time-related outcome measures are not yet evaluable, but there is a concern that a putatively suboptimal dose of rociletinib from an efficacy perspective might be related to the early evolution to resistance.A more robust efficacy assessment entirely relies on the data to be provided by the Applicant from all ongoing studies in the second round of the authorisation procedure. Of note, an accelerated assessment is no longer appropriate due to the complexity of outstanding issues.

3.3.8. Clinical safety

Patient exposure

The size of the safety population (i.e. any patient who received at least 1 dose of rociletinib) is sufficient for an assessment of common adverse reactions.

In Studies CO-1686-008 (TIGER-X) and CO-1686-019 (TIGER-2), a total of 457 patients were exposed to rociletinib (19 patients initiated treatment with 900 mg FB BID, 90 with 500 mg hydrobromide BID, 209 with 625 mg HBr BID, 95 with 750 mg HBr BID, and 6 with 1000 mg HBr BID).

Exposure, TIGER-X and TIGER-2 combined

	< 900 mg FB BID N = 38	900 mg FB BID N = 19	500 mg HBr BID N = 90	625 mg HBr BID N = 209	750 mg HBr BID N = 95	1000 mg HBr BID N = 6	Overall N = 457
Number of Cycles Initiated							
Mean (StD)	5.8 (5.87)	10.6 (8.61)	7.1 (5.27)	6.2 (4.16)	8.5 (4.80)	10.7 (7.47)	7.0 (5.10)
Median	3.0	9.0	4.0	6.0	9.0	9.5	6.0
Range	1-22	1-28	1-22	1-23	1-22	2-20	1-28
Duration of Treatment (Days)							
Mean (StD)	121.2 (127.65)	218.6 (183.69)	139.4 (110.45)	127.9 (87.89)	170.0 (99.81)	219.7 (158.83)	143.3 (107.25)
Median	57.0	170.0	77.0	126.0	171.0	201.0	126.0
Range	10-461	21-597	8-460	1-478	12-443	42-409	1-597
Duration of Treatment (n [%])							
< 6 months	29 (76.3)	10 (52.6)	60 (66.7)	160 (76.6)	51 (53.7)	2 (33.3)	312 (68.3)
6-12 months	6 (15.8)	2 (10.5)	27 (30.0)	46 (22.0)	40 (42.1)	2 (33.3)	123 (26.9)
> 12 months	3 (7.9)	7 (36.8)	3 (3.3)	3 (1.4)	4 (4.2)	2 (33.3)	22 (4.8)
Relative Dose Intensity[a]							
Mean (StD)	1.16 (0.496)	0.75 (0.196)	0.90 (0.162)	0.87 (0.160)	0.78 (0.195)	0.83 (0.211)	0.88 (0.237)
Median	1.00	0.77	0.98	0.94	0.82	0.93	0.94
Range	0.7-3.6	0.3-1.0	0.5-1.3	0.1-1.0	0.4-1.0	0.5-1.0	0.1-3.6

The median number of cycles was 4 for the 500 mg BID group and 6 for the 625 mg BID group. The median duration of treatment was also longer for the 625 mg BID dose level, 126 vs. 77 days. The mean dose intensities for these dose levels were similar, 0.90 vs. 0.87.

As of the data cut-off date, 184 of the 415 patients (44.3%) in TIGER-X and 19 of the 42 patients (45.2%) in TIGER-2 are ongoing; 52 of the 90 patients (57.8%) at 500 mg rociletinib in TIGER-X are ongoing.

As for baseline characteristics, no apparent imbalances are observed across doses and formulations.

Regarding discontinuations: of the 254 patients who discontinued in either study, the primary reason for discontinuation of rociletinib was disease progression: 86.8% in TIGER-X (500 mg BID), 65.2% in

TIGER-2 (625 mg BID, i.e. cohort A, the only dose group so far presented by the Applicant, as no data are available for the 500 mg dose group B). Overall, the discontinuations caused by AEs are low so far: in TIGER-X, 5.3% for the 500 mg BID group; in TIGER-2, 8.7% in the 625 mg BID group.

Adverse events

Common adverse events

The most frequently reported TEAEs (≥10% of patients overall) by SOC were GI disorders (78.3%, mostly diarrhoea), metabolism (68.5%, mainly hyperglycaemia), general disorders (61.1%, mainly fatigue), and investigations (58.9%, namely QT prolongation).

The most common (> 25%) TEAEs by PT, irrespective of relationship to rociletinib, were diarrhoea (49.7%), nausea (47.0%), hyperglycaemia (46.2%), fatigue (39.8%), decreased appetite (33.0%), vomiting (28.0%), and QT prolongation (27.8%).

The most common TEAEs for patients who initiated treatment with the 500 mg BID dose were diarrhoea (50.0%), hyperglycaemia (44.4%), nausea (43.3%), fatigue (36.7%), QT prolongation (28.9%), decreased appetite (26.7%) and vomiting (25.6%).

AEs ≥ gr3

The overall incidence of TEAEs≥gr3, regardless of causality, was 68.7%. The most frequent TEAEs≥gr3 was hyperglycaemia, 27.8%. Other than PD (16.4%), QT prolongation (9.2%), fatigue (4.4%), pneumonia (4.4%), vomiting (3.7%), hyponatremia (3.3%), and nausea (3.3%), the remaining TEAEs≥gr3 occurred in less than 3% of patients.

The proportion of patients experiencing events ≥gr3 was lower when treatment was initiated at 500 mg BID (62.2%), compared to the higher dose groups (69.4% at 625 mg BID, 81.8% at 750 mg BID).

The most common TEAEs≥gr3 for patients at 500 mg BID dose were hyperglycaemia (24.4%), PD (12.2%), vomiting (6.7%), QT prolongation (6.7%), nausea (4.4%), hyponatremia and fatigue (3.3%).

AESI

The following AEs were identified as presenting special interest:

- hyperglycaemia
- QTc prolongation/torsades de pointes and cardiac arrhythmia
- ILD
- acute pancreatitis
- rash/skin disorders
- diarrhoea
- cataract

Hyperglycaemia

The mechanism for hyperglycemia was elucidated during the rociletinib development program, after it was first observed in patients. Hyperglycaemia is likely caused by reversible inhibition of IGF1R/INSR kinases by rociletinib metabolite, M502. Oral medications that were effective at managing a state of insulin resistance, such as metformin, glitazones and sodium-glucose co-transporter-2 inhibitors were used.

