14 November 2019
EMA/CHMP/654949/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tavlesse

International non-proprietary name: fostamatinib

Procedure No. EMEA/H/C/005012/0000

Note

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

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Administrative information

Name of the medicinal product:	Tavlesse
Applicant:	Rigel Pharmaceuticals B.V. Avenue Ceramique 223 6621 KX Maastricht NETHERLANDS
Active substance:	Fostamatinib disodium hexahydrate
International Non-proprietary Name/Common Name:	fostamatinib
Pharmaco-therapeutic group (ATC Code):	Blood and blood forming organs, antihemorrhagics, vitamin K and other hemostatics, other systemic hemostatics, (B02BX09)
Therapeutic indication(s):	Tavlesse is indicated for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (see section 5.1).
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	100 mg and 150 mg
Route(s) of administration:	Oral use
Packaging:	bottle (HDPE)
Package size(s):	60 tablets

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List of abbreviations

5-FU	5-fluorouracil
AAS	Atomic Absorption Spectrometry
ADME	Absorption, distribution, metabolism, and excretion
AE	Adverse event
AH	ambient humidity
AIHA	Autoimmune hemolytic anemia
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Applicant's Part (or Open Part) of an ASMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
AS	active substance
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
BCR	B-cell receptor
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BFC	Blue film-coated
bid	Twice daily
BP	Blood pressure
CBC	Complete blood count
CEP	Certificate of Suitability of the Ph.Eur.
CFU	Colony Forming Units
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CLL	Chronic lymphocytic leukemia
Cmax	Maximum serum concentration
CMCS	chloromethylchlorosulfate
CMS	Concerned Member State
CoA	Certificate of Analysis
CQA	critical quality attributes
CRS	Chemical Reference Substance (official standard)
CSR	Clinical study report
CV	Coefficient of variation
CYP	Cytochrome P450
DAUC	Daily AUC at steady state
DCP	Decentralised (Application) Procedure
DMF	Drug Master File = Active Substance Master File
DSC	Differential Scanning Calorimetry
DVS	Dynamic Vapor Sorption
DVT	Deep vein thrombosis
EC50	50% effective concentration

EDQM European Directorate for the Quality of Medicines
EMA European Medicines Agency
EO Ethylene oxide
EtO Ethylene oxide
EU European Union
FcR Fc receptor
FDA Food and Drug Administration
FDH Fostamatinib disodium hexahydrate
Fos-PCP Fostamatinib subjects treated in the Placebo-Controlled Period
FP finished product
FTIR Fourier transformed infrared spectroscopy
GC Gas Chromatography
GCP Good Clinical Practice
GI Gastrointestinal
GMP good manufacturing practice
HCV Hepatitis C virus
HDPE High Density Polyethylene
HPLC High Performance Liquid Chromatography
HSCT Hematopoietic stem cell transplantation
IBLS ITP bleeding scale
IC ion chromatography
ICH International Conference on Harmonisation
ICP-MS Inductively coupled plasma mass spectrometry
IgAN Immunoglobulin A nephropathy
IL Interleukin
IND Investigational new drug application
IPC In-process control
IR Infrared spectroscopy
ISE Integrated Summary of Efficacy
ISS Integrated Summary(ies) of Safety
ITP Immune thrombocytopenia
ITAM Immunoreceptor tyrosine-based activation motif
ITT Intent-to-treat
IU International Units
IV Intravenous
IV anti-DIg Intravenous anti-D immunoglobulin
IVIG Intravenous immunoglobulin
KF Karl Fischer
LDPE Low Density Polyethylene
LOA Letter of Access
LOCF Last observation carried forward
LOD Limit of Detection
LOQ (1) Limit of Quantification, (2) List of Questions
MA Marketing Authorisation
MAA Marketing authorisation application
MAH Marketing Authorisation Holder

MHRA	Medicines and Healthcare Products Regulatory Agency
MMP	Matrix metalloproteinase
MS	Mass Spectrometry
N/A	Not applicable
ND	Not detected
NDA	New drug application
NLT	Not less than
NMR	Nuclear Magnetic Resonance spectroscopy
NMT	Not more than
NT	Not tested
ODD	Orphan drug designation
OFC	Orange film-coated
OOS	Out of Specifications
PARs	proven acceptable ranges
PD	Pharmacodynamic(s)
PDCO	Paediatric Committee
PDBP	potassium di-t-butyl phosphate
PDE	Permitted Daily Exposure
PE	Polyethylene
PET	Preservative Efficacy Test
P-gp	P-glycoprotein
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	Pharmacokinetic(s)
PP	Polypropylene
PPM	parts per million
PVC	Poly vinyl chloride
qd	Once daily
QbD	quality by design
QOS	Quality Overall Summary
QTPP	quality target product profile
R406	Major metabolite of fostamatinib
RA	Rheumatoid arthritis
RES	Reticuloendothelial system
RH	Relative Humidity
Rigel	Rigel Pharmaceuticals, Inc.
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of an ASMF
RRT	Relative retention time
RSD	Relative standard deviation
SAE	Serious adverse events
SAP	Statistical analysis plan
SD	Standard deviation
SLE	Systemic lupus erythematosus
SMQ	Standardized MedDRA Query
SPC	Summary of Product Characteristics

SYK	Spleen tyrosine kinase
TGA	Thermo-Gravimetric Analysis
TLC	Thin Layer Chromatography
TLR	Theoretic Logarithmic Reduction Factor
TMA	3,4,5-trimethoxyaniline
TPO	Thrombopoietin
ULN	Upper limit of normal
UV	Ultraviolet spectrometry
VEGFR	Vascular endothelial growth factor receptor
WHO	World Health Organization
XR(P)D	X-Ray (Powder) Diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Rigel Pharmaceuticals B.V. submitted on 17 September 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Tavlesse, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 March 2018.

The applicant applied for the following indication:

Tavlesse is indicated for the treatment of thrombocytopenia in adult patients with chronic or persistent immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0195/2018 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products. However, the orphan market exclusivity of NPlate expired during the procedure.

New active Substance status

The applicant requested the active substance fostamatinib contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Sinan B. Sarac Co-Rapporteur: Andrea Laslop

The application was received by the EMA on	17 September 2018
The procedure started on	4 October 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	20 December 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	20 December 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	9 January 2019
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	31 January 2019
The applicant submitted the responses to the CHMP consolidated List of Questions on	26 April 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	05 June 2019
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	13 June 2019
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	27 June 2019
The applicant submitted the responses to the CHMP List of Outstanding Issues on	20 August 2019
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	04 September 2019
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	17 October 2019
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Tavlesse on	14 November 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Primary immune thrombocytopenia (ITP) is an acquired immune mediated disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count less than 100 x 109/L, impairment of platelet production, a variable bleeding tendency and the absence of any underlying cause. Until recently, the abbreviation ITP stood for idiopathic thrombocytopenic purpura, but due to the current knowledge of the immune mediated mechanism of the disease, and the absence or minimal signs of bleeding in most cases, have led to a revision of the terminology.*

ITP is classified by duration into newly diagnosed, persistent (3-12 months' duration) and chronic (≥ 12 months' duration). Whereas ITP in adults typically has an insidious onset with no preceding viral or other illness and it normally follows a chronic course, ITP in children is usually short-lived with at least two-thirds recovering spontaneously within 6 months (See *Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia*, EMA/CHMP/153191/2013, Oncology Working Party)

The proposed indication by the applicant is as follows:

Tavlesse is indicated for the treatment of thrombocytopenia in adult patients with chronic or persistent immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

2.1.2. Epidemiology

The reported incidence data for ITP in the European Union (EU) ranges from 1.6 to 4.4 per 100,000 (Moulis 2014; Schoonen 2009; Neylon 2003; Frederiksen 1999). The prevalence is 9.5 per 100,000 adults (Lambert and Gernsheimer, 2017). Secondary ITP constitutes around 20% of ITP diagnoses (Cines et al, 2009) but this group is not part of the intended indication. There is an increasing incidence with older age and equal for the sexes except in the mid-adult years (30-60 years), when the disease is more prevalent in women. Childhood ITP has an incidence of between 1.9 and 6.4 per 100,000 per year with equal distribution between the sexes. There are an estimated 50,000 adult patients with chronic ITP in the EU (Gernsheimer 2008).

2.1.3. Aetiology and pathogenesis

Primary ITP in adults has no known trigger or obvious cause.

ITP is characterized by immune-mediated thrombocytopenia resulting from increased clearance of normal platelets and decreased platelet production

Fcγ receptor (FcγR) signaling in monocytes and macrophages plays an important role in the initiation and propagation of autoimmune responses. The activating FcγR is associated with a signaling subunit, referred to as the FcRγ chain, whose *phosphorylation subsequent to receptor activation* results in the recruitment and *activation of spleen tyrosine kinase (SYK)*. Spleen tyrosine kinase is an important component of the signaling system of activated Fc receptors, as well as the B-cell receptor (BCR).

Aggregation of the Fc receptors, induced by *antibody-antigen complexes*, can induce a multitude of cellular functions (including degranulation, arachidonic acid metabolism, antibody-dependent cellular cytotoxicity, phagocytosis and cytokine secretion) depending on the cell type, and leads to tissue damage and the propagation of inflammatory responses. *FcγR have been implicated in immune destruction of platelets*. Accelerated clearance of circulating IgG-coated platelets via Fcγ receptor-bearing macrophages in the spleen and liver is a key mechanism in ITP.

According to Lambert and Gernsheimer (2017) the patophysiological mechanisms of primary ITP include:

- pathologic antiplatelet antibodies
- impaired megakaryocytopoiesis
- T-cell–mediated destruction of platelets

with each pathologic mechanism playing varying roles in each patient.

2.1.4. Clinical presentation, diagnosis

Signs and symptoms vary widely. Many patients have either no symptoms or minimal bruising, whereas others experience serious bleeding, which may include gastrointestinal haemorrhage, extensive skin and mucosal haemorrhage, or intracranial haemorrhage. The severity of thrombocytopenia correlates to some extent but not completely with the bleeding risk. Additional factors may increase the risk (e.g., advanced age, lifestyle factors, concomitant medications, congenital or acquired bleeding disorders) and should be evaluated before the appropriate management is determined (Provan et al, 2010). Although haemorrhagic death is a major concern it has been reported that the estimated rate of fatal haemorrhage is around 0.02 to 0.04 cases per adult patient-year risk (*Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia*, EMA/CHMP/153191/2013, Oncology Working Party).

Diagnosis of ITP is one of exclusion, when the history, physical examination, complete blood count and examination of peripheral blood smear do not suggest other aetiology for the thrombocytopenia. Physical examination should be normal apart from bleeding signs. The peripheral blood count reveals isolated thrombocytopenia and normal red cell and white cell indices. If significant bleeding occurs there may be anaemia proportional to the degree of bleeding with possible iron deficiency. The peripheral blood smear reveals normal to large platelets in size and no abnormalities should be seen in red and white cell morphology. Bone marrow examination is currently not routinely conducted in patients with typical ITP presentations but reserved to selected cases such as those with an atypical presentation (*Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia*, EMA/CHMP/153191/2013, Oncology Working Party).

2.1.5. Management

The major goal for treatment of ITP is to provide a platelet count that prevents major bleeding rather than correcting the platelet count to normal levels. The management of ITP should be tailored to the individual patient and it is rarely indicated in those with platelet counts above 50 x 109/L in the absence of bleeding, trauma, surgery or high-risk factors (e.g. patients on anticoagulation therapy). The management of ITP varies widely. First-line treatment options for ITP include corticosteroids, intravenous immunoglobulin (IVIG),

and intravenous anti-D immunoglobulin (IV anti-D Ig). Many patients fail to achieve a durable remission, or will find the long-term side effects of corticosteroids unacceptable (George 2012).

Second-line treatment options for adult ITP patients have been reviewed through an international consensus report on the investigation and management of primary ITP (Provan et al, 2010). The main goal of second-line therapy is to attain a sustained increase of the platelet count that is considered hemostatic for the individual patient.

Available medical treatment modalities have quite different mechanisms of action and can be broadly categorized into those that are given only once (or for only 1 course) and are intended to induce long-term remission (splenectomy, rituximab), and those that need continued or chronic administration (corticosteroids, immunosuppressive agents [azathioprine, cyclosporine A, cyclophosphamide, mycophenolate mofetil], and thrombopoietin (TPO)-receptor agonists [romiplostim and eltrombopag]).

ITP is a disease of increased platelet destruction but recent evidence suggests that suboptimal platelet production by suppression of megakaryocyte function also occurs. Thrombopoietin receptor (TPO-R) agonists activate the thrombopoietin receptor (c-Mpl) which is the primary factor that regulates platelet production. Treatment aimed at increasing the platelet production has become a potential treatment option and TPO-R agonists have been approved in the EU for the treatment of chronic ITP splenectomised adult patients who are refractory to other treatments or as second line therapy for non-splenectomised patients where surgery is contraindicated. Long-term risks/effects from use of TPO-receptor agonists are still being determined. Potential risks with eltrombopag are bone marrow fibrosis and thrombosis, and hepatic and ocular toxicities. Romiplostim requires a weekly injection. TPO-receptor agonists as a class are associated with overshoot and potential thrombosis.

Rituximab is also used off-label, which can be associated with severe toxicities in 2% to 6% of patients. According to the American Society of Hematology practice guideline for ITP (2011), rituximab may be considered for patients at risk of bleeding who have failed 1 line of therapy such as corticosteroids, IVIG, or splenectomy (Ghanima 2012; Neunert 2011).

Splenectomy provides long-term efficacy in approximately 60% of cases. Nonetheless, splenectomy is invasive, irreversible, associated with postoperative complications, and its effectiveness is currently unpredictable, leading many physicians and patients toward postponement and use of alternative approaches.

According to the ASH Guideline (Neunert et al, 2011) it is recommended that "despite a plethora of novel agents and new information on success of treatment, there is no evidence to guide a sequence of treatments for patients who have recurrent or persistent thrombocytopenia associated with bleeding after an initial treatment course with corticosteroids (or IVIg or anti-D). Splenectomy remains the only treatment that provides sustained remission off all treatments at 1 year and beyond in a high proportion of patients with ITP; sustained remission rates with rituximab are disappointing and the thrombopoietin receptor agonists produce off-treatment sustained remissions very infrequently."

They recommend:

- Splenectomy for patients who have failed corticosteroid therapy (grade 1B).
- Thrombopoietin receptor agonists for patients at risk of bleeding who relapse after splenectomy or who have a contraindication to splenectomy and who have failed at least one other therapy (grade 1B).

Furthermore they suggest:

- Thrombopoietin receptor agonists may be considered for patients at risk of bleeding who have failed one line of therapy such as corticosteroids or IVIg and who have not had splenectomy (grade 2C).
- Rituximab may be considered for patients at risk of bleeding who have failed one line of therapy such as corticosteroids, IVIg, or splenectomy (grade 2C)."

Fostamatinib is also a continuous treatment although with shorter follow-up compared to the TPO-RAs.

About the product

Fostamatinib is a prodrug of a spleen tyrosine kinase (Syk) inhibitor, converted in vivo to R940406 (R406), the active component of fostamatinib; R406 is a potent and relatively selective inhibitor of Syk and consequently of the activating Fc receptor (FcR) and B-cell receptor (BCR) signaling pathways. Fc receptor γ (FcRγ) signaling in monocytes and macrophages plays an important role in the initiation and propagation of autoimmune responses induced by autoantibodies. The activating FcR is associated with a signaling subunit, referred to as the FcRγ chain, whose phosphorylation subsequent to receptor engagement results in the recruitment and activation of Syk. Activated Syk kinase plays a central role in mediating downstream signaling of activated FcRs, as well as the BCR.

Aggregation of the FcRs, induced by antibody-antigen complexes, can activate a multitude of cellular functions (including degranulation, arachidonic acid metabolism, antibody dependent cellular cytotoxicity, phagocytosis and cytokine secretion) depending on the cell type, and leads to tissue damage and the propagation of inflammatory responses. FcRγ have been implicated in immune destruction of platelets. Accelerated clearance of circulating IgG coated platelets via FcRγ-bearing macrophages in the spleen and liver is believed to be a pathogenic mechanism in ITP.

Therefore, fostamatinib appears to prevent platelet destruction by interrupting Fc receptor-mediated platelet engulfment on macrophages through inhibition of SYK signaling. Fostamatinib should be initiated at a dose of 100 mg taken orally twice daily (bid). After a month, if platelet count has not increased to at least 50,000/μL, the fostamatinib dose should be increased to 150 mg bid. Fostamatinib has been proposed by the applicant for the treatment of thrombocytopenia in adult patients 18 years of age and older with persistent or chronic immune thrombocytopenia (ITP), who have had an insufficient response to a previous treatment.

Type of Application and aspects on development

The clinical development programme in support of the intended indication comprises 4 clinical studies. These clinical studies were conducted in adult patients with persistent or chronic ITP with at least one previous ITP treatment. Supportive data derive from studies with fostamatinib in healthy volunteers, rheumatoid arthritis patients and oncology patients.

The Applicant sought Scientific Advice from the Medicines and Healthcare Products Regulatory Agency (MHRA) to discuss clinical and regulatory aspects of fostamatinib development for treatment of persistent of chronic ITP. Presubmission meetings were held with the rapporteur (Denmark) on 16 July 2018 and 17 July 2018 with the co-rapporteur (Austria) who provided guidance on the content of the application.

The Phase 3 ITP protocols characterized persistent/chronic ITP in accordance with the ASH 2011 Practice Guidelines (Neunert 2011) and the EMA Guideline EMA/CHMP/153191/2013 (EMA 2014) on clinical

development for the treatment of ITP. The design of the Phase 3 studies was based upon the design of the Phase 3 studies conducted by one of the major therapies currently used in the intended population, the TPO-receptor agonists, romiplostim, as well as guidance by recognized thought leaders in the United States and Europe.