M502 has a short half-life (<24 hours). Therefore, if symptomatic hyperglycaemia is not controlled by anti-hyperglycaemic medication, a brief dose interruption will result in rapid symptom control and

blood glucose reduction. Rociletinib may then be restarted concurrently with the selected anti-hyperglycaemic medication.

Overall, prior use of anti-hyperglycaemic medication was reported in 9.2% of patients; 41.4% received concomitant anti-hyperglycaemic medication during rociletinib treatment. The most common concomitant agent was metformin (35.9%). For patients who initiated treatment at the 500 mg BID dose, the concomitant use of metformin was 36.7%. A total of 24 (49.0%) patients with a history of hyperglycaemia at baseline received concomitant anti-hyperglycaemic medication.

Of 408 patients without a history of hyperglycaemia at baseline, 165 (40.4%) required concomitant treatment with anti-hyperglycaemic therapy.

In the subgroup of patients who required anti-hyperglycaemic medication, most patients started therapy within the first 6 weeks of rociletinib treatment.

Studies CO-1686-008 and CO-1686-019		
Identified Risk	**500 mg HBr BID N = 90**	**Overall N = 457**
Hyperglycaemia/New Onset Diabetes Mellitus (SMQ) (All CTCAE grades)	45 (50.0%) [95% CI: 39.3%-60.7%]	236 (51.6%) [95% CI: 47.0%-56.3%]

Outcome of SAEs of Hyperglycaemia/New Onset Diabetes Mellitus (SMQ)	**Number (%) of Patients**	
	500 mg HBr BID N = 90	**Overall N = 457**
Recovered/Resolved	10 (11.1%)	27 (5.9%)
Recovered/Resolved with Sequelae	0	3 (0.7%)
Not Recovered/Not Resolved	0	1 (0.2%)
Total Patients with SAEs	**10 (11.1%)**	**31 (6.8%)**

In patients with a history of hyperglycaemia (n=49), the incidence of gr≥3 hyperglycaemia was 42.9% (21 patients). None of the TEAEs of hyperglycaemia in these patients led to discontinuation of rociletinib. The dose of rociletinib was interrupted in 14 (28.6%) patients, and reduced in 12 (24.5%) patients with a history of hyperglycaemia at baseline.

It may be concluded that hyperglycaemia caused by rociletinib is manageable in clinical praxis.

QTc Prolongation / Torsades de Pointes and Cardiac Arrhythmia

ECG data from 104 patients (including 50 patients treated at doses of 500 mg BID or higher) in the Phase 1 dose escalation portion of TIGER-X. Integrated analyses of ECGs and cardiac safety data derived from TIGER-X and TIGER-2 are detailed in the stand-alone Integrated Cardiovascular Safety Report.

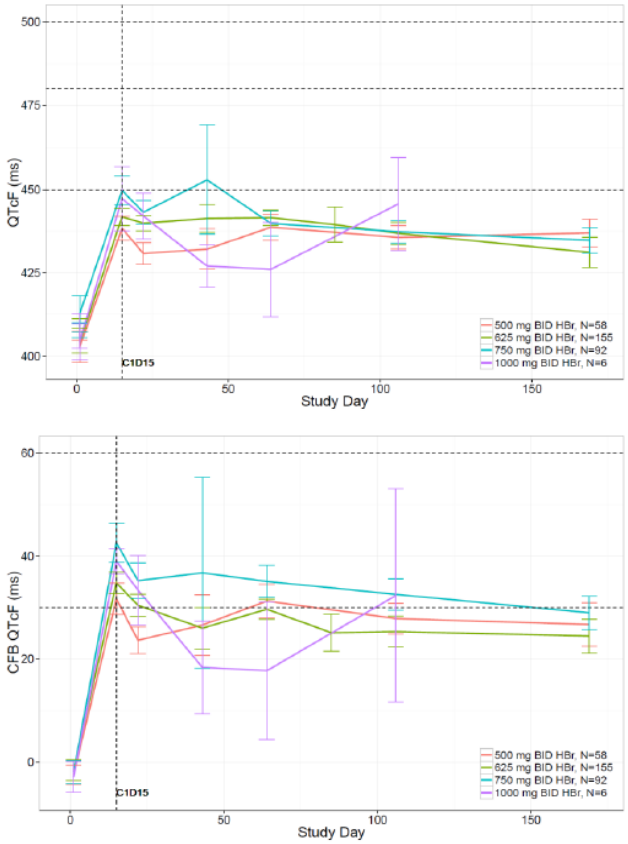
Following rociletinib dosing, QTcF prolongation was not observed on the first day of dosing, but was evident by Cycle 1 Day 15, the next assessment point, before leveling off or declining slowly with continued treatment with rociletinib.

In both TIGER studies, 12-lead electrocardiograms were measured regularly. Triplicate 12-lead ECGs were performed. If QTc prolongation of gr3 was observed, rociletinib was to be held until the event had improved to gr1. Rociletinib could then be re-started at a reduced dose. In TIGER-X and TIGER-2, if gr3 or above QTc prolongation recurred after 2 dose reductions, then rociletinib was to be discontinued.

If QTc prolongation of gr4 was observed at any time in the studies, rociletinib was to be discontinued permanently. Medications known to prolong the QT interval were to be avoided during the studies. However, in both studies if a drug that had the potential to cause QTc prolongation was indicated to control AEs (eg, serotonin [5HT3] receptor antagonists for nausea/vomiting), and the investigator

believed that the patient was benefiting from rociletinib therapy, then additional ECGs were performed to monitor QTc changes.

Pre-dose QTcF and CFB QTcF (ΔQTcF) Versus Time Profiles



Source: Figure 14 of Report QS-CLV-002 (Section 5.3.4.2).

Abbreviations: BID = twice daily; CFB = change from baseline; HBr = hydrobromide; QTcF = QT interval corrected using Fridericia's method; ΔQTcF = baseline-adjusted QTcF.

Upper panel: QTcF versus study day profiles; Bottom panel: QTcF CFB versus study day profiles. Mean (±SE) QTcF and QTcF CFB are shown. Horizontal dashed lines are at 450, 480, and 500 msec for the QTcF plots (upper panels) and at 30 and 60 msec for the CFB QTcF plots (bottom panels). Dose levels in the legend represent the nominal (starting) dose levels. Dose adjustments during treatment were not reflected in this analysis.