On 16 February 2018, the Applicant submitted to the EMA an application for a product-specific waiver for all subsets of the pediatric population for the treatment of ITP (EMEA-001196-PIP02-17). The ground for the waiver request is based on nonclinical evidences of a likely lack of safety for all pediatric subsets, due to the effects of fostamatinib on growth plates. On this ground on 01 June 2018, the Paediatric Committee (PDCO) recommended granting a waiver for all subsets of the pediatric population (0 to 18 years of age) in the condition of treatment of ITP.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 126.2 or 189.3 mg of fostamatinib disodium hexahydrate equivalent to 100 mg or 150 mg of fostamatinib as active substance.

Other ingredients of the tablet core are: mannitol, sodium hydrogen carbonate, sodium starch glycollate, povidone, and magnesium stearate. Ingredients of the film coating are: hypromellose, macrogol 400, titanium dioxide, yellow iron oxide, and red iron oxide.

The product is available in white opaque HDPE bottles with a desiccant insert, closed with polypropylene child resistant closures and foil induction seals.

2.2.2. Active Substance

General information

The chemical name of fostamatinib is [6-({5-fluoro-2-[(3,4,5-yl}amino)-2,2-dimethyl-3-oxo-2,3-dihydro-4H-trimethoxyphenyl)amino]pyrimidin-4- pyrido[3,2-b]- 1,4-oxazin-4-yl]methyl disodium phosphate hexahydrate. It corresponds to the molecular formula $C_{23}H_{24}FN_6Na_2O_9P \cdot 6H_2O$, its relative molecular mass is 732.52 (fostamatinib disodium hexahydrate) and 580.46 (free acid) and it has the structure shown in Figure 1.

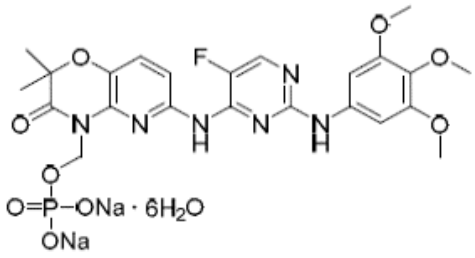


Figure 1. Structure of fostamatinib disodium hexahydrate

The structure of the active substance (AS) was elucidated by a combination of elemental analysis, MS, ^{1}H-, ^{13}C-, ^{19}F-, and ^{31}P- nuclear magnetic resonance spectroscopy (NMR), infrared spectroscopy (IR), ultra-violet spectrometry (UV). X-ray powder diffraction, Thermal Gravimetric Analysis (TGA), Differential Scanning Calorimetry (DSC) and Dynamic Vapor Sorption (DVS) studies were performed to characterise the crystal form of the active substance.

Fostamatinib disodium hexahydrate (FDH) appears as a white to off-white non-hygroscopic powder. It is practically insoluble to very slightly soluble in acidic aqueous buffers, slightly soluble in ethanol, sparingly soluble in neutral to alkaline aqueous buffers and soluble in methanol. Its partition coefficient ($LogD_{ow}$) was determined to be -0.6 and three pKa values were determined to be pKa1: 1.7 and pKa2: 4.2 and pKa2: 6.5.

Only one crystal form for FDH has been described (Form A) and isolated. Data concerning formation of FDH under different crystallization conditions have been given. Form A is a stable crystal form, which is consistently produced by the proposed manufacturing process. Stability data demonstrated that there is no change in crystal/polymorphic form during storage.

The active substance exhibits no stereogenic centres and is therefore achiral.

Based on the information provided by the applicant, fostamatinib is considered to be a new active substance (NAS).

Manufacture, characterisation and process controls

The synthesis is described in eight converging overall steps, seven of which comprises actual synthetic steps (bond breaking/formation) and a last salt formation step. Based on the documentation presented, the five starting materials proposed are acceptable. Sodium 2-ethylhexanoate is used as the source for sodium ions in the active substance, but is considered a reagent; this is acceptable. Reaction schemes for the starting materials as well as adequate details on manufacturers have been provided. Discussion on possible impurities has been presented. Multiple manufacturers of each starting material are proposed. Equivalent quality of appropriate intermediate or final active substance has been demonstrated to justify the use of multiple starting material manufacturers.

Elements of enhanced development (ICH Q8 and Q11) have been used to identify critical quality attributes and critical process parameters and correlate these to the control strategy. The applicant has clarified that critical process parameters, operating parameters and IPCs were determined with a combination of risk assessment, design of experiments, statistical modelling and scientific judgement and were subsequent used to establish proven acceptable ranges (PARs). No design space is claimed. Suitable specifications were presented for the isolated intermediates.

The characterisation of the AS and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities (including genotoxic impurities) were well discussed with regards to their origin and characterised. The fate of impurities and their derivatives as well as intermediates through processing seems well understood and supported by purge studies. Control and carry-over of potential impurities (unchanged or as derivatives) from the starting materials to the final AS have been discussed, with the exemption of PDBP (see "Specification"), which should be included in the specification of the AS.

Differences between synthetic processes (from Process A, to Process B (primary stability batches), to Process C (Phase 3 ITP studies), and to the commercial process) and sites used throughout product development

have been clearly presented and batch analysis data during process development has been summarised. The final commercial manufacturing process has been used for process validation and stability batches.

The active substance is packaged in double, transparent LDPE bags, which are placed in a HDPE drum. Specification for the LDPE material has been presented and confirmation given that the materials comply with Ph. Eur. chapter 3.1.3 and EU legislation for plastic materials intended to come into contact with food, respectively.

Specification

Fostamatinib disodium hexahydrate active substance specification includes appropriate tests and limits for description (visual), identification (FTIR), assay (HPLC), impurities (HPLC), residual solvents (GC), sodium content (IC), residual sodium 2-ethylhexanoate (^{1}H-NMR), water content (Ph. Eur.), particle size distribution (laser diffraction) and microbiological quality (Ph. Eur.).

A comprehensive risk based approach per ICH M7 was used to identify which actual impurities (specified and unspecified impurities on the AS specification) and potential impurities (starting materials, reagents, and intermediates) could be genotoxic impurities in the AS manufacturing process, and to assess the likelihood of their presence in the AS and finished product. The TTC for fostamatinib was calculated in accordance with the ICH M7. Using a TTC of 1.5 µg/day limit based on lifetime exposure, the genotoxic impurity limit for fostamatinib would equate to 5 ppm based on a maximum allowable daily dose of 300 mg. Compound specific assessment conducted for the starting materials present as impurities in the final active substance. It is recognised that the process capability to remove these impurities has been shown. However these impurities should be subjected to control strategy and thus, control of the starting materials should be introduced in specification for the AS. The CHMP recommended to introduce the control of starting materials in the AS specification for the release of all future batches of active substance for commercial manufacturing in the EU, together with the respective validated methods by Q4 2020. It is acceptable that fulfilment will be done post-approval by way of submitting relevant variation(s) according to current variation regulation.

A discussion on elemental impurities in line with ICH Q3D has been provided. Potential sources of elemental impurities have been outlined. Elemental impurity discussion is adequate and omission of testing in the final AS specification is justified. The overall approach on the control of elemental impurities is acceptable. However since the batch data was collected in the past the CHMP recommended to monitoring new AS batches made for relevant residual catalysts. It has been also recommended to introduce the control for residual catalysts in the AS specification and the respective validated method by way of submitting variation(s) according to current variation regulation by Q4 2020. The levels of residual catalysts observed in those new batches will be evaluated and the specification limit for relevant residual catalysts will be revised as appropriate to be in alignment with that batch data.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data has been provided for 4 batches of the active substance manufactured by the synthetic process proposed. Batch analysis data from another 24 batches used for non-clinical, clinical, stability studies, process validation and covering commercial scale has been provided. The presented data complies with the proposed specifications; consistency of active substance has been demonstrated.

Stability

Stability data on three commercial scale batches of active substance stored in the intended commercial packaging for up to 48 months under long term conditions (25 °C / 60% RH), and for up to 6 months under accelerated conditions (40 °C / 75% RH) was provided according to the ICH guidelines. Supportive data from three further pilot batches from process B for up to 68 months under long-term conditions (30 °C / 65% RH) and 6 months under accelerated conditions (40 °C / 75% RH) was also provided. One of the three pilot batches was subjected to an accelerated heat study at 50°C/ambient humidity for 6 months.

Parameters investigated: description, assay, impurities, crystal form by XRPD, water content, particle size distribution and microbiological purity. Crystal form, particle size distribution and microbiological purity have not been investigated for commercial scale batches, which have been satisfactorily justified with reference to substantial development batch data. The analytical methods used correspond to the release methods, while acceptance criteria were those at time of testing.

Regardless of storage conditions and synthetic process used for AS manufacture, results complied with the specifications. No change in crystalline structure was observed. A tendency for one impurity (R940406) to increase in the accelerated heat study was noted.

Photostability
Photostability study in line with ICH Q1B has been conducted on one of the pilot batches. Parameters investigated were: description, assay, impurities, crystal form by XRPD, water content, particle size distribution and microbiological purity. The active substance has been demonstrated stable towards light.

Forced degradation studies
Forced degradation studies on a pilot batch under different stress showed varied degree of degradation depending on the conditions. In addition the HPLC method for impurities has been shown to be stability indicating.

Based on the provided data, the proposed retest period of 6 years for the active substance when stored in the proposed primary packaging without any special storage conditions, is considered acceptable.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

The finished product is an immediate release film-coated tablet presented in two strengths 100 mg and 150 mg. Each strength contains 126.2 mg or 189.3 mg FDH, respectively, corresponding to 100 mg or 150 mg fostamatinib, respectively. The tablet strengths can be differentiated by shape, size, colour and debossing. The 100 mg strength tablet is round with diameter of 9 mm, biconvex, dark orange film-coated and bossed with "R" on one side and "100" on the other. The 150 mg strength tablet is oval with dimensions 7.25 mm x 14.5 mm, biconvex, light orange film-coated tablet and debossed with "R" on one side and "150" on the other. The finished product (FP) pharmaceutical development and control strategy are considered traditional. However, principles of QbD such as definition of a quality target product profile (QTPP) presented in Table 1, associated FP critical quality attributes (CQA) as well as formulation and process risk assessments have been utilised in formulation and process development to develop control strategy. A design space has not been claimed but PARs have been defined.

Table 1. Tavlesse film-coated tablets quality target product profile.

Quality Attribute of the Drug Product	Target	CQA (Yes/No)	Justification
Dosage form	Immediate release tablet for oral administration	NA[a]	Suitable physical, biopharmaceutical, chemical and pharmacokinetic characteristics
Dose	100 mg and 150 mg of fostamatinib per tablet	NA[a]	Desired for clinical dosing
Description 100 mg	Round, biconvex, orange film coated tablets debossed with 'R" on one side and "100" on the reverse	Yes	Gross major appearance defects that may be caused by problems in hardness and/or friability.
Description 150 mg	Oval, biconvex, orange film coated tablets debossed with 'R" on one side and "150" on the reverse	Yes	Gross major appearance defects that may be caused by problems in hardness and/or friability.
Hardness	Mechanically robust enough to withstand coating, packaging and transport processes and consistent with dissolution specification	No	Hardness itself will not impact safety and efficacy and therefore is not considered as a CQA. Hardness variability may impact 'Dissolution' and 'Description' which are CQAs. Appropriate limits for hardness will be defined and controlled during process development.
Friability	Shall comply with relevant pharmacopoeial acceptance criteria	No	Friability itself will not impact safety and efficacy and thus is not considered as a CQA. Friability will be defined and controlled during the in-process control.
Identification	Positive for fostamatinib disodium hexahydrate	Yes[b]	Identification is critical for safety and efficacy and is considered as a CQA. This CQA can be effectively controlled by the quality management system and monitored at release. Formulation and process variables do not impact identity. Therefore this CQA will not be discussed during formulation and process development.
Assay	90.0% to 110.0% label claim	Yes	Assay variability will affect safety and efficacy and is considered as a CQA. Assay and/or uniformity of dosage units will be evaluated throughout formulation and process development.
Uniformity of dosage units	Shall comply with the relevant pharmacopoeial acceptance criteria	Yes	Variability in uniformity of dosage units will affect safety and efficacy and is considered as a CQA. This CQA will be evaluated throughout formulation and process development.
Disintegration	≤15 minutes	No	This is a precursor to dissolution, which is a CQA.

Dissolution	Greater than 85% release at 30 minutes in pH range of 1 to 7.4	Yes	Dissolution is considered as a CQA. Failure to meet the dissolution target can impact bioavailability and therefore efficacy. Both formulation and process variables could affect the dissolution profile. This CQA will be investigated throughout formulation and process development. Container closure system and storage condition could also affect dissolution and these will be assessed via stability testing during development.
Degradation products	Control of named degradation products (R940406 and R936003), individual unspecified degradation products and total degradation products. Refer to m3.2.P.5.1	Yes	Degradation products can impact safety and is considered as CQA. This CQA will be controlled based on compendial/ICH requirements to limit patient exposure. Formulation and process variables can impact degradation products. Therefore, they will be assessed during formulation and process development. Container closure system and storage condition could also have an impact on degradation products and these will be assessed via stability testing during development.
Residual solvents	Shall comply with the relevant pharmacopoeial acceptance criteria	Yes[b]	Residual solvents can impact safety and is considered as a CQA. No solvent is used in the drug product manufacturing process. Residual solvents are controlled through drug substance.
Water content	Level suitable to achieve acceptable compaction properties of granules	No	Water content itself will not impact patient safety and efficacy and thus is not considered a CQA. Increased water content may impact dissolution and microbial limits that are CQAs. Appropriate limits for water content will be defined and controlled during process development.
Microbial limits	Product free from microbial contamination. Shall comply with the relevant pharmacopoeial acceptance criteria.	Yes[b]	Process variables may impact this CQA due to inadequate removal of water. Appropriate limits for water content will be defined and controlled during process development.

[a] NA: not applicable.
[b] Formulation and process variables are unlikely to impact the CQAs and therefore they will not be investigated and discussed in detail in formulation and process development.

Fostamatinib disodium hexahydrate (FDH) is a prodrug that converts to the pharmacologically active moiety, R940406 in vivo, via hydrolysis catalysed by alkaline phosphatases. Compared to R940406, the FDH provides increased solubility and enables much higher absorption of R940406 from an immediate release formulation. Since FDH is a prodrug that converts to R940406 for absorption, the AS cannot be strictly classified in the Biopharmaceutics Classification System (BCS). However, to approach the product development and manage development risk, the AS is treated as a BCS Class IV compound, which is considered sound. Since fostamatinib disodium hexahydrate is considered as a BCS Class IV compound, particle size of the AS could theoretically impact the performance of the solid dosage form by affecting the dissolution and thus is controlled in the AS specification. It has been demonstrated by batch data, stability data and relevant XRD that the crystal form of the AS remains unchanged during manufacture of the final finished product as well as during storage even when subjected to severe thermal stress conditions.

The choice and function of each excipient in the formulation have been described and justified. All excipients are commonly used for tablets and with exception of the colouring materials, all excipients are of pharmacopoeial quality and compatible with the AS, as demonstrated by stability data. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. Excipients were selected to enable rapid tablet disintegration and thereby minimize the potential for gelling of the AS in the tablet matrix which was observed in the earlier formulation. The gel formation is observed at or around the pH range in

which fostamatinib is present predominantly as zwitterion. The gel is likely to be held together by a combination of opposite charges on the molecule, aromatic pi-interactions, or H-bonding, although other mechanisms of gel formation are possible. The fact that the gelling occurs in pH range of 1.7 to 4.2 suggests that charge interactions are the dominant force causing the gel formation. An alkalizing diluent, sodium hydrogen carbonate, was selected to modify local pH, produce effervescence and increase ionic concentration to interfere with drug-drug molecular interactions, in order to prevent gel formation.

A common granule blend is used for both the 100 mg and the 150 mg tablets strengths and the two tablet strengths are dose proportional with regard to tablet core composition.

Initial non-clinical and clinical studies were conducted with R940406. However, its pharmaceutical properties (mainly its limited aqueous solubility) made it infeasible for commercial development, while FDH had more robust pharmaceutical properties and after oral intake FDH was rapidly and extensively converted to R940406.

Studies were conducted using varying concentration of all excipients in the finalised composition to investigate the robustness and to optimise the concentration of excipients. Overview of the different formulations and their compositions has been presented. Several strengths have been used during clinical development, manufactured first at formulation development sites and finally at the proposed site. During development the potential failure mechanisms were identified and addressed. Gelling, disintegration, AS particle size and moisture ingress during storage were evaluated and appropriate measures and /or in-process controls were introduced. Bridging between development batches and commercial production batches has been ensured by clinical studies in combination with bioequivalence and bioavailability studies. Bioequivalence studies were performed to establish equivalency of the tablet formulations for phase 3 studies and commercial over the course of development.

Throughout the development of the commercial formulation, two dissolution methods were used to study how critical process parameters and material attributes affect the final product performance.

The first method was used during formulation development to ensure that the gelling failure mode had been completely eliminated. The amount of sodium hydrogen carbonate included in the formulation is set at a level to ensure that the active substance gelling is overcome during routine manufacture. It is therefore not necessary for QC release test to detect this attribute.

Method development, including investigation of discriminatory power, was conducted in several media (buffer type, buffer concentration, pH, volume) and varying rotation speeds. The discriminatory power of method has been demonstrated with regard to the granulation process parameters, composition, moisture ingress during storage and particle size of the AS.

The core tablet is manufactured with standard wet granulation processes; the core tablet is coated with a non-functional, cosmetic, orange film coating using a conventional coating process. Studies for manufacturing process development were conducted at lab and pilot scale using equipment representative of that proposed for commercial manufacture. The lab and pilot scale studies were used to identify the process parameters that could impact FP performance. Subsequently, the process parameters were applied to manufacture at commercial scale to confirm that relationships established at lab and/or pilot scales were still valid and to identify appropriate working ranges for relevant process parameters at commercial scale. A risk-based approach to identify, classify and mitigate risk parameters by establishing appropriate controls and ranges for these critical process parameters at the manufacturing site was applied. The in-process controls and PARs determined for the process have been based on the outcomes of the risk assessments with supporting process development data.

Film-coated tablets are packed in double LDPE bags placed in a HDPE container. Desiccant is placed between the bags. Specifications for the LDPE bag and the desiccant have been presented and they include specific identification testing (IR) and dimensions. Furthermore, moisture content is controlled in the specification for the desiccant.

The finished product is packed in a white 75 cc HDPE bottle with a child-resistant white PP cap. In the bottle there are two white HDPE desiccant canisters, each containing 1 g of silica gel (total 2 g). Specifications and drawings for the HDPE bottle, the desiccant canister and the PP cap have been presented and are satisfactory. The packaging materials in immediate contact with the finished product (bottle, cap and canister) including the silica gel conform to relevant Ph. Eur. chapters and/or comply with EU quality requirements for plastic materials to come into contact with food. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The proposed manufacturing process is a standard process involving dry mixing and wet granulation, lubrication and tablet compression with subsequent film-coating and packaging.

Critical step/process parameters have been identified. The critical parameters are controlled by suitable PARs which are justified by development and process validation data.

The bulk holding time for film-coated tablets of maximum 30 days that will be applied for film-coated tablets has been supported by data. Bulk stability has been investigated and 24 months stability demonstrated. If the bulk stage hold time exceeds 90 days, the applicant will re-test the bulk product against the release specifications as a condition for final release of the lot.

Major steps of the manufacturing process have been validated by a number of studies on commercial scale batches at the proposed manufacturer. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for description (visual), identification (UV, HPLC), assay (HPLC), degradation products (HPLC), dissolution (Ph. Eur., UV), uniformity of dosage units (Ph. Eur.) and microbiological quality (Ph. Eur.).

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data on three batches using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

The analytical methods used have been adequately described and validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

A summary of 25 representative batches (development phase, registration/primary stability, and process validation/stability) were presented for both tablet strengths. These data come from the development

manufacturing sites and commercial scale batches from the proposed site using active substance obtained from the commercial synthesis. All batches were analysed using the methods current at the time and comply with the specification confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data on six commercial scale batches of finished product for each strength for up to 36 months under long term conditions at 25°C/60%RH and 30°C/65%RH and for six months under accelerated conditions at 40°C/75%RH according to ICH guidelines have been presented. Three batches of each strength were subjected to stressed conditions (50°C/AH) for six months. The six commercial scale batches were filled into the proposed container closure system.

For all studies conducted the following parameters have been investigated: Description, assay, degradation products, dissolution and microbiological purity. Analytical methods were the same as those used for release.

Regardless of storage conditions and tablet strength, results comply the specifications. A slight tendency to increase in degradation product R940406 and consequently total degradation products was observed. Stability data for tablets, stored in the proposed bottles with desiccant, show little or no changes in description, assay, degradation products, dissolution and microbiological quality at 36 months under long-term storage conditions (30°C/65% RH and 25°C/60% RH).

For samples stored under accelerated (40°C/75% RH) and stressed (50°C/AH) conditions for 6 months, there is little or no change in description, assay, dissolution and microbiological quality (40°C/75% RH sample only). Increases in the two specified degradation products, R940406 and R936003, are observed but the levels remained well within the specification limits. The data of assay and degradation products at 40°C/75% RH and 30°C/65% RH demonstrates the robustness of the FP.

Photostability
One commercial scale batch of each tablet strength has been subjected to photostability testing in accordance with ICH Q1B. Results comply with specifications. The photostability data show that light has no significant effect on the physical and chemical characteristics of the tablets.

In-use stability
In-use stability studies were conducted for both strengths at 25°C/60% RH and 30°C/75% RH conditions, and study duration run for up to 13 weeks. The batches used were development batches differing from composition proposed with regard to coating (blue instead of orange), manufacturing site and synthesis of active substance (process B instead of commercial, difference minor and explained. The following parameters have been investigated: description, assay, degradation products, dissolution, microbiological purity and water content. Results complied with specifications and all parameters were well within limits. The in-use stability data up to 3 months duration suggest that the FP performance is not impacted even when water content increases significantly under artificially induced stress conditions.

Based on the overall stability data, the claimed shelf life of 3 years without any special temperature storage conditions when stored in tightly closed bottle to protect from moisture, is acceptable (SmPC sections 6.3 and 6.4).

Adventitious agents

None of the excipients used in Tavlesse film coated tablets are of animal or human origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective the product should have a satisfactory and uniform clinical performance. At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

- to introduce the control of starting materials in the AS specification for the release of all future batches of active substance for commercial manufacturing in the EU, together with the respective validated methods by way of submitting variation(s) according to current variation regulation by Q4 2020.

- to introduce the control of relevant residual catalysts in the AS specification and the respective validated method by way of submitting variation(s) according to current variation regulation by Q4 2020. In addition to evaluate the levels of relevant residual catalysts in new batches of AS and revise the specification as appropriate to be in alignment with that batch data.

2.3. Non-clinical aspects

2.3.1. Pharmacology

Fostamatinib, a small molecule Spleen Tyrosin kinase (SYK)-inhibitor, blocks SYK-mediated responses across a broad range of cell types involved in the initiation and progression of inflammatory and autoimmune diseases in both primary and cultured human cells.

SYK is present in a broad range of cells. SYK is present in hematopoietic cells such as mast cells, basophils, B-cells, T-cells, neutrophils, dendritic cells (DCs), macrophages, monocytes, erythrocytes, and platelets, as

well as non-hematopoietic cells, such as osteoclasts, epithelial cells, fibroblasts, hepatocytes, and neuronal and vascular endothelial cells.

All *in vitro* primary pharmacodynamics studies have been conducted with R406 and not with fostamatinib. This in line with the fact that fostamatinib is rapidly converted to its active component R406 *in vivo*.

R406 potently inhibited *in vitro* biochemical SYK activity in human, mouse and rat (mean IC_{50} of 25 nM, 20 nM, and 30 nM, respectively) in a Caliper assay measuring inhibition of peptide phosphorylation.

R406 blocks FcεRI-dependent activation of cultured human mast cells in a dose-dependent manner with an EC_{50} of approximately 43 nM as assessed by measuring tryptase released upon degranulation. However, R406 did not inhibit ionomycin-induced degranulation of cultured human mast cells. Thus, R406 appears to be specific to FcR signaling, and not degranulation per se.

R406 was shown to potently abolish FcεRI and FcγRI stimulation in human mast cells, macrophages, neutrophils, and platelets. R406 also blocked FcγR signaling in both murine and human dendritic cells. Furthermore, R406 inhibited B-Cell receptor (BCR) signaling in both primary human B cells and human B cell lines. Furthermore, R406 blocked BCR activation of murine primary B cells. R406 inhibited IL-1β secretion from murine bone marrow-derived dendritic cells, which appears to be due to inhibition of Immune-receptor-Tyrosine-based-Activation-Motif (ITAM) signaling via SYK. R406 also inhibited the differentiation, proliferation and function of mouse primary osteoclasts and bone marrow osteoclast.

Collectively, R406 potently inhibited all tested ITAM-mediated signaling, including activation of FcR, BCR and C-type lectin receptor (CLR). These data are consistent with R406 being a SYK inhibitor.

In vitro data primary with human and murine based systems and some data from rat *in vitro* systems have been provided. No data on inhibition of SYK in cynomolgus monkey and rabbit have been submitted, however it was documented that the amino acid sequences of SYK kinases are highly conserved within mammals. Hence, monkey and rabbit can be considered as species in which R406 is pharmacologically active.

Fostamatinib was evaluated for its efficacy in a mouse models of ITP. CD-1 mice and C57BL/6 mice were injected with rat anti-mouse GPIIb antibody to induce platelet clearance. Mice pre-treated orally with fostamatinib, were significantly protected from thrombocytopenia. Fostamatinib appears to mitigate antibody-induced thrombocytopenia in both a dose- and schedule-dependent manner. Due to the rapid decrease in plasma R406 concentrations over time, significant mitigation of antibody-mediated platelet depletion was observed only when a dose of 80 mg/kg fostamatinib was administered every 4 hours. These data support that fostamatinib treatment mitigates clearance of platelets in murine models of autoantibody-mediated thrombocytopenia, consistent with suppression by SYK inhibition of FcγR-mediated phagocytosis in macrophages.

R406 specifically inhibited SYK-dependent collagen-mediated platelet activation, but not platelet activation induced with adenosine 5’ diphosphate (ADP). High systemic exposures of R406 did not prolong bleeding times in mice with normal platelet count. Thus, the data indicates that R406 is unlikely to severely affect hemostasis in patients with normal platelet count. As fostamatinib is to be used in patients with thrombocytopenia, it might cause prolonged bleeding, when collagen-mediated platelet activation is inhibited. It appears that even though the collagen-mediated platelet activation is inhibited by R406 in patients, increased bleeding is not observed in responders to R406 treatment. This could be due to other compensatory mechanisms or that, in these patients, the amount of platelets was sufficient to secure hemostasis despite inhibition of collagen-mediated platelet activation. However, it is acknowledged that in

the context of severe thrombocytopenia, close monitoring for bleeding events, particularly in the skin, is warranted.

Although fostamatinib significantly increased relative thrombosis blood flow (RTBF) in an arterial thrombosis rat model at 100 mg/kg (38.2±15.1%), no such significant increase was observed at clinically relevant doses of 30 and 10 mg/kg, respectively. However, a tendency towards increased RTBF (16.6±9.01% at 10 mg/kg and 30.4±11.7% at 30 mg/kg) could also be assumed at lower doses, according to the submitted data. Acetylsalicylic acid (ASA) treatment alone increased RTBF by 26.1±10.4%, thus to a lesser extent than the medium dose of R406. The combination of ASA and R406 strongly increased the RTBF at all doses tested (up to 70.8±16.8% when dosing ASA together with 10 mg/kg of R406). Similar data was also observed with time to occlusion (TTO). Fostamatinib/ASA combination treatment slightly decreased thrombus size, however not significantly. This effect could theoretically increase the bleeding risk for patients treated with fostamatinib in combination with ASA. However, altogether fostamatinib appears to show a weak antithrombotic effect in this animal model without increasing the cutaneous bleeding time.

Furthermore, it is acknowledged that SYK inhibition per se may be beneficial for ITP patients by affecting different signalling pathways involved in platelet destruction, and prevention of inflammation-associated bleeding and thrombosis, respectively, and that according to recent literature molecular and cellular mechanisms of haemostasis and thrombosis can be separated.

No statistical significant prolongation of bleeding time was observed in this rat study. Compared to the ICR-mouse study discussed above, treatment of ASA alone ('positive control') or in combination with fostamatinib up to 137 µmol/kg did not increase the bleeding time in the rat model. The coupled rat arterial thrombosis assay appears to be less sensitive compared to the direct bleeding time assay conducted in mice. Clarification that ASA treatment in rat per se did increase the relative thrombotic blood flow from 5.0% (vehicle/vehicle) to 26% (vehicle/ASA) have been provided, thus showing an expected effect when treating with the positive control ASA in the rat model as well.

In a murine model of lung damage after mesenteric ischemiareperfusion (I/R) injury, SYK inhibition with fostamatinib improved I/R injury score, but did not show significant effects on platelet function and hemostasis. In a murine model of autoimmune hemolytic anemia (AIHA), fostamatinib effectively suppressed FcR-mediated antibody-induced red blood cell destruction.

To further assess the anti-inflammatory mechanism of fostamatinib and confirm the proposed mode of action, fostamatinib and R406 were also tested in additional supporting animal models representing several SYK-dependent diseases.

R406 and fostamatinib decreased immune-complex mediated inflammation and clinical rheumatoid arthritis symptoms in rats, thus confirming the broad anti-inflammatory potential of the drug. Results indicated that both R406 and its prodrug fostamatinib inhibit immune complex-induced local inflammation and reduce vascular permeability in a dose-dependent manner (dosed up to 30 mg/kg). Histological analysis conducted in the clinical arthritis collagen antibody-induced arthritis (CAIA) mouse model indicated that R406 at 3 mg/kg ameliorated the destruction of cartilage and bone, whereas this could not be observed when dosing 7 mg/kg.
In the K/BxN serum transfer model in mice, fostamatinib dosed orally at 10 mg/kg delayed the onset and reduced the severity of clinical arthritis in a SYK dependent manner after passive transfer of arthritogenic serum from K/BxN mice as shown by comparison to transfer to SYK -/- mice where disease was not inducible, which confirms the importance of SYK in arthritic disease.

In the Syngeneic Louvain (LOU) rat, respectively Lewis rat collagen induced arthritis (CIA) model, both fostamatinib and R406 reduced disease severity starting from 7 days after initiation of therapy. Treatment led to a significant reduction in clinical score and radiographic joint damage as quantified by micro-computed tomography analysis in the CIA rat model. Fostamatinib alone or in combination with methotrexate (0.4 mg/kg) protected against bone damage. Antibodies to type II collagen were not decreased in CIA rats treated with fostamatinib or R406 alone, but reduced antibody levels were observed following combination with methotrexate, suggesting that disease attenuation following combination treatment may be attributable to inhibition of humoral collagen specific immunity. In vitro, R406 abrogated the differentiation, proliferation and function of mouse primary osteoclasts and bone marrow osteoclast precursor cells cultured with murine M-CSF and RANKL. In the Lewis rat CIA model R406 dosage resulted in significant reduction of bone erosion.

R406 and fostamatinib showed promising results in transgenic mouse models of Chronic Lynphocytic leukemia (CLL) by induction of tumor regression and increased survival of animals, when tumor progression was BCR-dependent, but no beneficial effects could be observed in Eμ-MYC mice with BCR-independent tumors. Similar effects could also be observed in other hematological malignancy models, e.g. B-lineage acute lymphoblastic leukemia and acute myeloid leukemia.

The effect of fostamatinib in immune-mediated glomerulonephritis (GN) was studied in different rodent models. Fostamatinib treatment prevented onset of GN when treatment started before induction of disease, whereas significant improvement of symptoms (e.g., reduced proteinuria, glomerular macrophages and serum creatinine, respectively, reduction in renal injury consistent with suppression of TGFß and renal fibrosis, dependent on the animal model used) could be achieved when already diseased animals were treated. Additionally, fostamatinib/R406-dependent SYK inhibition showed beneficial effects on the onset and development of kidney damage and lupus skin in murine models of systemic lupus erythematosus.

In the LDLr-/-murine atherosclerosis model fostamatinib mitigated inflammation and atherogenesis. The anti-inflammatory effect of R406 could also be observed in multiple models of allergic asthma, where treatment positively affected airway hyperresponsiveness (AHR) and lung inflammation by blocking IgE-dependent mast cell repsonse via FcεRI. In non-obese diabetic mice fostamatinib delayed the onset of spontaneous disease as well as progression of already established early diabetes.

R406 bound to a broad range of kinase targets in biochemical assays. R406 was shown to inhibit Jak family kinase-dependent activation of CD23 expression by IL-4 as well as IL-2 driven primary T-cell proliferation. However, in cell-based functional assays R406 off-target binding occurred only to a lesser extent (~ four times lower inhibitory function) than the inhibition of Syk-dependent pathways, and no functional inhibition of immune signalling could be observed in more complex models.

RET kinase inhibitory function of R406 was shown in all model systems tested and is further discussed in the toxicology section, as it adversely affected embryo-fetal development including among other findings renal agenesis. Additionally, R406 was a potent inhibitor of VEGFR-2 downstream signalling in *in vitro* biochemical assays and HUVEC assay, which may be the reason for the blood pressure increases observed in the safety pharmacology studies discussed below.

R406 had slight effects on the innate immune response, but these appears not to be clinically relevant.

The pharmacological profile of R406 was assessed using *in vitro* radioligand binding, enzyme, and electrophysiological assays at a total of 326 non-kinase targets, covering enzyme, receptor, ion channel and transmembrane transporter classes. R406 had activity (defined as IC50 <1 μM) at four targets: the adenosine A3 receptor (K_i 17 nM, antagonist), UDP glucuronosyltransferase UGT1A1 (IC_{50} 143 nM, inhibitor), phosphodiesterase PDE5 (IC_{50} 310 nM, inhibitor) and the adenosine transporter (K_i 630 nM, uptake inhibitor).

Regarding the antagonistic effect on the A3 receptor, the A3 knock out mouse appear viable and to develop normally. Furthermore, targeting the A3 receptor by antagonists may prove beneficial in inflammatory diseases, since antagonists are in clinical development against psoriasis and ulcerative colitis. This indicate that the A3 receptor target is not likely to be of any safety concern for the use of fostamatinib.R406 binding was assessed in a set of 378 competition-binding assays. Binding was detected at 209 kinases other than SYK. Binding Kd values were equal to or more potent than the SYK Kd (12 nM) for 16 kinases, and within 10-fold of the SYK Kd for a further 68. The clinically relevance of the 16 kinases (JAK2, PLK4, STK16, RET, FLT3, KIT, PDGFRB, NEK5, MAP3K10, PLK3, NEK6, JAK3, EIF2AK4, MAP3K9, IRAK3, MAP3K11) with binding Kd values equal to or more potent than the SYK Kd is outlined below divided into three groups.

Group 1: Cytokine-growth factor receptor signaling (JAK2, JAK3, RET, FLT3, KIT, PDGFRb);

Group 2: Cell-cycle regulation (PLK3, PLK4, NEK5, NEK6, STK16)

Group 3: Stress-induced response signaling (MAP3K9, MAP3K10, MAP3K11, EIF2AK4, IRAK3).

For group 1, off-target effects are potential cytopenias, hypopigmentation of skin and hair and peripheral edemas. These effects are anticipated to be routinely collected as adverse events. The R406 potent inhibitory effect on RET leads to teratogenicity, which is already covered by SmPC, since women of childbearing potential are required to use effective contraception during treatment with fostamatinib.

For Group 2, the potent off-target biochemical effects were explained to be less potent when examined in cell-based assays. Nevertheless, the complex pharmacology behind these targets is not completely understood and could be implicated in the common adverse effect of diarrhea. This is adequately described in SmPC.

For Group 3, although adequate selectivity to SYK appear to be present when using cell-based assays, potential in vivo inhibition of these targets could actually be beneficial in the indication.