AEs of QTc Prolongation/Torsades de Pointes and Cardiac Arrhythmia

Based on the combined terms (SMQ Torsade de Pointes/QT prolongation [broad and narrow scope]), TEAEs of Torsades de Pointes/QTc prolongation were reported in 29.5% of patients overall. Most of these events were ECG abnormalities without clinical sequelae. Combined terms of cardiac arrhythmia (SMQ Cardiac arrhythmias) were reported in 32.8% of patients overall; SAEs and TEAEs of cardiac arrhythmia that led to discontinuation of rociletinib were less frequent (3.1% and 2.2%, respectively).

The overall frequencies of QTc prolongation were 30.0% at 500 mg BID, 34.4% at 625 mg BID, and 31.6% at 750 mg BID, respectively. The severity of QTc prolongation is dose-related, based on both AE reporting (gr3 or higher in 6.7% at 500 mg BID; 12.9% at 625 mg BID; 14.7% at 750 mg BID), and on the frequency of QTcF ≥ 501 msec (8.9% at 500 mg, BID; 10.5% at 625 mg BID; 17.9% at 750 mg BID). Only 1 patient who initiated treatment with rociletinib at 500 mg BID discontinued treatment due to a TEAE of QTc prolongation (gr1, no associated arrhythmia). The overall frequencies of cardiac arrhythmia were 34.4% in patients initiating treatment at 500 mg BID, 36.8% at 625 mg

BID, and 35.8% at 750 mg BID. The incidences of gr3 or higher cardiac arrhythmia were 6.7%, 13.4% and 14.7% at 500, 625 and 750 mg BID, respectively.

SAEs reported in the SMQ Cardiac arrhythmias (14 [3.1%] patients) included electrocardiogram QT prolonged (3 [0.7%] patients); atrial fibrillation, supraventricular tachycardia, and sudden death (2 [0.4%] patients each); cardiac arrest, palpitations, Torsade de Pointes, ventricular fibrillation, ventricular tachyarrhythmia, and syncope (1 [0.2%] patient each). There were 4 events of ventricular arrhythmia in which rociletinib could have played a role, and rociletinib was permanently discontinued. One patient died to cardiac arrest.

QTc prolongation in relation to dose

The relationship between the plasma concentration of rociletinib and its major metabolites and potential changes in QTcF was evaluated in both TIGER-X and TIGER-2.

Post Baseline Results	< 900 mg FB BID N = 38	900 mg FB BID N = 19	500 mg HBr BID N = 90	625 mg HBr BID N = 209	750 mg HBr BID N = 95	1000 mg HBr BID N = 6	Overall N = 457
	n (%)						
QTcF Post-Baseline							
≥ 450 msec	4 (10.5)	9 (47.4)	42 (46.7)	114 (54.5)	60 (63.2)	4 (66.7)	233 (51.0)
≥ 481 msec	0	2 (10.5)	15 (16.7)	42 (20.1)	28 (29.5)	2 (33.3)	89 (19.5)
≥ 501 msec	0	1 (5.3)	8 (8.9)	22 (10.5)	17 (17.9)	0	48 (10.5)
Two or more ≥ 501 msec within 3 days	0	1 (5.3)	3 (3.3)	8 (3.8)	10 (10.5)	0	22 (4.8)
QTcF, Change from Baseline							
> 30 msec	9 (23.7)	8 (42.1)	65 (72.2)	144 (68.9)	81 (85.3)	5 (83.3)	312 (68.3)
> 60 msec	0	0	20 (22.2)	64 (30.6)	43 (45.3)	2 (33.3)	129 (28.2)
QTcB Post-Baseline							
≥ 450 msec	16 (42.1)	13 (68.4)	67 (74.4)	161 (77.0)	82 (86.3)	5 (83.3)	344 (75.3)
≥ 481 msec	0	5 (26.3)	31 (34.4)	84 (40.2)	43 (45.3)	2 (33.3)	165 (36.1)
≥ 501 msec	0	1 (5.3)	12 (13.3)	35 (16.7)	23 (24.2)	0	71 (15.5)
Two or more ≥ 501 msec within 3 days	0	1 (5.3)	3 (3.3)	15 (7.2)	16 (16.8)	0	35 (7.7)
QTcB, Change from Baseline							
> 30 msec	8 (21.1)	11 (57.9)	63 (70.0)	148 (70.8)	75 (78.9)	5 (83.3)	310 (67.8)
> 60 msec	1 (2.6)	1 (5.3)	20 (22.2)	57 (27.3)	40 (42.1)	2 (33.3)	121 (26.5)

Source: Table 3.6.1.1.1 and Table 3.6.1.1.2 (Section 5.3.5.3).

Abbreviations: BID = twice daily; FB = free base; HBr = hydrobromide; QTcB = QT interval corrected using Bazett's method; QTcF = QT interval corrected using Fridericia's method.

Note: Data are presented for the number of patients with QTc above the specified threshold. For all other patients, QTc values were below the specified threshold.

In conclusion, the clinical cardiac events possibly related to QTc prolongation, irrespective of dose are:

- atrial fibrillation, supraventricular tachycardia, and sudden death (2 [0.4%] patients each);
- cardiac arrest, palpitations, Torsade de Pointes, ventricular fibrillation, ventricular tachyarrhythmia, and syncope (1 [0.2%] patient each).
- there were 4 events of ventricular arrhythmia in which rociletinib could have played a role, and rociletinib was permanently discontinued.
- one patient died to cardiac arrest.

Acute Pancreatitis

Studies CO-1686-008 and CO-1686-019		
Identified Risk	**500 mg HBr BID N = 90**	**Overall N = 457**
Acute Pancreatitis (SMQ) (All CTCAE grades)	4 (4.4%) [95% CI: 1.2%-11.0%]	13 (2.8%) [95% CI: 1.5%-4.8%]

Seriousness/Outcomes:

In the 500 mg HBr BID dose group and overall, SAEs in the SMQ of acute pancreatitis were reported in 3 (3.3%) and 7 (1.5%) patients, respectively. Overall, these included SAEs of pancreatitis (7 [1.5%] patients). The outcomes of these SAEs are provided below:

Outcome of SAEs of Acute Pancreatitis (SMQ)	Number (%) of Patients	
	500 mg HBr BID N = 90	**Overall N = 457**
Recovered/Resolved	3 (3.3%)	7 (1.5%)
Total Patients with SAEs	**3 (3.3%)**	**7 (1.5%)**

Severity and Nature of Risk:

At the 500 mg HBr BID dose and overall, ≥ Grade 3 AEs of acute pancreatitis were reported in 3 (3.3%) and 8 (1.8%) patients, respectively. Overall, no patients discontinued rociletinib due to an event of acute pancreatitis.

Interstitial lung disease

ILD is a "known" effect of EGFR inhibitors and other TKIs. The overall incidence was low (11 patients [2.4%]); 5 (1.1%) experienced gr≥3 ILD, and 4 (1.0%) reported a SAE; there were no fatal cases of ILD. There were no reports of ILD in patients who initiated treatment at 500 mg BID.

Of the 11 total cases of ILD, 4 were SAEs, and 7 were judged to be related to rociletinib. Of the 11 cases of ILD, 7 patients were able to continue with rociletinib (upon steroid treatment) beyond the initial event.

Studies CO-1686-008 and CO-1686-019		
Potential Risk	**500 mg HBr BID N = 90**	**Overall N = 457**
Interstitial Lung Disease (SMQ) (All CTCAE grades)	0	11 (2.4%) [95% CI: 1.2%-4.3%]

Outcome of SAEs of Interstitial Lung Disease (SMQ)	Number (%) of Patients	
	500 mg HBr BID N = 90	**Overall N = 457**
Recovered/Resolved	0	1 (0.2%)
Recovered/Resolved with Sequelae	0	1 (0.2%)
Not Recovered/Not Resolved	0	2 (0.4%)
Total Patients with SAEs	**0**	**4 (0.9%)**

Rash

Toxicity associated with first- and second-generation EGFR TKIs (eg, erlotinib, gefitinib and afatinib) includes cutaneous effects (rash, paronychia, and stomatitis), which are associated with inhibition of wild-type EGFR in the skin. As rociletinib has demonstrated specificity for mutant forms of EGFR, while sparing the wild-type receptor, patients receiving rociletinib should experience lower frequency and less severe AEs when compared with the approved EGFR TKIs.

The overall incidence of rash reported with rociletinib (9.8%) was much lower than that associated with e.g erlotinib (75%) or afatinib 70%). The frequencies were 6.7% at 500 mg BID, 10.0% at 625 mg BID, and 9.5% at 750 mg BID.

In addition, paronychia (0.4%) and stomatitis (1.5%) were reported less frequently in patients receiving rociletinib than in patients receiving erlotinib, gefitinib or afatinib.

Diarrhoea

Diarrhoea was one of the most common TEAEs reported (49.7%), including treatment-related diarrhoea in 40.3% of patients overall.

Similar frequencies were observed across the dose groups (500 mg BID, 50.0%; 625 mg BID, 52.2%; 750 mg BID, 52.6%). SAEs of diarrhoea were observed in 9 (2%) patients, and diarrhoea leading to study discontinuation in 1 (0.2%) patient. TEAEs led to dose reduction in 5.3% of patients, and to treatment interruption in 5.9% of patients. Only 2.4% of patients experienced gr3 diarrhoea.

Diarrhoea thus registers unexpectedly high figures for a drug designed to spare the WT EGFR. In order to contextualise, diarrhoea related to gefitinib treatment ranges from 27 to 35%, erlotinib causes diarrhoea in 55% of patients and afatinib in 80-90% of patients. This finding may warrant further investigation, since diarrhoea seems not related to a rociletinib systemic effect on WT EGFR (i.e. very low incidence of rash).

Cataracts

At the time of the data cut-off, there were 7 cases of cataract in the database, 4 at 750 mg BID and 3 at 625 mg BID. One of the 7 also had an event of posterior capsule opacification. As of July 7th 2015, six additional cases had been reported to the clinical database in patients contained in the current dataset, with onset after the data cut-off date; 2 at 1000mg BID and 4 at 750mg BID. Overall, the median date of onset was 321 days after starting rociletinib [range 107-474 days].

The event might appear dose related. No patients have discontinued rociletinib as a result of these events. There is currently no mechanistic explanation.

Serious adverse events and deaths

The frequency of treatment-related TEAEs ≥ Grade 3 increased with dose. The effect was consistent across a range of effects, including investigator reported events of hyperglycaemia, of QTc prolongation and fatigue. In addition, the frequency of dose reductions was lower at 500 mg BID (37.8%) than 625 mg (44.0%) or 750 mg (67.4%) BID.

Other SAEs

Overall, SAEs were experienced by 43.5% of patients, most frequently PD (15.3%) and hyperglycaemia (6.3%). The most common SAEs for patients who initiated treatment at 500 mg BID were PD (11.1%), hyperglycaemia (10.0%), vomiting (5.6%), nausea and pancreatitis (both 3.3%).

Treatment-related SAEs were experienced by 15.3% of patients, most frequently hyperglycaemia (6.3%). The most common treatment-related SAEs for patients who initiated treatment at 500 mg BID were hyperglycaemia (10.0%) and pancreatitis (3.3%).

Deaths

TEAEs with an outcome of death were reported in 66/457 (14.4%) patients, mainly as a consequence of PD: 57/66 [86.4%]).

There were 5 patient deaths from pneumonia, and 2 sudden deaths (both in TIGER-X). The remaining TEAEs with outcomes of death were single reports of cardiac arrest, pulmonary embolism, sepsis, and status epilepticus.

A total of 10 patients who initiated treatment at 500 mg BID experienced TEAEs with an outcome of death: PD, 8 patients, pneumonia and sepsis with 1 patient each.

In total, 5 patient deaths were considered treatment-related: 2 sudden deaths, 2 PD and 1 pneumonia at 500 mg BID.

Laboratory findings

Hyperglycaemia

	< 900 mg FB BID N = 38	900 mg FB BID N = 19	500 mg HBr BID N = 90	625 mg HBr BID N = 209	750 mg HBr BID N = 95	1000 mg HBr BID N = 6	Overall N = 457
	n (%)						
Patients with any post-baseline glucose > 13.9 mmol/L (> 250 mg/dL)	3 (7.9)	8 (42.1)	22 (24.4)	52 (24.9)	33 (34.7)	2 (33.3)	120 (26.3)
Patients with two or more post-baseline glucose > 13.9 mmol/L (> 250 mg/dL)	1 (2.6)	3 (15.8)	10 (11.1)	24 (11.5)	12 (12.6)	0	50 (10.9)
Patients with any post baseline glucose > 27.8 mmol/L (> 500 mg/dL)	0	0	2 (2.2)	0	2 (2.1)	0	4 (0.9)
Patients with two or more post baseline glucose > 27.8 mmol/L (> 500 mg/dL)	0	0	1 (1.1)	0	0	0	1 (0.2)

Source: Table 3.6.1.2 (Section 5.3.5.3).