Safety pharmacology effects of R406 on the central nervous system was assessed using the Irwin Test in conscious male Sprague Dawley rats for up to 2 hours after a single oral dose of 0 (vehicle), 5, 15, or 50 mg/kg. The NOEL was set to 15mg/kg due to reduced touch response, decreased startle response, decreased locomotion and decreased grooming, together with vocalization in the 50mg/kg group. The effects of R406 on respiratory rate and tidal volume were assessed in male Sprague Dawley rats after a single oral dose of 0, 5, 15 or 50 mg/kg with no effect on respiratory rate or tidal volume at any dose tested (NOEL 50 mg/kg). The assessment of effects on the central nervous system and the respiratory system appears to be conducted in line with the ICH S7A guideline.

R406 was tested for its effect on the hERG-encoded potassium channel at a nominal concentration of 2 µmol/L and it appears that R406 was inactive. However, the study was only conducted with one concentration of R406 and was not GLP compliant. The single concentration assay was due to the inherent poor solubility of R406. The concentration of 2 µM was the highest concentration achievable and corresponds to 0.79-fold the clinical plasma concentration measured in patients exposed to the supratherapeutic dose of 300 mg BID. Hence, testing lower concentrations would not be of clinical relevance. Nonclinical in vivo studies in monkeys and the human QT study supersedes any in vitro study and provide evidence that R406 meets the criteria set by the ICH E14 guidance for a negative thorough QT study.

In cardiovascular studies (CVS), a slight reduction on heart rate and a trend to increased blood pressure was observed at 50 mg/kg R406 in monkeys (the highest dose tested). According to the calculations, this corresponds to a peak plasma concentration of ~1910 ng/ml, calculated as the average of the four values obtained at the high dose of 50 mg/kg.

Cardiovascular effect of R406 and fostamatinib were investigated in a range on non-GLP compliant study in rats. A single dose of fostamatinib evoked a dose-dependent elevation in Blood Pressure (BP) in conscious telemetered male Sprague Dawley rats. The time course of the BP effect correlated closely with changes in R406 plasma concentration with an estimated EC_{50} of 20nM, which is comparable to the mean free plasma concentration of R406 (49 nM) in patients. The highest dose tested (100 mg/kg) appeared to decrease heart rate and prolong QA and PR intervals. The increase in BP was also seen in a 28 day repeat dose study. In the repeat dose study the QA interval was increased relative to vehicle treatment on Day 1 following 30 mg/kg (indicative of a decrease in cardiac contractility), but reversed to a decrease in the QA interval by Day 14 (indicative of increased contractility).

The cardiovascular effects were further studied in anaesthetized Sprague Dawley rats following IV infusion of R406. A reduction in mean arterial blood flow was seen at 3 mg/kg. At 5 mg/kg an increase in arterial BP and a reduction in dP/dt_{max} were also observed. Furthermore, a small decrease in heart rate associated with a parallel increase in PR interval was also seen.

R406 had no direct effect on coronary flow, heart rate and cardiac contractility when investigated in isolated Langendorff perfused rat hearts at all concentrations tested. R406 had no vasoconstrictive or vasorelaxant effects in an in vitro rat aorta study. Likewise, R406 had no direct effect on vascular tone of human subcutaneous resistance arteries. However, when pre-incubated with R406 an attenuation of the effect of a thromboxane A2 receptor agonist was seen.

Effects of R406 on endothelial function was investigated in anaesthetised Sprague Dawley rats. R406 consistently caused increases in systolic and diastolic blood pressure in all experiments. R406 appeared not to have any effect on arterial blood flow, vasodilatory actions of acetylcholine and conductance during the hyperaemic response following arterial occlusion. However, R406 did inhibit the vasodilatory actions of VEGF. The effect on VEGF might be the mechanism behind in effect on BP seen in rats. In vitro studies with human endothelial cells were used to further investigate the effect of R406 on VEGF. R406 inhibited VEGF-induced synthesis of NO with an IC_{50} of 0.34 µM.

The effects of anti-hypertensive agents on the BP of conscious telemetered male Sprague-Dawley rats treated with R406 was investigated. It appears that nifedipine (a calcium channel blocker), captopril (an angiotensin-converting-enzyme inhibitor) or atenolol (a selective β1 receptor antagonist) could reduce BP. The effects of nifedipine on BP, heart rate, and ECG parameters were also investigated in conscious telemetered male Sprague-Dawley rats. Fostamatinib-induced increases in blood pressure and increases in QA interval appeared to be prevented by co-administration of oral nifedipine.

Overall R406 appears to have a significant effect on BP at clinically relevant exposure. This was confirmed in the clinic and from a nonclinical point of view, these findings are adequately reflected in the SmPC.

Combinatorial treatment of female ApoE3 Leiden mice with fostamatinib + the cholesterol lowering drug rosuvastatin in combination with western-type diet (containing 0.75% cholesterol) in the atherosclerosis study led to death of 7 of the 15 treated animals after six days of treatment. Examination revealed enlarged liver. Surviving mice showed weight loss and increased ALT levels, indicating liver damage, at higher rates when compared to rosuvastatin treatment alone. Fostamatinib treatment alone resulted in grey fur on the ventral side, spleen weight reduction and decreased total cholesterol levels after dosing of 330 mg/kg/day and in increased total cholesterol levels after dosing of 110 mg/kg bw/day. However, no dead animals were observed and fostamatinib alone did not affect atherosclerosis development in the mouse model. Reference is made to the toxicology section for a summary of the toxicology study conducted to further investigate these deaths and adverse liver findings.

2.3.2. Pharmacokinetics

The nonclinical ADME (absorption, distribution, metabolism, and excretion) studies were performed to support the clinical development of fostamatinib disodium, and conducted in the same species, also used in the pharmacology and toxicology studies.

In rats dosed with fostamatinib there was no systemic exposure of fostamatinib following oral dosing. Furthermore, plasma concentration profiles of fostamatinib and R406 were evaluated in portal vein cannulated rats following an oral dose of fostamatinib. No fostamatinib was observed in portal vein or jugular vein plasma samples. Thus, it is presumed that conversion of fostamatinib to R406 occurs rapidly in the gastrointestinal tract, within the first hour of oral dosing. R406 have moderate to high permeability in in vitro systems with both Caco-2 cells and MDR expressing MDCK cells. Furthermore, R406 is a substrate of P-gp in Caco-2 cells.

Single dose pharmacokinetics of R406 was determined in mice, rats, rabbits, and monkeys after oral administration of R406 or fostamatinib, and after intravenous administration of R406. Bioavailability of R406 from oral fostamatinib dosing was between 40% to 80% with monkeys having highest bioavailability and rabbits the lowest bioavailability. Mice and rats had approximately 60% bioavailability. Pharmacokinetics of R406 appear to be dose proportional at the doses tested in single dose studies with the exception of rabbits having a higher than dose proportional increase in AUC.

Gender differences in pharmacokinetics of R406 were seen in both rats and mice. Female rats and male mice exhibited higher levels of R406 than male rats and female mice. These gender differences were attributed to disparities in the hepatic metabolism of R406. Hepatic microsomes from female mice metabolise R406 at a rate 5.4-fold greater than males. However, this cannot explain the gender difference observed in female mice (G-935788-0010) having higher C_{max} at the 150 mg/kg/dose on both study days, instead this can be explained by saturation of the female specific metabolism pathway.

Sex differences were not observed in monkeys, except in one study (G-935788-0005). Higher mean C_{max} and AUC values were found in female animals compared to male monkeys. No explanation was given on the detected gender differences. There is no difference known in the metabolism of hepatic microsomes from Cynomolgus monkeys of either gender. These differences were explained by interindividual variability. Human hepatic microsomes from females metabolise R406 at a 2-fold greater rate than those from males (N-940406-0020).

Protein binding of R406 is high in all species tested (mice: 98.6%, rats: 97.9%, rabbits: 99.5%, monkeys: 98.5%, and humans: 98.3%). Some distribution to red blood cells was seen, but the distribution to red blood cells appeared to be reversible.

Tissue distribution of ^{14}C-drug related material has been investigated in male albino and male pigmented rats following oral dosing of ^{14}C-fostamatinib 20 mg/kg. It appears that R406 is widely distributed to all tissues with the exception of the CNS. R406 is apparently not able to cross the blood-brain barrier.

Mass balance studies were performed in rats using ^{14}C-R406 and in mice, monkeys, rabbits, and humans with ^{14}C-fostamatinib. Recovery of radioactivity (> 89%) was adequate in all species with only small amounts retained in the carcass (< 1% in mouse, rat and rabbit).

However, the eye (uveal tract), the liver, and the contents of the small intestine had low levels of radioactivity at 168 hours post-dose. Fostamatinib related radioactivity appeared to decline rapidly in liver and uveal tract initially. At 96 and 168 hours after dosing, only trace amounts was left in these tissues. The

calculated half-life of radioactivity of eye (72.6 h) and the liver (50.3 h) at terminal phase of the study have been provided. Since no histopathological findings were evident in these tissues in either, rat or monkey in pivotal toxicity studies, the limited clinical relevance is supported.

R406 is able to cross the placenta in rats and rabbits and this has been reflected in the SmPC section 5.3 including a statement on placental transfer.

Metabolite profiles have been investigated in mice, rats, rabbits, monkeys and humans. No human specific metabolites were identified in plasma. R406 is the major metabolite of fostamatinib in all species. R406 is in humans primarily metabolised to O-Glucuronide of R529 (O-demethylated R406), O-Sulfate of R529 and N-Glucuronide of R406. All three of those are present in monkeys. However, they have not been quantified in monkeys. O-Glucuronide of R529 is present in all species tested and in larger amounts in mouse, rat and rabbit than in humans. O-Sulfate of R529 is present in rabbit and monkey and in larger amounts in rabbits than in humans. N-Glucuronide of R406 is present in rat and monkey and in larger amounts in rats than in humans. Mice, rats and monkeys were the primary toxicological species used to characterize general toxicity of fostamatinib. O-Glucuronide of R529 was present in all three species, N-Glucuronide of R406 was present in rats and monkeys. However, of the three primary toxicological species O-Sulfate of R529 was only present in monkeys. O-Sulfate of R529 has not been quantified in monkeys, nevertheless, since the O-sulphate is a phase two metabolite and comprise of less than 10% of total exposure in human plasma, further studies are not deemed necessary. This is in line with ICH M3(R2) and MIST guidelines.

Fostamatinib is rapidly and completely hydrolysed to R406 in an *in vitro* system with purified alkaline phosphatase. No hydrolysis was observed in the absence of alkaline phosphatase. Thus, fostamatinib is generally believed to be rapidly and almost completely hydrolysed to R406 in the intestine before absorption.

R406 was metabolized in liver microsomes from human and animal species, the main metabolite was para O-demethylated R406 (R529) (N-940406-0020, and N 935788-0025). CYP3A4 and CYP2C9 appeared to be responsible for metabolism. All other human CYP450 isoforms tested did not metabolize R406. CYP3A4 appears to be the predominant human CYP450 isoform responsible for the O-demethylation of R406.

In human hepatic microsomes one major and two minor R406 glucuronide conjugates were observed. The major glucuronide conjugate formed in hepatic microsomes mediated by UGT1A9 corresponded to the major urinary R406 glucuronide. The N-glucuronide that predominated in plasma was a product of UGT1A1 and UGT1A4.

3,5-benzene diol metabolite only observed in faeces was found following incubation of R529 with human and monkey gut bacteria under anaerobic conditions.

Hepatic microsomes from female rats metabolize R406 at a rate 3.9 fold slower than males. Whereas, hepatic microsomes from female mice metabolized R406 at a rate 5.4 fold greater than males. These results were consistent with the in vivo gender difference. Thus, different doses were administered in male and female animals in rodent toxicity studies to achieve similar exposure in the groups.

Excretion studies to investigate routes of excretion using recovery of radioactivity following administration of ^{14}C-R406 to rats or ^{14}C-fostamatinib has been conducted in mice, rabbits, monkeys and humans. Total recovery of radioactivity was above 89 in all studies. Faecal excretion was the primary route of excretion with approximately 80% of radioactivity excreted in faeces in all species tested. Urinary excretion covered from 4% to 19%.

Studies of bile excretion has been conducted in rats and moneys, showing from 46.7% to 83.9% recovery of radioactivity in bile. Thus, it appears that bile excretion is the predominant excretion path.

In rodents, R406 was detected in maternal milk in concentrations 5- to 10-fold higher than in maternal plasma. The risk to the newborns/infants in breast-feeding cannot be excluded and the SmPC includes relevant warnings and risk minimisation measures.

In vitro studies using human liver microsomes showed that R406 can cause inhibition of CYP3A4 and CYP2C8. R406 appears also to be an inhibitor of UGT1A1 and UGT1A. R406 was a substrate of P-gp. However, fostamatinib was determined to be an inhibitor of P-gp-mediated 3H-digoxin transport. This was followed up upon in a clinical study, where it was shown that fostamatinib at clinically relevant doses increased AUC of digoxin with 37% and Cmax with about 70%. Fostamatinib and R406 were not substrates of human BCRP in an in vitro vesicle test system. However, fostamatinib and R406 were potent inhibitors of human BCRP mediated transport of ^{3}H-estrone-3-sulfate in the same system. This interaction has been further investigated in a clinical study where fostamatinib co-administration increased the AUC of rosuvastatin by approximately 2- fold. Interaction with BCRP and P-gp is adequately described in SmPC. R406 was not a substrate of OATP1B1, MRP2, OAT1, OCT2 and OAT3. Furthermore, R406 did not inhibit OATP1B1, MRP2, OAT1, OCT2 and OAT3. Treatment of hepatocytes with R406 caused increases in the activity CYP2C8. A clinical pharmacology study was conducted to investigate the impact of possible induction of CYP2C8 on pioglitazone pharmacokinetics.

2.3.3. Toxicology

Single dose toxicity

Only one single dose toxicity study was reported. This was the pilot study for setting the doses in the mouse micronucleus study. However this still provide valuable information on acute toxicity of fostamatinib in the mouse. A dose of 400 mg/kg dosed as two doses of 200 mg/kg 3 hours apart led to death of 1 male mouse out of 3 males and 3 females. As for the 200 mg/kg dose, no deaths occurred. Following dose administration of 200 mg/kg, ataxia and lethargy were observed. These animals were normal by the end of Day 1 and during the course of the study. Based on these findings, the high dose for the definitive mouse micronucleus study was set at 200 mg/kg.

Repeat dose toxicity

Table 3.2.3.1. Overview of repeat-dose toxicity studies:

Study ID	**Species/ Sex/ Number/ Group**	**Dose/Route** (mg/kg/day)	**Duration***	**NOAEL (mg/kg/ day)**	**Major findings**
G-935788-0010	Mouse/M/F/15	0, 10, 30, 100, 300 Fostamatinib	13 weeks	100 mg/kg/ day	Increased liver weights along with increased AST and centrilobular hypertrophy. Decreased spleen weight along with spleen lymphoid depletion. Bone marrow depletion.

G-940406-0004	Rat/M/F/10	0, 10, 30, 100 R406 free base	28 days	10 mg/kg/day	Reversible reductions in organ weights (liver, spleen and thymus) and minimal to mild hematopoietic hypocellularity in some Mid and High dose animals, with no apparent gender-relationship. Hypocellularity was reversible to a great extent during the 14-day recovery period
G-935788-0001	Rat/M/F/10	0, 2.5, 10, 30, 100/50 R788 calcium salt	28 days	10 mg/kg/day	Reductions in organ weights (liver, spleen, thymus >80% reduction, prostate, testes, uterus, pituitary, thyroids etc.) Hematopoietic hypocellularity, spleen and thymus atrophy, mineralization of the stomach, myocardial necrosis, chondrodystrophy of femoral head, which were found to be partially reversible
G-935788-0004	Rat/M/F/10	0, 5, 17, 60 Fostamatinib (R788 sodium salt)	28 days	17 mg/kg/day	Hematopoetic hypocellularity (not found in recovery animals), femur: white creamy material surrounding the head, chondroid dysplasia, increased osteoclastic activity (chondroid findings still present in recovery animals), testicular atrophy and oligo/aspermia (not found in recovery animals)
G-935788-0003	Rat/M/F/10 For 13 weeks part M/F/20 for 26 weeks part	M: 0, 5, 17, 60/40 F: 0, 5, 17, 60/30 Fostamatinib	13 or 26 weeks	17 mg/kg/day	Clinical signs of poor fur quality and thin condition before dose reduction from 60 mg/kg/day to 40 (M) and 30 (F). Lowered white blood cell and lymphocytes and increased platelets. High incidence of hematopoietic hypo-cellularity of femoral and sternal bone marrow, apparently reversible. Low incidence of moderate femoral head hypoplasia. Higher erythroid production and lower myeloid production.

G-940406-0005	Monkey/M/F/3	0 (water, 0 (vehicle), 10, 30, 100 R406 besylate	28 days	100 mg/kg/ day	Reversible mild to moderate hematopoetic hypocellularity in the high dose group with minimal to mild in the mid dose group. Slight decrease in absolute lymphocyte counts and an increase in platelets, mainly in the high dose animals, also reversible.
G-935788-0005	Monkey/M/F/4	0, 5, 17, 60 (lowered to 34 at week 14) Fostamatinib sodium salt	13 or 39 weeks	17 mg/kg/ day	Reversible hematopoetic hypocellularity (minimal to mild). Diarrhea. Two high dose males, were sacrificed on Days 69 and 87 based on clinical observations most likely due to severe anemia.

*: All studies included at least one 2 or 4 week recovery group.

Mouse

A repeat-dose toxicity study was conducted in mice in order to set the doses for a 2-year carcino-genicity study. Fostamatinib was dosed b.i.d. with total daily doses of 0, 10, 30, 100 or 300 mg/kg/day for 13 weeks. Target organs in the high dose group were liver (increased weight and AST) and spleen (decreased weight and lymphoid depletion) and bone marrow depletion. Reversibility was not determined, since no recovery group was included. NOAEL was set to 100 mg/kg/day. Safety margin to human exposure (AUC0-24htotal ~ 11,000 ng/mL*h) was 4.23 (total) or 3.48 (free) for exposure in mice at 100 mg/kg/day (AUC0-24htotal = 46,504 ng/mL*h).