Abbreviations: BID = twice daily; FB = free base; HBr = hydrobromide.

The rate of ≥ Grade 3 AEs of hyperglycemia has declined from 24.4% to 14.1% following the implementation of the glucose management guidance.

Safety in special populations

Patients with a history of hyperglycaemia

There were no notable differences in the overall incidences of TEAEs, treatment-related TEAEs, SAEs, TEAEs with an outcome of death, TEAEs leading to rociletinib discontinuation, or TEAEs leading to rociletinib interruption in patients with (N = 49) and without (N = 408) a history of hyperglycemia at baseline.

TEAEs of gr3 or higher severity were more frequent in patients with a history of hyperglycemia at baseline than those without (77.6% versus 67.6%). Conversely, TEAEs leading to rociletinib dose reduction were less frequent in patients with a history of hyperglycaemia at baseline than those without (38.8% versus 45.1%).

In patients with a history of hyperglycaemia, the incidence of gr≥3 was 42.9% (21 patients). None of the TEAEs of hyperglycaemia in these patients led to discontinuation. Rociletinib dosing was interrupted in 14 (28.6%) patients, and dose was reduced in 12 (24.5%) patients with a history of hyperglycaemia due to hyperglycaemia TEAEs.

Age

In the safety population 197 (43.1%) patients were > 65 years of age. Overall, the median age of patients was 62.0 years. No dose adjustment is required for patients aged 65 years and older based on population PK analyses. No overall difference in safety or efficacy was observed in comparison with patients aged < 65 years.

There were no notable differences in the proportions of patients ≥ 65 years (N=197) and < 65 years (N=260) who experienced TEAEs, treatment-related TEAEs, or TEAEs leading to rociletinib dose interruption or reduction.

SAEs were more frequently reported in patients aged < 65 years than those aged ≥ 65 years (47.3% versus 38.6%), while treatment-related SAEs were experienced by similar proportions of patients (16.5% versus 13.7%, respectively). Treatment-related gr≥3 TEAEs were similar in both subgroups (< 65 years, 45.0%; ≥ 65 years, 45.2%).

TEAEs with an outcome of death were more frequent in patients aged < 65 years than those aged ≥ 65 years (16.9% versus 11.2%); however, both subgroups had low proportions of patients with treatment-related TEAEs excluding PD leading to death (1.2% [3 patients] versus 1.5% [3 patients], respectively). Compared to patients ≥ 65 years, patients < 65 years experienced higher incidences of TEAEs leading to rociletinib discontinuation (21.9% versus 16.2%).

Gender

In general, there were no notable differences in the proportions of male (N=133) and female (N=324) patients who experienced TEAEs, treatment-related TEAEs, SAEs, TEAEs of Grade 3 or higher severity, TEAEs with an outcome of death, TEAEs leading to rociletinib discontinuation, or TEAEs leading to rociletinib dose interruption or reduction.

Race

In the safety population 66.1% (302/457) and 21.7% (99/457) of patients were White and Asian, respectively. It is unclear whether differences in the AEs profile were registered in these two racial groups. The remaining patients were not categorised as White or Asian, or for whom data were not available (56 [12.3%] patients). The small subgroup of non-White, non Asian patients experienced a higher incidence of all types of AEs.

History of CNS metastasis

The proportions of patients with TEAEs, SAEs, gr≥3 TEAEs and TEAEs leading to discontinuation were comparable between the 2 subgroups. Both subgroups had a low proportion of patients with treatment-related TEAEs with an outcome of death (0.5% versus 2.0%). TEAEs and treatment-related TEAEs leading to dose reduction or interruption were more frequent in patients without a history of CNS metastasis (59.9% versus 53.8%, and 53.0% versus 44.3%, respectively).

Renal insufficiency

Studies CO-1686-008 and CO-1686-019 allowed enrolment of patients with mild renal impairment (serum creatinine ≤ 1.5 x upper limit of normal [ULN]). However, the safety and effectiveness of rociletinib has not been evaluated in patients with moderate or severe renal impairment.

Hepatic insufficiency

Studies CO-1686-008 and CO-1686-019 allowed enrolment of patients with gr1 or 2 increased alanine aminotransferase [ALT]/aspartate aminotransferase [AST] and/or gr1 hyperbilirubinemia. Rociletinib has not been evaluated in patients with total bilirubin > 2 × ULN, or AST and ALT > 3 x ULN, [AST/ALT > 5 x ULN if hepatic metastases]. There is no information about the pharmacokinetics in patients with cirrhosis, irrespective of gradePaediatric population

NSCLC constitutes a waiver.

Immunological events

NA

Safety related to drug-drug interactions and other interactions

At this stage there are no major concerns related to pharmacokinetic DDI.

Dose reduction, interruption and discontinuation due to AES

TEAS, overall

Incidence of TEAEs	98.5%
TEAEs gr ≥ 3	68.7%
TEAEs leading to dose interruption	48.4%
TEAEs leading to dose reduction	44.4%
TEAEs leading to dose discontinuation	10.1% (excluding neoplasm progression)
TEAEs with outcome death	14.4%

Treatment-related TEAEs

Incidence	88.0%
Grade ≥3	45.1%
Leading to dose interruption	39.2%
Leading to dose reduction	40.5%
Leading to discontinuation	6.8%
With outcome death	1.3%

The frequency of treatment-related TEAEs ≥ Grade 3 increased with dose. The effect was consistent across a range of effects, including investigator reported events of hyperglycemia, of QTc prolongation and fatigue. The frequency of dose reductions was lower at 500 mg BID (37.8%) than 625 mg (44.0%) or 750 mg (67.4%). Mean dose intensities were 0.90 for 500 mg BID and 0.87 for 625 mg BID.

SAEs

Incidence	43.5%
Treatment-related SAEs	15.3%

Patients initiating treatment at 500 mg HBr BID

TEAEs, overall

Incidence	97.8%
TEAEs gr ≥ 3	62.2%
Leading to dose interruption	50.0%
Leading to dose reduction	37.8%
Leading to discontinuation	7.8%
With an outcome death	11.1%

Treatment-related TEAEs

Incidence	83.3%
TEAEs gr ≥ 3	40.0%
Leading to dose interruption	36.7%
Leading to dose reduction	34.4%
Leading to discontinuation	5.6%
With outcome death	1 patient (1.1%)
SAEs	41.1%

3.3.9. Discussion on clinical safety

Rociletinib is a small molecule TKI that irreversibly binds and inhibits EGFR with the common activating (L858R, Del19) and T790M resistance mutations, with improved selectivity against wild-type EGFR.

Rociletinib causes QTc prolongation and, in contrast to licensed EGFR TKIs, induces hyperglycaemia. These effects are related to metabolites and were not detected in conventional non-clinical studies.

SAEs reported in the SMQ Cardiac arrhythmias (3.1%) included electrocardiogram QT prolonged (0.7%); atrial fibrillation, supraventricular tachycardia, and sudden death (0.4% each); cardiac arrest, palpitations, Torsade de Pointes, ventricular fibrillation, ventricular tachyarrhythmia, and syncope (0.2% each). Prolonged QTc can be associated with the development of serious cardiac arrhythmias. The frequencies of reporting of AES of tachycardia, arrhythmia, syncope which should be further evaluated. A deeper discussion about the possible association of syncope with QTc-prolongation and arrhythmias is warranted.

Hyperglycaemia appears clinically manageable, whilst QT prolongation constitutes a concern reinforced by the likely role of the polymorphic enzyme N-acetyltransferase. Genotyping, phenotyping or other means to identify patients at increased risk appear essential for the safe use of rociletinib in clinical practice.

Otherwise rociletinib has a safety profile apparently similar to other third-generation selective TKIs currently under development/approval, but 40.3% of patients experienced treatment-related diarrhoea. Diarrhoea thus registers unexpectedly high figures for a drug designed to spare the WT EGFR. In order to contextualise, diarrhoea related to gefitinib treatment ranges from 27 to 35%, erlotinib causes diarrhoea in 55% of patients and afatinib in 80-90% of patients. This finding may warrant further investigation, since it does not seem related to a rociletinib effect on WT EGFFR.

Other class-effects, such as rash, have an overall low incidence, 9.8% (6.7% in the 500 mg BID dose level). ILD is also viewed as a class-effect of EGFR inhibitors; the incidence of ILD with rociletinib was comparable to that of other TKIs. The confounding effect of the underlying disease is fully acknowledged, therefore any conclusions as regards relatedness should be cautiously drawn.

Regarding discontinuations, of the 254 patients who discontinued in either study, the primary reason for discontinuation of rociletinib was disease progression: 86.8% in TIGER-X (500 mg BID), 65.2% in TIGER-2 (625 mg BID, i.e. cohort A). Overall, the discontinuations caused by AEs are low so far: in TIGER-X, 5.3% for the 500 mg BID group; in TIGER-2, 8.7% in the 625 mg BID group.

TEAEs with an outcome of death were reported in 66/457 (14.4%) patients, mainly as a consequence of PD: 57/66 [86.4%]).

There were 5 patient deaths from pneumonia, and 2 sudden deaths (both in TIGER-X). The remaining TEAEs with outcomes of death were single reports of cardiac arrest, pulmonary embolism, sepsis, and status epilepticus. A total of 10 patients who initiated treatment at 500 mg BID experienced TEAEs with an outcome of death: PD, 8 patients, pneumonia and sepsis with 1 patient each.

3.3.10. Conclusions on clinical safety

The safety database is limited and immature, especially with the 500 mg BID dose recommended for licensure. At this stage QT prolongation constitutes a major issue where further measures are needed in order to reduce the risk for severe and fatal arrhythmias.

3.4. Risk management plan

Safety concerns

Safety Specification (Part II, SI-SVIII) as submitted by the Applicant, RMP version 1.0, dated 24-07-2015:

Safety Concerns
Important Identified Risks – Hyperglycaemia – QTc Prolongation ≥ CTCAE Grade 3 – Pancreatitis
Important Potential Risks – ILD
Missing Information – Effect of rociletinib on the human foetus – Concentration of rociletinib in breast milk – Effect of renal impairment on rociletinib PK – Effect of hepatic impairment on rociletinib PK

3.4.1. Conclusions on the safety specification

It is questionable if the list should include hyperglycaemia as this is a well-defined, pharmacology related event, where the SmPC already now should include proper measures to reduce the risk and where further specific studies are not expected.

Effects on the human foetus are missing, but future aims should not include the gathering of such information. This is not expected as regards the concentration of rociletinib either.

Hyperglycaemia should be considered an important identified risk.

Foetal harm should be captured as 'developmental toxicity' and reclassified as important potential risk.

Based on the evidence currently available, a routine RMM through product information is likely to be sufficient at this stage.

Regarding the safety specifications, the following missing information was identified: Elderly patients >75 years , patients with ECOG ≥ 2, the safety concerning prolonged use, the risk of disease flare if treatment is stopped, and the risk of off label use.

Interstitial lung disease (ILD) should be reclassified from an important *potential* risk,to an important *identified* risk.

Overall, the safety population comprised 457 rociletinib-treated patients (receiving dosages from 150mg once daily up to 1000mg twice daily), of which 90 patients received the proposed dosage regimen for the EEA (500mg, taken twice daily [BID]). The median duration of treatment was 126 days, and 77 days for the patients receiving the 500mg BID regimen. At the time of initial submission, the two pivotal (single arm phase I-II) studies were still on-going (TIGER-X and TIGER-2). These studies will be submitted (along with further confirmatory data from other ongoing studies) with the responses to the Day 120 LoQ. The safety and efficacy data are therefore relatively limited and immature, especially with regard to the proposed 500mg BID dosage regimen.

Half of the rociletinib-treated patients (49.7% overall, and 50.0% within the 500mg BID group) developed diarrhoea, which led to dose reductions or interruptions in 6.1% of the patients (2.2% in 500mg BID group). Moreover, diarrhoea may lead to secondary dehydration, renal impairment and hypokalaemia. The risk of hypokalaemia is of special concern, as hypokalaemia is associated with the risk of QT-prolongation and torsades des pointes, which is an identified risk for rociletinib, given the

high incidence of diarrhoea, in combination with the finding that diarrhoea may lead to treatment interruptions and the fact that secondary hypokalaemia may predispose patients to cardiac arrhythmias.