Rat

Repeat–dose toxicity studies of 28 days duration including a 2 weeks recovery period was reported for both the active moiety R406 as free base and the calcium and the sodium salt of fostamatinib. Fostamatinib will be marketed as the sodium salt. The three studies showed overlap in target organs of toxicity, which included the expected hematopoetic hypocellularity, which is considered the pharmacological effect. The study of the free base R406 also revealed reduction in organ weights (liver, spleen and thymus). The study of the calcium salt of fostamatinib also showed reduction of weight of testes, uterus, pituitary and thyroids. Furthermore, mineralization of stomach, myocardial necrosis and chondrodystrophy were observed. In the final 28-days toxicity study, testicular atrophy and oligo/aspermia were observed confirming the finding in testes from the previous study on fostamatinib. The findings in bone was extended from the previous studies by an observation in femur of white creamy material surrounding the head. The chondroid findings appeared not to be reversible. In the study of the sodium salt of fostamatinib, the NOAEL was set to 17 mg/kg/day. This is supported. Safety margin to human exposure (AUC0-24htotal ~ 11,000 ng/mL*h) was 1.45 (total) or 1.79 (free) for exposure in rat at 17 mg/kg/day (AUC0-24htotal = 15980 ng/mL*h).

The pivotal 13/26-weeks toxicity study in rats was initiated with the same doses as the 28-days study with the sodium salt of fostamatinib, however the high dose had to be lowered for both male and female rats due to extensive clinical signs and low body weight gain showing already between day 12 and 27. Both the 13 and the 26-weeks part of the study included recovery groups for all doses. See Table 3.2.3.2 for overview of study design.

Table 3.2.3.2. Study design of a 13 and 26 weeks toxicity study in rat (G-935788-0003)

Study Design

Treatment Group	Dose Level ** (mg/kg bid)	Total Daily Dose (mg/kg/day)	Dose Conc. (mg/mL)	Number of Animals									
				13-Week Main		13-Week Recovery		26-Week Main		26-Week Recovery		Toxicokinetic (26-Week)[#] [###]	
				M	F	M	F	M	F	M	F	M	F
1.Control*	0	0	0	10	10	5	5	20	20	8	8	0	0
2.Low	2.5	5	0.5	10	10	5	5	20	20	8	8	10	10
3.Mid	8.5	17	1.7	10	10	5	5	20	20	8	8	10	10
4.High	30	60	6.0	10	10	5	5	20	20	8	8	10	10

* Control animals received Control/Vehicle article only
** Represents the dose level for each administered dose
[#] Toxicokinetic animals were dosed for 26 weeks
[###] 4 animals/sex/group (included in the table) were dosed and used as replacement animals as necessary to ensure a complete TK profile should insufficient blood samples be obtained at any time point during the Study.

Details of Dose Reduction for High Dose Animals

Treatment Group	Dose Level (mg/kg bid)	Total Daily Dose (mg/kg/day)	Dose Conc. (mg/mL)	Number of Animals									
				13-Week Main		13-Week Recovery		26-Week Main		26-Week Recovery		Toxicokinetic (26-Week)	
				M	F	M	F	M	F	M	F	M	F
4.High	20	40	6.0	10	0	5	0	20	0	8	0	10	0
	15	30	6.0	0	10	0	5	0	20	0	8	0	10

The clinical signs were extensive and known from previous studies to demand dose reduction. This was seen especially in high dose female during the first few weeks of testing and included dehydration, loose fur/fur loss, pallor and thin body condition. Following the dose level reduction, from 60 mg/kg/day to 40 mg/kg/day for males and to 30 mg/kg/day for females, clinical observations, during the first 13-week, diminished. It should although be mentioned here that, in up to two thirds of high dose females, misaligned, loose, missing, broken and malocclusion of teeth were noted from approximately 3 to 4 weeks of treatment.

Clinical observations during the last 13 weeks of the Study, in animals at all dose levels, consisted primarily of observations related to reduced grooming. During the last 13-weeks of the study some animals were still noted with oral-dental malocclusion and/or teeth misalignment, however, the incidence of these findings was much lower than during the first 13 weeks of the study.

Otherwise, similar pattern of findings related to pharmacological effect of fostamatinib was evident in this long term study, such as hematopoetic hypocellularity, dose-related decrease in organ weight (spleen and thymus). In addition changes in several hematological parameters were observed, however all changes were resolved at the end of the recovery period.

The NOAEL was set to 17 mg/kg/day. This is supported. Safety margin to human exposure ($AUC_{0\text{-}24htotal}$ ~ 11,000 ng/mL*h) was 1.85 (total) or 2.28 (free) for exposure in rat at 17 mg/kg/day ($AUC_{0\text{-}24htotal}$ = 20347 ng/mL*h).

Monkey

A 28-days toxicity study including 2 weeks recovery in monkey was conducted with R406 besylate and not fostamatinib. Again, the main finding was mild to moderate hematopoietic hypocellularity in the high dose group with lower severity and incidence in the mid- and low-dose group. This effect is considered mild, reversible and related to the pharmacological effect of fostamatinib, hence it is agreed that the effect is of little importance in relation to toxicity. The NOAEL was set to 100 mg/kg/day. Safety margin to human

exposure (AUC0-24htotal ~ 11,000 ng/mL*h) was 2.3 (total) or 2.03 (free) for exposure in monkey at 100 mg/kg/day (AUC0-24htotal = 25338 ng/mL*h).

The pivotal 13/39-weeks toxicity study in monkeys was initiated with the same doses as the 13/26-weeks study in rats with fostamatinib sodium salt, however the high dose had to be lowered for both male and female monkeys due to poor clinical condition at the end of the 13-week period. At this time, two male monkeys had to be sacrificed in extremis. Both the 13 and the 39-weeks part of the study included recovery groups for the high dose group. Due to unscheduled sacrifice of two male animals, the number of animals in the 39-weeks part of the study was reduced. See Table 3.2.3.3 for overview of study design.

Table 3.2.3.3. Overview of study design of 13/39-weeks toxicity study in monkey

Details of Dose Reduction for Group 4 Animals

Treatment Group	Dose Level** (mg/kg bid)	Total Daily Dose (mg/kg/day)	Dose Conc. (mg/mL)	Number of animals#							
				13 weeks Main		13 weeks Recovery		39 weeks Main		39 weeks Recovery	
				M	F	M	F	M	F	M	F
4.High	17	34	6.0	0	0	0	0	3	4	1	2

** Represents the dose level for each administered dose

Only animals from the 39-week phase of the Study received the reduced dose.

Study Design

Treatment Group	Dose Level** (mg/kg bid)	Total Daily Dose (mg/kg/day)	Dose Conc. (mg/mL)	Number of animals							
				13 weeks Main		13 weeks Recovery		39 weeks Main		39 weeks Recovery	
				M	F	M	F	M	F	M	F
1.Control*	0	0	0	3	3	2	2	4	4	2	2
2.Low	2.5	5	0.5	3	3	0	0	4	4	0	0
3.Mid	8.5	17	1.7	3	3	0	0	4	4	0	0
4.High	30	60	6.0	3	3	2	2	4	4	2	2

* Control animals received Control/Vehicle article only

** Represents the dose level for each administered dose

The incident of the two monkeys has been described as follows: *As a result of the unscheduled sacrifice (due to poor clinical condition) of two males dosed at 60 mg/kg/day on Days 69 and 87, the high dose was reduced to 34 mg/kg/day from Day 92, after 13-weeks, for both sexes. The two males that were sacrificed were both assigned to the 39-week phase of the study. The clinical signs noted in these animals included, but were not limited to: dark feces, pale in color (gums, mucus membranes, skin on face or tongue), slight or severely decreased activity, weakened appearance, crouching, decreased appetite, cold to touch, and partially closed eyes. These signs appeared 3 to 4 days prior to sacrifice for both animals. Hematological investigations of these animals identified very low red blood cell counts, hemoglobin and hematocrit concentrations, and very elevated levels of reticulocytes. At necropsy, changes observed in one or both of these animals included but were not limited to: pale kidneys, liver, pituitary, lungs, pancreas, stomach and spleen, marrow, and urinary bladder. In one animal, the caecum, colon, ileum, jejunum, and duodenum were also noted as being pale; in the other animal, dark material (possibly melena) was noted as being present in the caecum, colon, and rectum.* As mentioned above, both animals were found to have severe anemia, possibly related to blood loss from the gastrointestinal tract, although a source was not identified. It has been concluded that the etiology of morbidity and possible linkage to treatment for two male primates dosed at 60 mg/kg/day prior to Week 13 remains equivocal. Thus, a measure of uncertainty exists if the MTD was exceeded in this study. The NOAEL was considered to be 17 mg/kg/day, when administered orally *bid* for both 13 and 39 weeks to cynomolgus monkeys. This conclusion is supported, as all other findings

were either minimal, reversible or observed in the control group at similar incidence. The only consistent findings in the groups dosed with fostamatinib and not found in control groups are findings related to the pharmacological effect of fostamatinib, namely hematopoetic hypocellularity, which seemed to be reversible. However, the signs of loose or liquid faeces observed with a slightly higher incidence in the high dose group during the last weeks of the 13-week period, should also be mentioned here, since diarrhoea is a common adverse effect in patients (SmPC).

Safety margin to human exposure ($AUC_{0\text{-}24htotal}$ ~ 11,000 ng/mL*h) was 0.91 (total) or 0.81 (free) for exposure in monkey at 17 mg/kg/day ($AUC_{0\text{-}24htotal}$ = 10052 ng/mL*h).

Genotoxicity

Fostamatinib was tested in a battery of genotoxicity tests. Bacterial reverse mutation assays were conducted on both the active moiety R406 and the prodrug R788 of two different salts, namely the sodium salt (fostamatinib) and the calcium salt. The studies were performed to GLP with use of adequate positive controls with and without rat S9 activation. Rat S9 activation is considered adequate, since the metabolism seemed similar between species and no unique human metabolite was identified. All three studies were performed with three strains of salmonella and one E coli and outcome was deemed negative. This is agreed. An in vitro mammalian chromosome aberration test was conducted with the active moiety R406 in human peripheral blood lymphocytes. This test was also conducted with adequate positive controls and with and without S9 activation. This test also came out negative for genotoxicity, which is agreed.

The mouse in vivo micronucleus study was performed in two phases, in which the first phase was intended for finding the dose range for the final study. The final study was conducted with R406 besylate dosed 20, 60 or 200 mg/kg euthanizing after 24 hours. Animals in the other two groups were treated either with the negative control or R406 besylate, at a dose of 200 mg/kg and were euthanized 48 hours after treatment. Cyclophosphamide 50 mg/kg was used as positive control. The study was interpreted as negative for chromosomal aberration even though males from the high dose group showed a significantly higher incidence of micronucleated polychromatic erythrocytes compared to vehicle, mid and low dose groups, see table 3.2.3.4 below This is agreed, since the number is low and within historical control values. Supporting data to justify the toxicokinetics in the mouse micronucleus test have been provided. These comprised of day 1 toxicokinetics data from the carcinogenicity study, which bracketed the high dose in the micronucleus study.In conclusion, no studies indicated a genotoxic potential of R406, the active moiety of fostamatinib or of fostamatinib itself.

Table 3.2.3.4. Summary of bone marrow micronucleus analysis following administration of R406 besylate in mice

Treatment	Sex	Time (hr)	Number of Mice	PCE/Total Erythrocytes (Mean +/- SD)	Change from Control (%)	Micronucleated Polychromatic Erythrocytes: Number per 1000 PCEs (Mean +/- SD)	Micronucleated Polychromatic Erythrocytes: Number per PCEs Scored[1]
Vehicle	M	24	5	0.537 ± 0.03	---	0.1 ± 0.22	1 / 10000
	F	24	5	0.578 ± 0.10	---	0.6 ± 0.42	6 / 10000
R940406 besylate							
20 mg/kg	M	24	5	0.569 ± 0.07	6	0.5 ± 0.35	5 / 10000
	F	24	5	0.603 ± 0.06	4	0.3 ± 0.45	3 / 10000
60 mg/kg	M	24	5	0.546 ± 0.06	2	0.2 ± 0.27	2 / 10000
	F	24	5	0.532 ± 0.07	-8	0.3 ± 0.67	3 / 10000
200 mg/kg	M	24	5	0.477 ± 0.04	-11	0.8 ± 0.27	**8 / 10000
	F	24	5	0.546 ± 0.05	-6	0.3 ± 0.27	3 / 10000
Cyclophosphamide							
50 mg/kg	M	24	5	0.371 ± 0.04	-31	23.3 ± 5.23	*233 / 10000
	F	24	5	0.386 ± 0.04	-33	23.4 ± 3.86	*234 / 10000
Vehicle	M	48	5	0.588 ± 0.06	---	0.5 ± 0.35	5 / 10000
	F	48	5	0.557 ± 0.05	---	0.5 ± 0.35	5 / 10000
R940406 besylate							
200 mg/kg	M	48	5	0.421 ± 0.07	-28	0.6 ± 0.65	6 / 10000
	F	48	5	0.530 ± 0.06	-5	0.3 ± 0.27	3 / 10000

[1]*Statistically significant, $p \leq 0.05$ (Kastenbaum-Bowman Tables)
[1]**Statistically significant, $p \leq 0.05$ (Kastenbaum-Bowman Tables), but not biologically relevant

Carcinogenicity

Mouse

The mouse carcinogenicity study design and conduct appear to be in line with Guidance on carcinogenic potential, CPMP/SWP/2877/00. The study was initiated with dose groups of 60 male and 60 female mice, which were administered fostamatinib, via oral gavage, bid (approximately 6 hours apart) at dose levels of 50, 150, 500, and 1200 mg/kg/day for up to 104 weeks. The study also included adequate number of animals for toxicokinetic evaluation. The dose of 500 mg/kg/day was reduced to 250 mg/kg/day after one year due to increased mortality at that particular dose. The high dose group (1200 mg/kg/day), was terminated very early in the study and was not subjected to histopathology evaluation. This is acceptable due to the premature time in the study (Day 14 for males and Day 44 females) and the fact that three lower dose groups were still present in the study. However, it is unclear why the dose group of 1200 mg/kg/day was initiated in the first place. It is acknowledged that the mouse 13-week study did not explicitly provided a maximum tolerated dose (High dose was 300 mg/kg), but 1200 mg/kg/day dosed to 120 animals seems to be going a bit too far in terms of 3R principles. As for the remainder of the animals, all animals including animals dead or euthanized early in the study, were subjected to microscopic evaluation. Adverse microscopic findings showed in general higher incidence in animals, which died early, than in animals

surviving to scheduled necropsy, indicating that fostamatinib induced higher mortality in a dose related manner in the study.

Mortality measured as percent surviving to scheduled necropsy (Day 729-733) was as follows for male animals in water, vehicle, 50, 150 mg/kg/day: 43, 53, 45, and 37%. In the 500/250 mg/kg/day group, the terminal necropsy occurred on Day 555 after the number of surviving males reached 15 animals (25%). Mortality measured as percent surviving to scheduled necropsy (Day 729-733) was as follows for female animals in water, vehicle, 50, 150 mg/kg/day: 38, 38, 45, and 53%. In the 500/250 mg/kg/day group, the terminal necropsy occurred on Day 494 after the number of surviving females reached 15 animals.

This is also in line with clinical signs of poor health, which progression appeared to be faster in the highest dose group. Fostamatinib-related clinical findings noted during the study included increased incidences of limb function impairment and rigid body at 500/250 mg/kg/day in both sexes, which likely correlated to microscopic findings of increased bone growth plate thickening involving the sternum of both sexes at ≥ 150 mg/kg/day and the proximal femur (head and/or greater trochanter) of both sexes at 500/250 mg/kg/day. These microscopic observations were sometimes macroscopically evident as bone deformity/malformation and surface irregularities. Additionally, vertebra from 4 females dosed with 500/250 mg/kg/day that were observed with macroscopically irregular surfaces, were microscopically examined and also exhibited growth plate thickening. Bone growth plate thickening is commonly observed in compounds that inhibit angiogenesis (Hall, Westwood et al. 2006). Increased incidences of hunched posture were also noted in both sexes at ≥ 150 mg/kg/day. In addition, higher incidences of thinness noted at 500/250 mg/kg/day correlated with the body weight effects noted in that group. This is supported. The findings related to chondrodystrophy is probably caused by the off target effect of fostamatinib as an inhibitor of VEGF. This was shown as an inhibition of VEGF-induced downstream pathways (IC50 = 0.34 µM, 1083KY), which is likely to be responsible for the adverse effect of increase in blood pressure as well. C_{max} in patients is reported to be 830 ng/mL corresponding to 1.13 µM - 3 times higher than IC50 on VEGF.

It is also acknowledged, that fostamatinib did not appear to increase number of tumors or severity of cancer in this study. Tumour incidence has been summarised as follows: Microscopically, there were no fostamatinib-related carcinogenic findings. There were no statistically significant increases in the incidence of neoplasms in the fostamatinib dosed groups compared to controls. All neoplasms in the study were of the type generally seen in mice of this age and strain. A few non-neoplastic microscopic findings were noted that were consistent with those seen in compounds with this pharmacological profile. The conclusion is supported.

Rat

The rat carcinogenicity study design and conduct appear to be in line with Guidance on carcinogenic potential, CPMP/SWP/2877/00. Four treatment groups of 60 male rats were administered fostamatinib sodium at respective dose levels of 10, 25, 45, or 80 mg/kg/day. Four treatment groups of 60 female rats were administered the test article at respective dose levels of 5, 12, 24, or 40 mg/kg/day. The study also included adequate number of animals for toxicokinetic evaluation. The vehicle or fostamatinib was administered via oral gavage, twice a day (approximately 6 hours apart) for at least 104 consecutive weeks as survival or early termination allowed. Additionally, 10 groups of 3 or 12 animals/sex/group served as toxicokinetic (TK) animals. An adequate number of animals survived to scheduled necropsy, See Table 3.2.3.5 below.