Pharmacovigilance plan

3.5. Summary of planned additional PhV activities from RMP

On-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Study / activity **Type, title and category (1-3)**	**Objectives**	**Safety concerns addressed**	**Status**	**Date for submission of interim or final reports**
CO-1686-022 (TIGER-1) Randomised study	Secondary: To evaluate the safety and tolerability of rociletinib versus erlotinib in patients with advanced/ metastatic NSCLC whose tumours have EGFR-activating mutations	The study enables confirmation of the safety profile of rociletinib in a larger patient sample and earlier line of treatment.	Ongoing	To be confirmed
CO-1686-020 (TIGER-3) Randomised study	Secondary: To compare the safety and tolerability of rociletinib with that of single-agent cytotoxic chemotherapy.	The confirmation of the safety profile of rociletinib in a larger patient sample.	Ongoing	To be confirmed

Additional pharmacovigilance activities to assess the effectiveness of risk minimisation measures

No additional risk minimisation measures have been proposed by the applicant.

Conclusions on the PhV Plan

The proposed post-authorisation PhV development plan is not sufficient to identify and characterise the risks of the product and the applicant should propose PhV studies.

Overall, the proposed set of pharmacovigilance strategies is considered too general, and it is unclear which safety concerns are addressed, and which outstanding issues will be investigated, within the studies described in the pharmacovigilance plan.

The occurrence of dose-dependent QT interval prolongation and associated risk of ventricular arrhythmias (torsades des pointes) is of particular concern. One of the metabolites of rociletinib (M460) was found to be responsible for the prolongation of the QT interval. Since M460 is further metabolised by the polymorphic enzyme N-acetyltransferase, accumulation of M460 may occur in patients who are slow acetylators, and these patients may therefore be at higher risk of QT-prolongation.

For the remaining safety concerns listed in the current RMP, no specific pharmacovigilance strategies are considered necessary at this point. Particularly the risk of hyperglycaemia seems reasonably well-defined in the current safety population, and was found to be manageable with the oral anti-hyperglycaemic drugs such as metformin.

The set of data submitted by the applicant is, however, still relative immature, and further results from ongoing studies are awaited in the next round. For any new safety concerns identified in the ongoing studies, or safety concerns recommended for inclusion in the RMP by the CHMP, appropriate pharmacovigilance measures should be proposed by the applicant.

Risk minimisation measures

Summary of risk minimisation measures from the RMP

Proposal from Applicant for risk minimisation measures: routine RMM.

Conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data is of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

4. Orphan medicinal products

N/A

5. Benefit risk assessment

The clinical program in support of the efficacy and safety of rociletinib for the treatment of patients with mutant EGFR NSCLC after failure of prior EGFR directed therapy and who have T790M-mediated resistant NSCLC is based on 2 ongoing clinical studies:

-Study CO-1686-008 (TIGER-X) - A Phase 1/2, open-label, safety, pharmacokinetic and preliminary efficacy study of oral rociletinib in patients with previously treated mutant EGFR NSCLC.

-Study CO-1686-019 (TIGER-2) - A Phase 2 open-label, multicenter, safety and efficacy study of oral rociletinib as second-line EGFR-directed TKI in patients with mutant EGFR NSCLC.

Benefits

As clinical data only refer to single arm studies, the only informative outcome measures are ORR and DOR/time in response. ORR was also the selected primary efficacy endpoint in both trials. Of note, by RECIST, independent assessment of confirmed response is considered the proper outcome measure in studies where ORR is the primary efficacy endpoint.

Beneficial effects

In TIGER-X, an apparent dose-response relationship was demonstrated in T790M positive tumours, 625 mg BID tending to be more active than 500 mg BID (see table below, note the non-randomised comparison). Of note, ORR data are immature in the 500 mg BID cohort as delayed responses might not have been captured at time of data cut-off.

	500 mg BID	625 mg BID
ORR by inv.	N=76 42.1% (95% CI 30.9-54)	121 48.8% (95% CI 39.6-58)

ORR by IRR	n=55 38.2% (95% CI 25.4-52.3)	n=87 52.9% (95% CI 41.9-63.7)
confirmed ORR by inv	n=48 31.3% (95% CI 18.7-46.3)	n=103 45.6% (95% CI 35.8-54.7)
confirmed ORR by IRR	23.5%	41.2%

In TIGER-2, patients were initially enrolled at 625 mg BID dose level (cohort A). The 500 mg BID was chosen later as the recommended dose for the proposed indication, as the B/R was judged to be the most favourable from the range of doses tested. Cohort B recently started enrolment at 500 mg BID, meaning that only results from cohort A are available; the ORR by IRR in evaluable patients show a 46.2% PR rate (no CR), while the confirmed ORR by IRR is 35.1%.

From the total of 40 T790M negative patients enrolled across all dose ranges in TIGER-X, 1 of the 5 patients in the 500 mg BID group had a PR best response; in the 625 mg BID dose level, 7 out of 18 patients had a PR as best response. These patients should be further characterised in terms of ORR and DOR and with respect to the presence of common EGFR sensitizing-, and other, rarer, mutations.

In the subgroup analyses, the L858R missense mutation showed lower responses than del19 as is expected based on experience from first and second generation EGFR-TKi.

Uncertainty in the knowledge about the beneficial effects

The efficacy data are immature. TIGER-X and TIGER-2 are ongoing (the latter is to be completed by late 2016), as are the confirmatory studies TIGER-1 and TIGER-3 (planned to end by late 2017).

Both studies have been extensively modified through multiple amendments. Despite the adaptive design, uncertainties remain, and the most significant is the optimal dose, as the 500 mg BID patient subgroup has the lowest ORR in comparison with 625 and 750 doses, probably a reflection of the immaturity of efficacy data in this group. Informative duration of response and other time-related outcome measures are not yet available for the regimen proposed for licensure, but there is a concern that a putatively suboptimal dose of rociletinib from an efficacy perspective might increase the risk for early development of resistance.

Risks

Unfavourable effects

In contrast to licensed EGFR TKIs, rociletinib causes QTc prolongation and induces hyperglycaemia. These effects are related to metabolites (mainly M502 and M460) and were not detected in conventional non-clinical studies.

Hyperglycaemia appears clinically manageable, whilst QT prolongation constitutes a concern as cases of sudden death, ventricular fibrillation and torsade de pointes have already been reported. This concern is reinforced by the likely role of the polymorphic enzyme N-acetyltransferase in the formation of these metabolites. Genotyping, phenotyping or other means to identify patients at increased risk appear essential for the reasonably safe use of rociletinib in clinical practice.

Otherwise rociletinib has a safety profile apparently similar to other third-generation selective TKIs currently under development, but 40.3% of patients experienced treatment-related diarrhoea. Diarrhoea thus registers unexpectedly high figures for a drug designed to spare the WT EGFR. In order to contextualise, diarrhoea related to gefitinib treatment ranges from 27 to 35%, erlotinib causes diarrhoea in 55% of patients and afatinib in 80-90% of patients.

This finding may warrant further investigation, since it does not seem related to a rociletinib effect on WT EGFFR as rash was clearly reduced in comparison with the non-selective medicinal compounds. In this context it is noticed that rociletinib shows activity against several kinases e.g. FAK, PLK4 at clinically relevant concentrations.

Uncertainty in the knowledge about the unfavourable effects

The major outstanding issue is whether the risk for QT prolongation can be reduced. Long(er) term safety data are also awaited in order to assess the safety profile of rociletinib. The underlying mechanisms for treatment-related diarrhoea should be investigated.

Effects Table

Favourable effects for Xegafri (rociletinib), for the treatment of adult patients with mEGFR NSCLC who have been previously treated with an EGFR-targeted therapy and have the EGFR T790M mutation:

	Dose regimen		Uncertainties
	500 mg BID	625 mg BID	Very limited efficacy data from ongoing studies TIGER-X and TIGER-2: DOR and secondary endpoint results not available at submission. No effect data for the proposed 500 mg BID dose regimen from TIGER-2.
ORR by inv.	N=76 42.1% (95% CI 30.9-54)	121 48.8% (95% CI 39.6-58)	
ORR by IRR	n=55 38.2% (95% CI 25.4-52.3)	n=87 52.9% (95% CI 41.9-63.7)	
confirmed ORR by inv	n=48 31.3% (95% CI 18.7-46.3)	n=103 45.6% (95% CI 35.8-54.7)	
confirmed ORR by IRR	23.5%	41.2%	

All unfavourable effects refer to studies TIGER-X and TIGER-2 considered together:

Treatment-related TEAEs	Overall	Patients initiating treatment at 500 mg HBr BID
Incidence	88.0%	83.3%
Grade ≥3	45.1%	40.0%
Leading to dose interruption	39.2%	36.7%
Leading to dose reduction	40.5%	34.4%
Leading to discontinuation	6.8%	5.6%
With outcome death	1.3%	1.1%
SAEs	43.5%	41.1%

AESI

1. Hyperglycaemia

	500 mg HBr BID	Overall	Metabolite M502
Hyperglycaemia/new onset DM	45/90 50%	236/457 51.6%	
SAEs	11.1%	6.8%	

2. QTc prologation/Torsades de Pointes/Cardiac arrhythmia

	500 mg BID	625 mg BID	750 mg BID	Metabolite 460, role of polymorphic N-acetyltranferase
QTc prolongation	30%	34.4%	31.6%	
Cardiac arrhythmia	34.4%	36.8%	35.8%	
SAEs	• atrial fibrillation, supraventricular tachycardia, and sudden death (2 [0.4%] patients each); • cardiac arrest, palpitations, Torsade de Pointes, ventricular fibrillation, ventricular tachyarrhythmia, and syncope (1 [0.2%] patient each). • there were 4 events of ventricular arrhythmia in which rociletinib could have played a role, and rociletinib was permanently discontinued. • one patient died to cardiac arrest.			

3. Diarrhoea

	Overall	Comment
TEAE	49.7%	In order to contextualise, diarrhoea related to gefitinib treatment ranges from 27 to 35%, erlotinib causes diarrhoea in 55% of patients and afatinib in 80-90% of patients. This finding may warrant further investigation, since diarrhoea seems not related to a rociletinib systemic effect on WT EGFR (i.e. very low incidence of rash, 9.8%).
Treatment-related	40.3%	
Grade ≥3	2.4%	
Dose reduction	5.3%	
Discontinuation	0.2%	
SAE	2%	

Balance

Importance of favourable and unfavourable effects

The activity of rociletinib in terms of ORR seems promising, although lower than expected, based on previous communications (e.g. ASCO). The efficacy and safety data, however, are too immature to allow a benefit assessment as all studies are ongoing.

Confirmed ORR by IRR is the customary outcome measure in exploratory trials and those findings should at day 120 be supported by mature durability of response data.

The effect of rociletinib on T790M negative patients is interesting, but it remains to be explained and characterised in terms of concomitant mEGFR. The very low incidence of rash in comparison with first and second-generation EGFR TKIs is a measure of the WT EGFR sparing. However, the high overall and the treatment-related diarrhea need alternative explanations and it may be so that diarrhoea is a common AE even for irreversible EGFR TKIs.

Rociletinib metabolites are responsible for hyperglycaemia and QT prolongation and unforeseeable variability in exposure due to e.g. polymorphism of N-AT is a concern. Whilst hyperglycaemia is clinically manageable, at this stage QT prolongation is a major concern based on possibly and probably related serious and fatal cardiac events.

Discussion on the benefit-risk assessment

Several third-generation EGFR TKIs are under development: AZD9291, rociletinib and HM61713.

Treatment of adult patients with metastatic / unresectable locally advanced, mutant-EGFR NSCLC, who previously have been treated with an EGFR-targeted therapy and have the T790M mutation is still an area of unmet clinical need. However, the current lack of informative clinical data especially as regards duration of response precludes a determination of the benefit for rociletinib.

The product shows positive effects on ORR, with better outcomes than with chemotherapy. These preliminary results should be confirmed / surpassed as the phase II (and III) studies progress.

The fact that the confirmatory studies target different populations than the original MA should be considered by the Applicant, as well as the lower than expected confirmed ORR by IRR, associated with the yet not determined DOR.

Uncertainties regarding the exposure-effect remain, and may also prompt a discussion on a possible early development of resistance at suboptimal dose levels.

Hyperglycaemia and QT prolongation are AESIs specific to rociletinib (caused by metabolites). Even if in the context of the clinical trials hyperglycaemia was easily manageable with dose interruption and restart with concurrent hypoglycaemic medication, the experience is still limited. The potential of QT prolongation to translate into clinically significant arrhythmias remains to be further characterised, especially with respect to risk groups from a PK perspective, but also as regards clinical risk groups such as patients with electrolyte disturbances, e.g. related to diarrhoea.

The safety profile of rociletinib is otherwise largely acceptable and manageable and due to relative selectivity vs. wild type EGFR-TTK, more favourable than for first and second-generation of EGFR-TKIs.

Due to data immaturity, B/R cannot be properly assessed, but it is considered essential that it is shown that the risk for QT prolongation can be reduced to such an extent that benefit shown only in terms of tumour control outweighs the risk.

5.1. Conclusions

The overall B/R of Xegafri is undetermined at this time.

Due to the complexity of the outstanding issues, an accelerated assessment is no longer an option.