Table 3.2.3.5. Survival to terminal necropsy of main study groups (of 60 animals in each group)

Table 1: Number of Animals Surviving to the Scheduled Terminal Necropsy (Week 105)[a]		
Dose Level; mg/kg/day; Male, Female	Male	Female
0, 0	22 (37%)	16 (27%)
10, 5	19 (32%)	32 (53%)
25, 12	25 (42%)	28 (47%)
45, 24	16 (27%)	16 (27%)
80, 40	0 (0%)[b]	15 (25%)

[a]Respective survival percentage calculations (in parentheses) include/reflect either death or necropsy at Week 105 of the study for groups surviving to scheduled terminal necropsy.
[b] On Day 95, at the request of the Sponsor with concurrence of the FDA, all remaining 80 mg/kg/day males were terminated (they had exhibited a 14% mean body weight decrease from Day 1 when compared to the control mean), as this dose level exceeded the maximum tolerated dose and would not be a viable dose level for a 2-year study duration. Therefore, tissues were not microscopically examined for this terminated male dose group.

However, it should be noted here that dosing had to be ceased for all females at 40 mg/kg/day due to rapidly decreasing survival, as well as a mean body weight decrease that exceeded that of the 80 mg/kg/day males that were terminated early on Day 95. On Day 612, dosing ceased for all males at 45 mg/kg/day after reaching a survival level of 20 animals. On Day 619, dosing ceased for all females at 24 mg/kg/day after reaching a survival level of 20 animals. The animals remained on study and evaluations were continued for these three main study groups until the scheduled terminal necropsy. All animals were subjected to microscopic evaluation except males dosed 80 mg/kg/day.

Clinical findings expected to be drug related were degenerative changes of odontodysplasia, impaired limb function and decreased body weight associated with decreased food consumption.

Microscopic evaluation revealed findings of thickening of the epiphyseal growth plate associated with, hypertrophic chondrocytes especially in the high dose groups. Mesangial nephropathy with increase in matrix of the glomerulus and large amounts of protein in the lumen of tubules was noted in a few female animals. Lymphoid depletion was observed in the mesenteric lymph node, thymus and spleen. Stomach ulcer/erosion and epithelial hyperplasia was observed at slightly higher incidence in both male and female animals, which died on study. Angiectasis/cystic degeneration in adrenal glands was found in slightly higher incidence in high dose male rats. Adrenal gland fibrosis (mild to moderate) was found in mid and high dose female rats.

A new finding, not observed in previous studies of shorter duration, was dose-related odontodysplasia, see table 3.2.3.6 for male rats. The incidence of this finding was similar in female rats. The effect was deemed minimal to moderate, however probably not relevant for humans as rat teeth keep growing over their full lifespan.

Table 3.2.3.6. Insert from Summary of Microscopic Observations – Male rats

Tissue Observation	Severity	0 mg/kg/day DOS	0 mg/kg/day SNC	10 mg/kg/day DOS	10 mg/kg/day SNC	25 mg/kg/day DOS	25 mg/kg/day SNC	45 mg/kg/day DOS	45 mg/kg/day SNC
Number of Animals Examined		38	22	41	19	36	24	45	15
tooth/teeth, incisor		(38)	(22)	(41)	(19)	(36)	(24)	(45)	(15)
odontodysplasia		1	1	7	5	10	4	24	5
	- minimal	0	0	3	1	2	0	8	0
	- mild	1	0	0	2	1	2	5	1
	- moderate	0	1	4	2	7	2	11	4
within normal limits		37	21	34	14	26	20	21	10

DOS - Died or euthanized on study
SNC - Scheduled necropsy
( ) - Number observed

A finding observed in rat carcinogenicity study and not in previous repeat-dose toxicity studies was mesangial nephropathy with increase in matrix of the glomerulus and large amounts of protein in the lumen of tubules. This finding was observed in female animals, which died on study at dose 24 mg/kg/day (6/44, moderate to severe) and dose 40 mg/kg/day (5/45, mild to severe). The finding of mesangial nephropathy in the rat carcinogenicity studyare considered to be of limited clinical relevance, since no such findings were seen in the s9 months study in monkeys and 6-months studies in rats. Furthermore, clinical experiences do not reveal concerns for nephropathy.

As for tumour findings, they have been summarised as follows: *Microscopically, there were no statistically significant increases in tumor incidence noted. Neoplasms seen in the study were of the type generally seen in rats of this strain.* No tumors were found in higher incidence or in a dose-related manner. Hence, the conclusion that fostamatinib is not carcinogenic is supported. It should be noted here, that the high dose groups in this study only provide a low safety margin to human exposure, although in a similar range as the other studies of 4 to 26 weeks duration in rat.

Reproduction Toxicity

Fertility and early embryonic development

Groups of 25 male and 25 virgin female Crl:CD(SD) rats were administered fostamatinib, via oral gavage, *bid* (approximately 6 hours apart) at dose levels of 0, 5, 14, and 40 mg/kg/day for males, and 0, 5, 11 and 25 mg/kg/day for females. The males were treated for 28 days before pairing until the day before scheduled necropsy. The females were treated for 14 days before pairing, throughout mating, and until Day 7 of gestation. Clinical condition, body weights and food consumption were monitored throughout the study. No mortality occurred and no clinical observations were deemed to be related to fostamatinib treatment.

Male fertility

All mating, sperm assessments and organ weight parameters in the male rats were unaffected by dosages of fostamatinib as high as 40 mg/kg/day. The apparent reduced fertility was suggested to be due to females being exposed to fostamatinib as well. However, since both males and females were treated simultaneous in the study, an effect on males cannot be excluded. Testicular atrophy and oligo/aspermia was observed in the 28 days toxicity study in main study rats, but not in the recovery group. Based on weight of evidence from all toxicity studies, fostamatinib most likely does not impact male fertility.

Female fertility

The fertility and pregnancy indices were both significantly ($p \leq 0.01$) reduced at 25 mg/kg/day. This reduction was suggested to be related to treatment with fostamatinib even though the numbers were within historical control values.

Embryonic development

The average number of nonviable embryos and percentage nonviable embryos per litter (post-implantation loss) at 25 mg/kg/day increased to 40.0% and 44.0%, respectively, compared to control values. The difference was not statistically significant, however still deemed related to fostamatinib treatment, since the average number of nonviable embryos per litter was outside of the historical control range of the testing facility.

It is therefore concluded that fostamatinib exert adverse effects on female fertility and embryonic survival. This is adequately described in SmPC section 4.6 and 5.3.

Embryofetal development

Rat

The study of embryofetal development in rat included groups of 25 pre-mated female rats, which were dosed via oral gavage bid at dose levels of 0, 5, 12.5 or 25 mg/kg/day. Rats were dosed on GD6 to 17 and subjected to caesarean examination on gestation day 20 were litter parameters were recorded. The study included TK animals.

Significant reduction in body weight and gravid uterine weight was observed, corresponding with an increase in post implantation loss for the 25 mg/kg/day group.

Edema was noted in 6 fetuses in one 25 mg/kg litter. Covariate-adjusted fetal weights (male, female and both sexes) at 25 mg/kg/day were significantly ($p<0.01$) decreased (by approximately 15%) when compared with controls. Significant ($p<0.01$) increases in the fetal and litter incidence of the fetal soft tissue variations including: absent innominate artery, renal pelvic cavitation and dilated ureters occurred at a dose of 25 mg/kg/day when compared with control. Fetal head variations in ventricles (dilated lateral) was observed at 25 mg/kg/day. Significant, treatment-related fetal soft tissue malformations were seen only at 25 mg/kg/day and included heart and/or great vessel malformations (22 fetuses in 15 litters) and renal agenesis (22 fetuses in 13 litters). A filamentous uterine horn was observed in a single high dose animal (25 mg/kg/day). Fetal skeletal malformation were observed at all dose levels, however, were only considered treatment related in the high dose animals. The malformations included forked and/or fused ribs, vertebral anomalie and split sternebrae. Malformations and variations considered clearly treatment-related (involving the major vessels and especially the renal system) and found in a high incidence, were not seen in the lower dose levels.

On gestation day 21, dam plasma R406 concentrations were greater than in the fetuses. The dam/fetus plasma concentration ratio ranged from 4.9 to 10.5 at all three dose levels.

In conclusion, in rat, fostamatinib appear to induce major vessel, renal/urogenital system and skeletal malformation in foetuses of fostamatinib-dosed dams (25 mg/kg/day). The malformations are most likely induced by the off-target effects of fostamtinib by inhibiting VEGF. This effect on embryofetal development in rat is adequate described in SmPC section 4.6 and 5.3.

Rabbit

Developmental toxicity including the teratogenic potential was also evaluated in the rabbit. Each dosing group consisted of 23 pregnant rabbits. These were dosed from GD7 to 19 and sacrificed at the time of ceasarian evaluation on Day 29. Rabbits were dosed either vehicle, 10, 22 or 50 mg/kg/day (oral gavage bid). The study included TK evaluation with maternal/fetal ratio of exposure. As for the rats, the main target organ for malformations in foetuses were the kidney and tissues associated with the kidney. Furthermore, malformations in patterns of vessel development from aorta was evident. These findings were observed at the higher doses 22 and 50 mg/kg/day with lower precedence in 22 mg/kg/day group. Rabbits seem to be less sensitive to fetal malformation as compared to the rat. NOAEL for maternal toxicity was set to 22 mg/kg/day and for fetal development at 10 mg/kg/day.

In general, the maternal plasma R406 concentrations were greater than the fetal plasma R406 concentrations. The maternal/fetal plasma concentration ratio ranged from 0.9 to 14.8 at all three dose levels investigated.

Prenatal and postnatal development, including maternal function

The purpose of this study was to detect adverse effects of fostamatinib treatment of female rats from implantation through lactation and weaning on gestation, parturition, lactation and maternal behavior and on the development of the F1 generation offspring of the treated F0 generation female rats. F0 dams were administered fostamatinib or the vehicle via oral gavage twice daily from day 7 of presumed gestation (GD 7) through day 20 of lactation (LD 20). The dosage levels were 0 (Vehicle), 2.5, 12.5, and 25 mg/kg/day. Observations were continued through sexual maturity of the F1 generation rats, and fetal gross external and soft tissue evaluations of F2 generation fetuses were conducted.

F0 generation rats showed reductions in body weight gain, feed consumption values and signs of dehydration in the 25 mg/kg/day dosage group during the gestation and lactation periods.

F1 generation showed reduced viability as pups and impaired growth in both mid and high doses groups. In the high dose group, several findings were observed. 1) Delay in sexual maturation, which correlation with body weight reductions. 2) Edema and swelling of paws and/or limbs. 3) Necropsy revealed agenesis or dysmorphogenesis of several organs (kidney, ureter, reproductive structures including testes and epididymis).

There was no adverse behavioural effects in the F1 generation male and female rats, based on performance in watermaze and passive avoidance tests, no remarkable immunological compromise as determined by developmental immunotoxicity testing, and no effects on mating or fertility.

As for the F2 generation, no adverse effects were observed.

In conclusion, fostamatinib was highly toxic to F1 generation of dams treated with 12.5 or 25 mg/kg/day, leading to organ malformation and/or agenesis. The effects did not translate to the F2 generation. The wording in SmPC section 4.6. is considered adequate and even specify that pregnancies occuring during clinical trials resulted in stillbirth/spontaneous abortion or miscarriages.

Juvenile animals

A study in juvenile rabbits was conducted in order to confirm the findings of chondrodystrophy and teeth malformations observed in rat toxicity studies. The study also served as supporting information for seeking a waiver of clinical trials in children.

Juvenile rabbits were dosed from 9 weeks of age for four weeks at doses 0, 10, 30 or 60 mg/kg/day. As expected, histopathology revealed treatment related dysplasia in growth plates. Also reduced bone marrow

cellularity, haemorrhage into the bone marrow and even fractures were observed in these animals. Bone findings were limited to mid and high dose groups. It should be mentioned, that necrotic ovarian follicles were observed in female rabbits at all dose levels. Both findings are consistent with VEGF inhibition. No NOAEL was identified in this study of fostamatinib in juvenile rabbits, hence no safety margin can be calculated. It is agreed that fostamatinib should not be indicated for children. The juvenile rabbit study is mentioned in section 5.3. of SmPC. In regard of the necrotic ovarian follicles observed in female rabbits at all dose levels only studies in juvenile rabbits showed degenerate and necrotic ovarian follicles. In the developmental toxicity study in adult rabbits (G-935788-0006), the mean number of corpora lutea and implantations compared favourably with the control across all groups. There was no evidence, for degenerate/necrotic ovarian follicles at necropsy. Conversely, it needs to be emphasized, that rabbits are induced ovulators and even in the absence of mating ovulation may be induced.
However, this ovarian follicular change has not been reported in any other study in rodents or especially in primates included in the chronic and carcinogenicity studies that were up to 2 years in duration. Nevertheless, even though the findings that occurred in the juvenile rabbit study should have no clinical impact for women of childbearing potential the following information has been added in section 5.3 of the SmPC: "Increased degenerate/necrotic ovarian follicles occurred in females at all fostamatinib dose levels (including 10 mg/kg/day), since the changes noted in the growth plates and ovaries are consistent with an anti-angiogenic effect."

Toxicokinetic data

As for toxicokinetics, exposure to the active moiety of fostamatinib R406 was well documented throughout the studies in mice, rats and monkeys. R406 showed some indications of nonlinear kinetics in the low end of the dose-range as if a clearance pathway become saturated, when doses increase. There was generally dose linearity between the mid and the high dose. There was observed gender differences in exposure in the rodent studies, where male mice showed higher exposure than female mice, whereas for the rat, it was the opposite way around. In vitro metabolism studies indicated that gender differences in clearance capacity of CYPs could be an explanation. Gender differences in exposure for the monkey could not be concluded upon, perhaps due to low number of animals and/or large variability in exposure between animals.

Bioanalysis was conducted to GLP under an audit program. Control samples were analysed for R406 in the mouse and the monkey study, but this important study quality marker of study conduct was apparently omitted in the rat study. Other data (dosing solution analysis) from the pivotal toxicity study in rats without toxicokinetic samples from control animals have been considered. These data indicate that the study was most likely not invalidated by these missing data, however cannot rule it out entirely.

Safety margins were calculated for all the GLP-compliant studies of R406 and fostamatinib. Safety margins are low and ranged from 0.55 to 1.85 in the rat (total) with the highest safety margin for the study of longest duration. The rat showed a range of target organs for the high dose groups including liver, heart and stomach, which are also organs showing adverse effects in patients. The identified adverse reactions requiring dose modification are hypertension, hepatotoxicity, diarrhoea and neutropenia (SmPC). In the rat, liver weights were reduced and in the mouse, centrilobular hypertrophy associated with increased AST was observed. The most prominent finding in the animals were bone marrow depletion or hematopoetic hypocellularity, which in turn may have led to neutropenia and is a common side effect in patient (6%). Monkeys seem to be less sensitive to organ toxicity compared to rat and mouse, however diarrhea was observed for the first 13 weeks of the 13-39 weeks study in monkey. Safety margin is close to unity for the monkey (0.91 total) in the 13/39 weeks study. Most of the observations from animal toxicity studies were

predictive for adverse effects in patients. The chondrodystrophy/ growth plate dysplasia in rodents and rabbit may be related to off target inhibition of VEGFR (Hall, Westwood et al, 2006) and is limited to actively growing bones (before growth plate closure). This finding should not be an issue in adult patients, where growth plate closure has occurred. However this was not out ruled in adult patients by any experimental means. It is however described by literature that closures of epiphysis in the bones of the upper limbs are found during the age of 14-18 years of human life, whereas epiphyseal closures of lower limbs (femur and tibia) are found during 18-25 years of age. A warning in regards to this aspect has been included in the SmPC.

Other toxicity studies

Immunotoxicity

The potential direct immunotoxic effect of fostamatinib was evaluated in three mouse models, the streptococcal, influenza and listeria host resistance models. Neither model indicated that fostamatinib impaired bacterial clearance in lung tissue from mice pretreated with fostamatinib for 7 days, 21 or 27 days. Dose levels selected were in the range of 10 to 80 mg/kg/day. Supportive toxicokinetic data from the mouse toxicity study indicate that the exposure for the high dose of mouse immunotoxicity studies was pharmacologically active and also provided a safety margin to patient exposure.

Furthermore, these models only evaluate the immune response to new foreign patogens. It is unclear how fostamatinib will affect the adaptive immune system, especially immune cell mediated responses that are guided by antigen-antibody complexes. On this ground, the effect of fostamatinib on specific antibody production by antibody-dependent B cells may be dependent on the context of immunization. Generally, nonclinical data indicate that fostamatinib induce only modest if any inhibition of the general immune system. Nevertheless, fostamatinib appears to have an adverse effect on the general immune system by increasing occurrence of opportunistic infections in fostamatinib treated patients and inducing neutropenia. However, this concern is adequately handled in SmPC section 4.4 as special warnings (Neutropenia) and in 4.8. where both effects are listed as common adverse drug reactions.

Impurities

A number of identified impurities were evaluated in the Ames test. Some impurities are demonstrated to be consistently purged below the threshold of toxicological concern (TTC) and others are subject to specification limits. All studies on genotoxic potential of impurities were conducted in compliance with GLP except the one on the genotoxic impurity 3,4,5 trimethoxyaniline (TMA). TMA was identified as a potential genotoxic impurity in a non-GLP compliant Ames test, (i.e., no positive control was included in the study). The lack GLP-compliance in this study of genotoxic potential of TMA has been justified by ensuring that TMA is controlled to comply with TTC as per ICH M7.

Phototoxicity

The phototoxic potential of R406 Besylate was evaluated in Balb/c 3T3 mouse fibroblasts as described in OECD guidelines 432 and to GLP. R406 showed limited cytotoxic potential both with and without UVA light, therefore fostamatinib and it's prodrug R406 provide limited concern for phototoxicity.

Fostamatinib Combination Treatment with Rosuvastatin in APOE*3 Leiden Mice

The combination treatment of fostamatinib and rosuvastatin appear to be excessively hepatotoxic in APOE*3 Leiden mice. On this effect prescribers are given the most relevant information from a human drug

interaction study in which it was shown that fostamatinib increased exposure of rosuvastatin by approximately 100%.

2.3.4. Ecotoxicity/environmental risk assessment

Regarding the Environmental Risk Assessment the logKow, a parameter for predicting the distribution of a substance in various environmental compartments, is -0.6 for Fostamatinib and 3.63 for Fostamatinib RIG-C. Both values are below the trigger 4.5. However, since the $PEC_{surfacewater}$ exceeds the action limit of 0.01 µg/L a further Phase II assessment is still required. The applicant has committed to provide this study in the post-approval phase.

2.3.5. Discussion on non-clinical aspects

Pharmacology

The Application regards the development of a competitive inhibitor of SYK in treatment of ITP. R406, the active metabolite of Fostamatinib, in *vitro* potently inhibits SYK activity in human, mouse and rat. Since amino acid sequences of SYK kinases are highly conserved between mammals, the monkey and rabbit used in the nonclinical safety studies can be considered as R406 pharmacological relevant species.

Fostamatinib was shown to mitigate antibody-induced thrombocytopenia in mice, which is consistent with suppression by SYK inhibition of FcγR-mediated phagocytosis in macrophages. However, R406 also inhibited SYK-dependent collagen-mediated platelet activation, but not platelet activation induced with ADP. High systemic exposures of R406 did not prolong bleeding times in mice with normal platelet count. Thus, the data indicates that R406 is unlikely to severely affect hemostasis in patients with normal platelet count. As fostamatinib is to be used in patients with thrombocytopenia, it might cause prolonged bleeding, when collagen-mediated platelet activation is inhibited, however clinical and nonclinical data collectively show that this effect is most likely not clinically relevant.

Secondary pharmacology studies revealed that R406 had antagonistic effects on adenosine A3 receptor as a K_i of 17nM is very close to the K_i for SYK. The A3 receptor by antagonists may prove beneficial in inflammatory diseases, since antagonists are in clinical development against psoriasis and ulcerative colitis. This indicates that the A3 receptor target is not likely to be of any safety concern for the use of fostamatinib.

Furthermore, R406 had binding Kd values equal to or more potent than the SYK Kd for 16 other kinases. Most of these targets appear to be clinically relevant and can be linked to various identified adverse drug reactions and risks, which are adequately handled in SmPC and RMP. Others appear to provide a beneficial effect in the indication.

Safety pharmacology studies revealed no clinically relevant effects on CNS and the respiratory system. However, clear effects were found on the cardiovascular system. Cardiovascular effect of R406 and fostamatinib were investigated in a range on non-GLP compliant study in rats. A single dose of fostamatinib evoked a dose-dependent elevation in BP in conscious telemetered male Sprague Dawley rats. The blood pressure elevation is suggested to be a consequence of increased vascular resistance or impaired vasorelaxation due to inhibition of VEGF-induced endothelial nitric oxide release, both induced by fostamatinib/R406. The time course of the BP effect correlated closely with changes in R406 plasma concentration with an estimated EC_{50} of 20nM, which is comparable to the mean free plasma concentration of R406 (49 nM) in patients.

Pharmacokinetics

Fostamatinib is converted to R406 in the gastrointestinal tract before absorption. Single dose pharmacokinetics of R406 was determined in mice, rats, rabbits, and monkeys after oral administration of R406 or fostamatinib. Bioavailability of R406 from oral fostamatinib dosing was between 40% to 80%. Pharmacokinetics of R406 appear to be dose proportional at the doses tested in single dose studies with the exception of rabbits having a higher than dose proportional increase in AUC. Gender related differences were seen in mice and rats.

Protein binding of R406 is high in all species tested. Some distribution to red blood cells was seen, but the distribution to red blood cells appeared to be reversible.

R406 is widely distributed to all tissues with the exception of the CNS following oral dosing of ^{14}C-fostamatinib. R406 is apparently not able to cross the blood-brain barrier.

Metabolite profiles have been investigated in mice, rats, rabbits, monkeys and humans. There were no human specific metabolites in plasma. R406 is the major metabolite of fostamatinib in all species and no plasma metabolite represented greater than 10% of R406 exposure. R406 is in human primarily metabolised to O-Glucuronide of R529 (O-demethylated R406), O-Sulfate of R529 and N-Glucuronide of R406. All three phase 2 metabolites are present in monkeys.

R406 was cleared at a low rate compared to hepatic blood flow with short half-life (ranging from 0.58 to 3.41 hours), with the exception of the mice, in which higher clearance and shorter half-lives were observed.

Faecal excretion was the primary route of excretion with approximately 80% of radioactivity excreted in faeces in all species tested. Urinary excretion covered from 4% to 19%.

There was no evidence of R406 accumulation after twice-a-day dosing of fostamatinib in all species.

Fostamatinib and R406 were not substrates of human BCRP in an in vitro vesicle test system. However, fostamatinib and R406 were potent inhibitors of human BCRP mediated transport of ^{3}H-estrone-3-sulfate in the same system. This interaction has been further investigated in a clinical study where fostamatinib co-administration increased the AUC of rosuvastatin by approximately 2- fold.

Toxicology

In general, the toxicological endpoints previously described as off-target class effects of antiangiogenic VEGFR inhibiting medicinal products have been confirmed for Fostamatinib. The extrapolation of the NOAELs derived from several animal model to the Human Equivalent Dose (HED) demonstrate consistently an alarming narrow safety window of less than 1.

Repeat-dose toxicity studies revealed that fostamatinib is toxic in animal species at exposure only 3-4 times typical patient exposure. Some toxicity could be ascribed to exaggerated pharmacology such as hematopoietic hypocellularity, which were consistently found in all studies. Fostamatinib was found to reduce fertility and to be teratogenic in rat and to induce bone malformations in the juvenile rabbit. The rat seemed to be the most sensitive species. In this species several off target findings were evident e.g. chondrodystrophy and teeth malformations, which were consistently found in growing rats and rabbits probably due to VEGF inhibition. This finding is not expected to be an issue in adult patients, where growth plate closure has occurred. Whether the changed bone metabolism is also relevant for young adult ITP patients and/or patients at risk of osteoporosis is not entirely clear. This concern was not out ruled in adult patients by any experimental means.

Other concerns derived from preclinical studies are the findings in several developmental and perinatal/postnatal reproduction studies in rats and rabbits. Fertility studies in rats demonstrated a significantly reduced pregnancy rate as well as an increased number of nonviable embryos at higher doses. Fostamatinib did not only induce increased maternal toxicity but also increased post-implantation loss, and decreased uterine weights, growth retardation of the foetus as well as variations and malformations of the offspring. The NOAEL for developmental toxicity in rats was considered 5 mg/kg/day. These toxicities were confirmed by the rabbit as 2nd animal species. Segment III studies addressing the pre- and postnatal development confirmed these findings. Also with this regard reference is made to the literature and to well-described off-target class effects.

It may be assumed that prescription of Fostamatinib does not exclude women of child-bearing potential. The findings regarding animal reproduction studies are listed in the Summary of products characteristics under section 4.4 (Special warnings and precautions for use). The use of fostamatinib is contraindicated during pregnancy in 4.6 (Fertility, pregnancy and lactation).

Fostamatinib was found to be severely liver toxic when administered in combination with rosuvastatin in APOE* Leiden mice. However these effects were ascribed to very high exposure, which was not clinically relevant. Instead, prescriber are informed of the results of a clinical drug interaction study between fostamatinib and rosuvastatin in SmPC.

Applicant committed to perform a standard Phase II environmental fate and effects analysis post approval, since $PEC_{surfacewater}$ was above the action limit of 0.01 µg/L. The analysis should focus on the active metabolite of fostamatinib; R406.

2.3.6. Conclusion on the non-clinical aspects

From a non-clinical point of view, fostamatinib is considered acceptable for marketing authorisation

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Overview of Efficacy Studies of Fostamatinib in ITP

Study ID	D4300-022	C788-047	C788-048	C788-049
Phase	Phase 2	Phase 3	Phase 3	Phase 3
Description	Pilot, Proof-of-Concept Study	Placebo-Controlled, efficacy and safety study	Same as C788-047	Open-Label, Extension to C788-047 and C788-048
Status/ Period	Completed/ Jan 2007-May 2010	Completed/ Jul 2014-Apr 2016	Completed/ Jan 2015 - Aug 2016	Ongoing/ Oct 2014 – Interim analysis, cut-off 08 March 2018
Study Sites	2 sites	35 sites	23 sites	53 sites
Efficacy Endpoints	Primary: Platelet count increased by ≥ 20,000/μL from baseline to a count ≥ 30,000/μL Secondary: Platelet count ≥ 50,000/μL; ≥ 150,000/μL (at each follow-up visit)	Primary: Platelet count ≥ 50,000/μL on at least 4 of last 6 visits (Weeks 14-24) Secondary: Platelet count ≥ 50,000/μL at Week 12; at Week 24 [Subjects with baseline count < 15,000/μL:] Platelet count ≥ 30,000/μL and ≥ 20,000/μL above baseline at Week 12; at Week 24 IBLS and WHO bleeding scoresa	Same as C788-047	Primary (see definitions in Section 2.3.1): Long-Term Stable Platelet Response (Endpoint Version 1): Non-comparative assessment over ≥ 12 months Placebo-Crossover Comparison (Endpoint Version 2): Within-subject comparison of fostamatinib with placebo over ≥ 12 weeks Secondary: Duration of platelet response
Study Population	ITP for ≥ 3 months Platelet count average < 30,000/μL (3 counts in 3 months) Tried ≥ 2 typical ITP regimens	Persistent or chronic ITP Platelet count average < 30,000/μL (3 counts in 3 months) Received ≥ 1 typical ITP regimen[a]	Same as C788-047	Completed Week 24 evaluation of prior study or had discontinued early (starting at Week 12) due to lack of response
Design and Type of Control	Open-label, dose-escalation, pilot study	Double-blind, randomized, placebo-controlled, parallel-group study	Same as C788-047	Open--abel, extension study
Planned Duration	6 weeks to 2 years	Up to 24 weeks	Same as C788-047	Up to approximately 5 years
Treatment Regimens	Fostamatinib at increasing starting doses (75 mg *bid* to 150 mg *bid*). Dose escalated by 25 mg *bid* every 2 weeks, if needed for efficacy and subject to tolerability; highest dose was 175 mg *bid*.	Fostamatinib 100 mg *bid*, increased to 150 mg *bid* at/after Week 4 if platelet count < 50,000/μL. Dose could be reduced to as low as 100 mg *qd* in the case of dose-limiting adverse events. Matching Placebo	Same as C788-047	If platelet counts at rollover ≥ 50,000/μL, previous fostamatinib regimen continued. If platelet counts at rollover < 50,000/μL, same as fostamatinib regimen in C788-047.
Number of Subjects	Planned: Up to 18 Treated: 18 (17 unique subjects; 1 subject was enrolled twice) (All Fostamatinib)	Planned: 75; Treated: 76 (Fostamatinib: 51; Placebo: 25)	Planned: 75; Treated: 74 (Fostamatinib: 50; Placebo: 24)	Planned: Up to 150 Treated: 123 (All Fostamatinib)

Note: *bid* = twice daily; ITP = immune thrombocytopenia; PK = pharmacokinetic(s); *qd* = once daily; IBLS = ITP Bleeding Scale.

[a] Typical regimens specified in the protocol were corticosteroids with or without splenectomy, IV immunoglobulin, and/or a TPO-RA (romiplostim, eltrombopag).

2.4.2. Pharmacokinetics

Fostamatinib (administered as fostamatinib disodium hexahydrate) is an immediate-release tablet intended for twice daily (bid) oral administration for the treatment of immune thrombocytopenic purpura (ITP). Fostamatinib (also referred to as R935788 or R788) is a prodrug that undergoes dephosphorylation in the gastrointestinal tract through the action of gut alkaline phosphatase (ALP) to produce R940406 (R406), the parent drug/active metabolite. The major analyte found in plasma is R406. Fostamatinib is typically not detected in plasma.

The pharmacokinetics of fostamatinib (R788) and/or its active metabolite R406 were evaluated in 28 clinical pharmacology or biopharmaceutic studies, one phase II study (Study D4300-022) and 3 phase III studies (Study C788-047, C788-048 and extension study C788-049). Data from the target patient population is limited to the findings of the PK substudy of extension trial C788-049 in twelve patients on 150mg bid as well as plasma levels taken at different time points from the phase II and III trials at varying dose levels. Furthermore, a population PK analysis has been submitted, which included data from 10 Phase I studies in healthy volunteers, four phase II studies and three phase III studies in patients with rheumatoid arthritis and finally, data from the three phase III studies in patients with ITP.

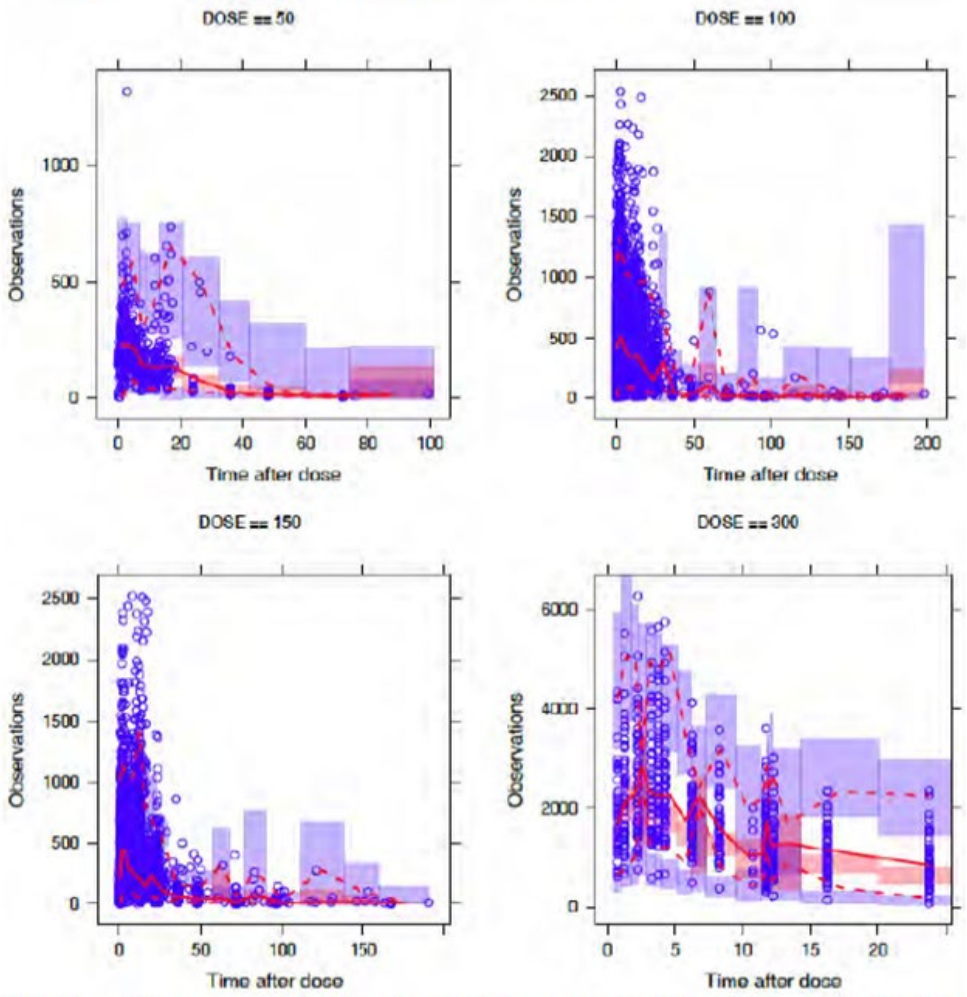
Methods

All bioanalysis was conducted by LC-MS/MS and was in general adequately performed and documented. Pharmacokinetic parameters were calculated by non-compartmental methods in WinNonlin. Pop PK and PD analyses were run in NONMEM with FOCEI. SAS and Excel was used for data preparation and R for data presentation. Descriptive statistics for pharmacokinetic parameters were derived using conventional software and methods (WinNonlin, Microsoft Excel or SAS).

Evaluation and Qualification of Models

A two-compartment population model with simultaneous first- and zero-order delayed absorption and first-order elimination was developed in HV and RA patients. Significant identified covariates were body weight and population. Body weight was linearly correlated with CL and V2 with exponents 0.662 and 1.23, respectively. Final estimates were with good precision (%RSE≤8.4%), however, IIV was high (>39-104%) and highest for ka and D1 describing the absorption phase. In addition, shrinkage for the IIV estimates was high (≥50.6%), except for CL (10.6%).

Figure 15 Visual Predictive Check of Final Model

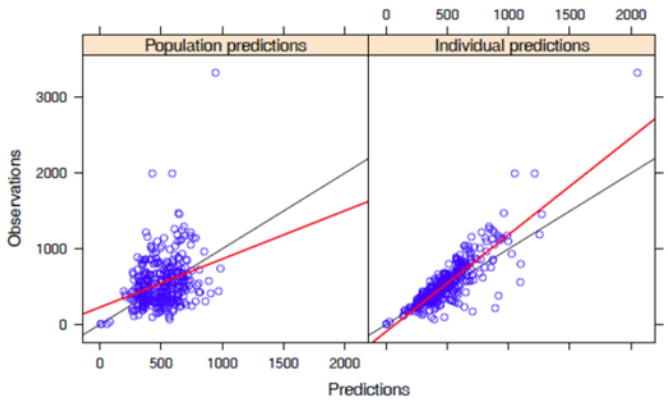


Notes: The solid line represents the median and the dashed lines represent the 5th and 95th percentiles of the final model-predicted concentrations in 1000 replicates. Open circles represent observed concentrations from individual subjects. The shaded areas represent the confidence bands around the prediction intervals within each data bin.

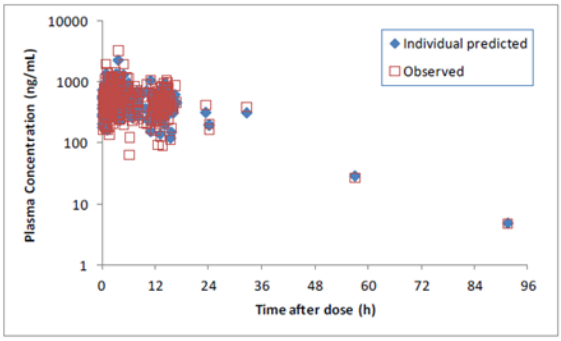
The high variability and high shrinkage for the parameters describing the conversion of fostamatinib to R406 in the gut and the absorption is also evident from GoF plots where the fit is poorer at higher concentrations. The VPC's representing 4 different doses is shown in Figure 15. A large amount of observations around Tmax falls outside the 95th percentile of model predicted concentrations. Hence, the provided model is considered a supportive tool, to evaluate the effect of certain intrinsic and extrinsic factors, but should not be used to establish firm recommendations in the SmPC.

Figure 2 Predicted vs. Observed Plasma Concentrations (ng/mL) of R406 in the ITP Population

(A) First Approach



(B) Second Approach



Notes: The black line is the unity line and the red line is the trend line. In the first approach, the final population PK model developed in healthy subjects and RA patients was rerun after incorporating the ITP population data from the 3 Phase 3 studies. In the second approach, the final population PK model developed using data in healthy subject and RA patients was fitted to the ITP data after fixing the PK parameter to the population values, except for the inter-individual variability terms.

The final population PK model developed in HV and RA subjects was rerun after incorporating the ITP population data. The dataset included 18044 observations from 2526 subjects (419 HV, 1994 RA patients, and 113 ITP patients). The final population PK model was also fitted to the ITP data after all model parameters were fixed to the population values, except for the IIV terms. The individual predicted concentrations were well correlated with the observed concentrations (Figure 2). It is expected that the addition of 332 observations from ITP patients would have limited influence on the established model.

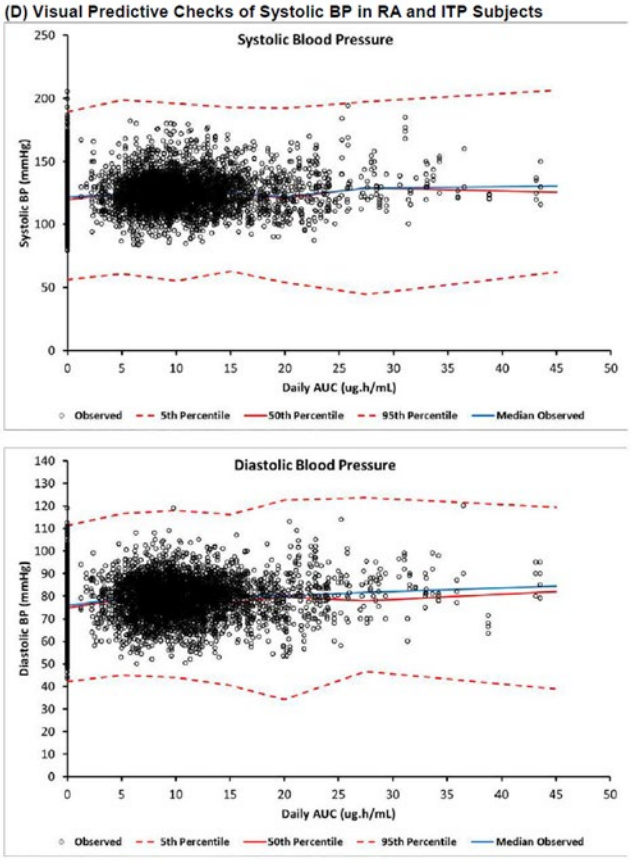
E-R relationships were evaluated for safety variables BP, ALT, BILI and ANC, and blood platelet count for efficacy. Of the 2535 subjects included in the PK/PD data set, 1675 subjects were on active treatment, of these were 102 subjects (6%) ITP patients with 3 blood samples taken per study (1 at Weeks 2, 6, and 24). Only PD data from ITP patients were included in the blood pressure analysis.

Table 6-2 **Summary of Baseline Demographics and Categorical Covariates of Subjects Included the PK/PD Dataset for Neutrophil Count, Bilirubin, ALT, AST, and Blood Pressure**

Covariate	Category	Placebo (N = 878) Number (%)	Active (N = 1657) Number (%)	Overall (N = 2535) Number (%)
Sex	Female	719 (81.9)	1360 (82.1)	2079 (82.0)
	Male	159 (18.1)	297 (17.9)	456 (18.0)
Race	White	666 (75.9)	1325 (80.0)*	1991 (78.5)
	Black/ African American	40 (4.6)	60 (3.6)	100 (3.9)
	Asian	27 (3.1)	40 (2.4)	67 (2.6)
	Other	60 (6.8)	115 (6.9)	175 (6.9)
	American Indian or Alaska Native	13 (1.5)	31 (1.9)	44 (1.7)
	Indian or Pakistani	49 (5.6)	86 (5.2)	135 (5.3)
	Missing	23 (2.6)	0 (0.00)	23 (0.90)

Notes: * Includes 78 subjects with Race labeled as Hispanic. Two subjects (1580 and 1581) had missing baseline values and therefore were removed from the BP analysis.

The probability of blood pressure increase (systolic and diastolic) was investigated both with regard to category (grade) and time-course. The daily R406 exposure seemed to slightly increase at higher grades and a linear regression model best described the probability of BP increase to exposure (DAUC).

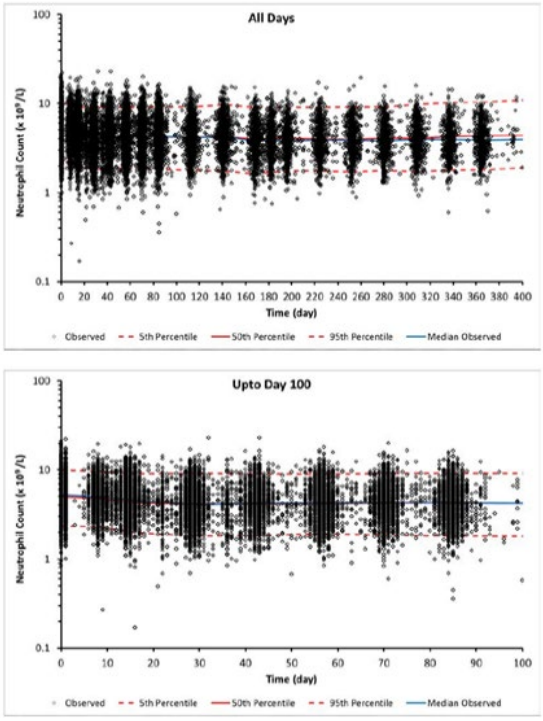


The probability of experiencing Grade 3 and 4 BP was relatively low, with the highest probability observed in older subjects with a history of hypertension at baseline. The maximum increase in SBP and DBP was predicted to be about 10 mmHg. The EC50 was 16 µg×h/mL which is close to the mean exposure after 150 mg bid fosatmatinib. Increase of R406 exposure had little effect on ALT, AST and BILI.

A linear E_{max} model best described the effect of R406 exposure on the probability of ANC grades (neutrophil decrease). All regression parameters were determined with acceptable precision. The Black/African-American

race and body weight remained significant predictors of E_{max} and EC_{50}. Although the effect of R406 exposure on race resulted in 2.3 times higher probability and a higher body weight seemed to decrease the probability of neutrophil decrease, the effect was limited.

(D) Visual Predictive Checks of Neutrophil Count in RA and ITP Subjects



The time-course of effect of treatment on neutrophil levels was also evaluated by a sigmoidal I_{max} function with a proportional error model. All parameters were estimated with good precision. The IIV was high (62.2 – 135%) for all parameters except baseline neutrophil count (BM0) (34.4%) and I_{max} (9%) with a shrinkage ≥ 47.2% for all IIV estimates except for BM0. No bootstrap evaluation was performed. The maximum decrease in neutrophil count was predicted to be 662×10E6/L.

The efficacy of R406 exposure in regard to platelet response was evaluated by linear regression at Week 12 since data were too sparse in Weeks 14-24 with only one observation per subject/week. IIV could not be estimated.

Table 6-46 Base Model Parameter Estimates for the PK/PD Analysis for Response on Week 12

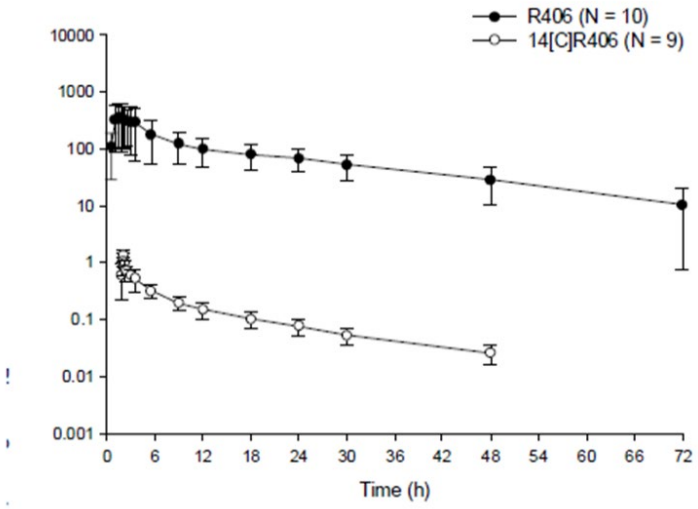
Parameter [Units]	Point Estimate	%RSE	95% CI
Placebo effect	-2.16	22.5	(-)3.11 – (-)1.21
Drug exposure effect (Slope)	0.109	28.9	0.0473 - 0.171

The probability of achieving a positive response at Week 12 was about 33% after 150 mg bid fostamatinib. Of note, the primary efficacy endpoint in the two conducted Phase 3 placebo-controlled trials was stable platelet response i.e. a platelet count of ≥50,000 counts/μL on at least 4 of the 6 visits between Week 14 to 24. It was not possible to fit a continuous PK/PD model for the platelet count-time profiles.

Absorption

Exposure to fostamatinib was assessed in Studies C788-001, C788-003, C788-004, C788-005, C788-014, and D4300-007. Fostamatinib is rapidly converted into highly permeable R406 in the gut and then absorbed. In vitro studies have indicated that R406 is a substrate of P-gp, but not BCRP, OCT2 or OATP1B3. The mean absolute bioavailability of R406 is determined to 55% (90% CI: 42.48, 70.29) after a single oral dose of 150 mg fostamatinib and a radiolabeled intravenous (IV) microtracer dose of 14C-R406 in healthy subjects (Study D4300-027). The wide confidence interval demonstrates that there is a large variability in BA. The variability ranged from 30 % to 85 %.

Figure 1 **Arithmetic mean (±SD) R406 and [^{14}C] R406 plasma concentration-time profile over 72 hours on logarithmic scale**



Source: Table 11.2.1 and 11.2.3.

T_{max} was approximately 1.5 hours regardless of single or multiple dosing. There was a dose-related increase in R406 exposure when dose increased from 80 to 250 mg, but no increase in R406 exposure between 250 and 400 mg in study C788-001. T½ of R406 is about 16 hours.

Bioequivalence

Nine biopharmaceutical studies have been conducted to describe bioavailability, bioequivalence and food effect. Bioequivalence between the different formulations were investigated in three BE studies: D4300-020, C788-052, and C788-054.

Earlier formulations were bridged to the formulation used in the ITP development program (formulation OFC-1; manufactured by AstraZeneca) which was further bridged to the proposed commercial tablet (formulation OFC; manufactured by Patheon) with bioequivalence established within the accepted 80 – 125 %CI margins. Large variability was observed for all formulations, especially for C_{max}.

Influence of food

Several studies demonstrated that food (high fat high calorie contents) increases R406 exposure (AUC) by 10 to 32%, while C_{max} changes in ranged from -60% to 15%, depending on the tablet formulation tested. In the phase III trials, fostamatinib tablets were taken with or without food according to protocol.

Table 24: Studies Characterizing the Effect of Food on Exposures of R406 from Fostamatinib

Study No.	Formulation Tested	Dose	N	Effect of Food on C_{max} (fed/fasted)	Effect of Food on AUC (fed/fasted)
C788-005	25 mg 8% w/w WU tablet	75 mg	18	↓60%	↑10%
C788-016	50 mg 36% w/w GFC tablet	100 mg	18	↑8%	↑31%
D4300-019	50 mg 25% w/w BFC tablet	150 mg	14	↓7%	↑14%
D4300-019	150 mg 38% w/w OFC-I tablet	150 mg	13	↑15%	↑23%

Distribution

R406 distributed to extravascular sites, and exhibited a volume of distribution at steady-state of 256 L, based on results from a radiotracer study (D4300-027).

Table 7 Summary of key R406 and [^{14}C] R406 pharmacokinetic parameters

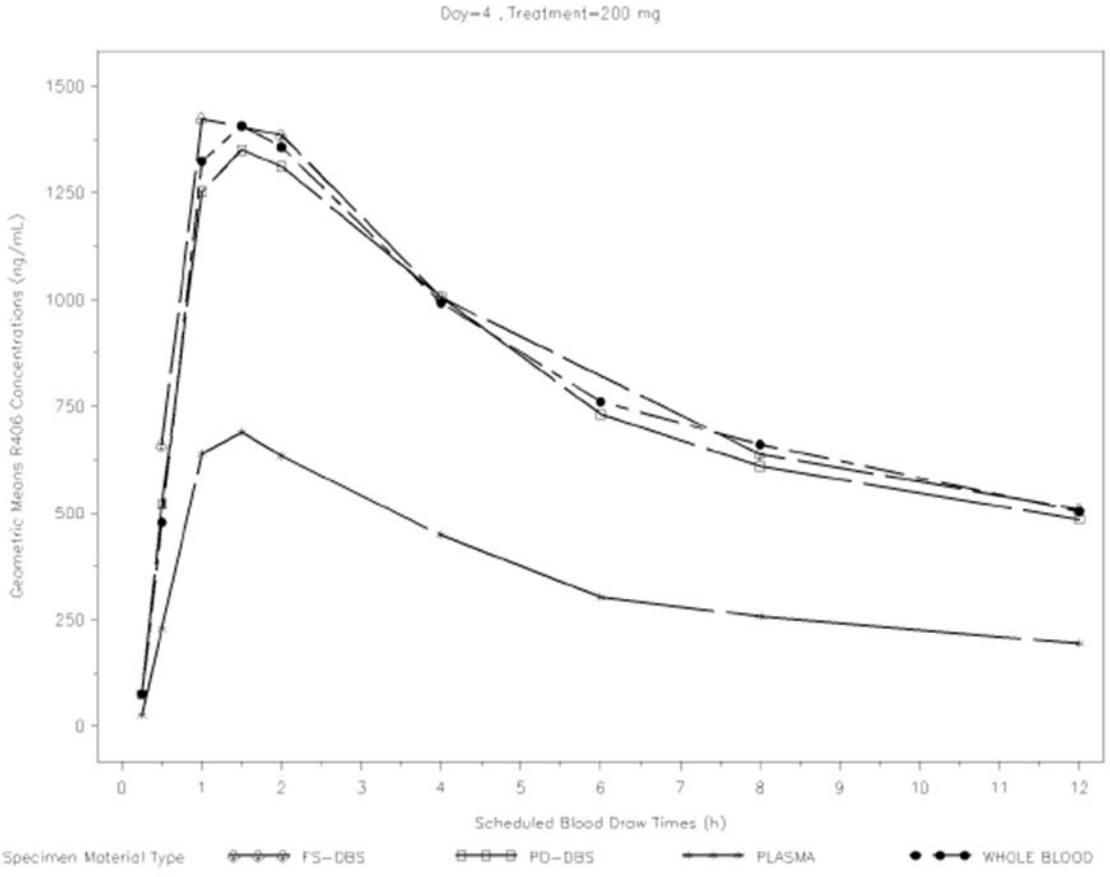
Parameter (unit)	Statistic	R406 (N = 10)	[^{14}C] R406 (N = 9)
AUC (ng·h/mL)	Geo. mean (CV%)	4430 (64.5%)	6.35 (25.1%)
C_{max} (ng/ml)	Geo. mean (CV%)	313 (81.0%)	1.35 (24.8%)
T_{max} (h)	median (min,max)	1.95 (0.5,3.5)	-
$t_{1/2}$ (h)	Geo. mean (CV%)	15.5 (36.0%)	15.3 (30.2%)
MRT (h)	Geo. mean (CV%)	22.2 (43.4%)	16.3 (33.5%)
MAT (h)	Geo. mean (CV%)	2.8 (186.7%)	-
F (%)	Geo. mean (CV%)	54.6 (42.4%)	
	(90% CI)	(42.48, 70.29)	-
CL (L/h)	Geo. mean (CV%)	-	15.7 (25.3%)
V_z (L)	Geo. mean (CV%)	-	345 (39.2%)
V_{ss} (L)	Geo. mean (CV%)	-	256 (37.4%)

Source: Table 11.2.4 and 11.2.5

^{14}C R406 had a mean binding to purified human serum albumin of 96.3%, as tested over the concentration range 100 to 4000 ng/mL and a mean binding to purified alpha 1 acid glycoprotein of 75.5% hence R406 is highly bound to plasma proteins.

Study D4300-032 demonstrated that R406 distributed preferentially into red blood cells at a ratio of approximately 2.5 to blood vs plasma. R406 concentration-time profiles in whole blood and plasma were similar for therapeutic doses of 100 to 200 mg.

Figure 14 **Geometric mean profiles for Day 4 – comparison between PK matrices for R406 concentrations, 200 mg.**



Animal data indicate that R406 distributes into breast milk. Distribution into semen was negligible.

Elimination

The geometric mean half-life of fostamatinib was assessed in single dose studies in healthy human subjects and ranged from 14.2 to 15.5 hours for 150 mg under fasted conditions. Half-life at steady state was investigated in study D4300-007. Half lives were similar for all cohorts (white, Japanese; 50, 100 or 200 fostamatinib bid) and ranged from approximately 12 to 17 hours. Based on results from a radiotracer study (D4300-027), clearance was estimated to 15.7 L/h, indicating that R406 is not a high clearance drug.

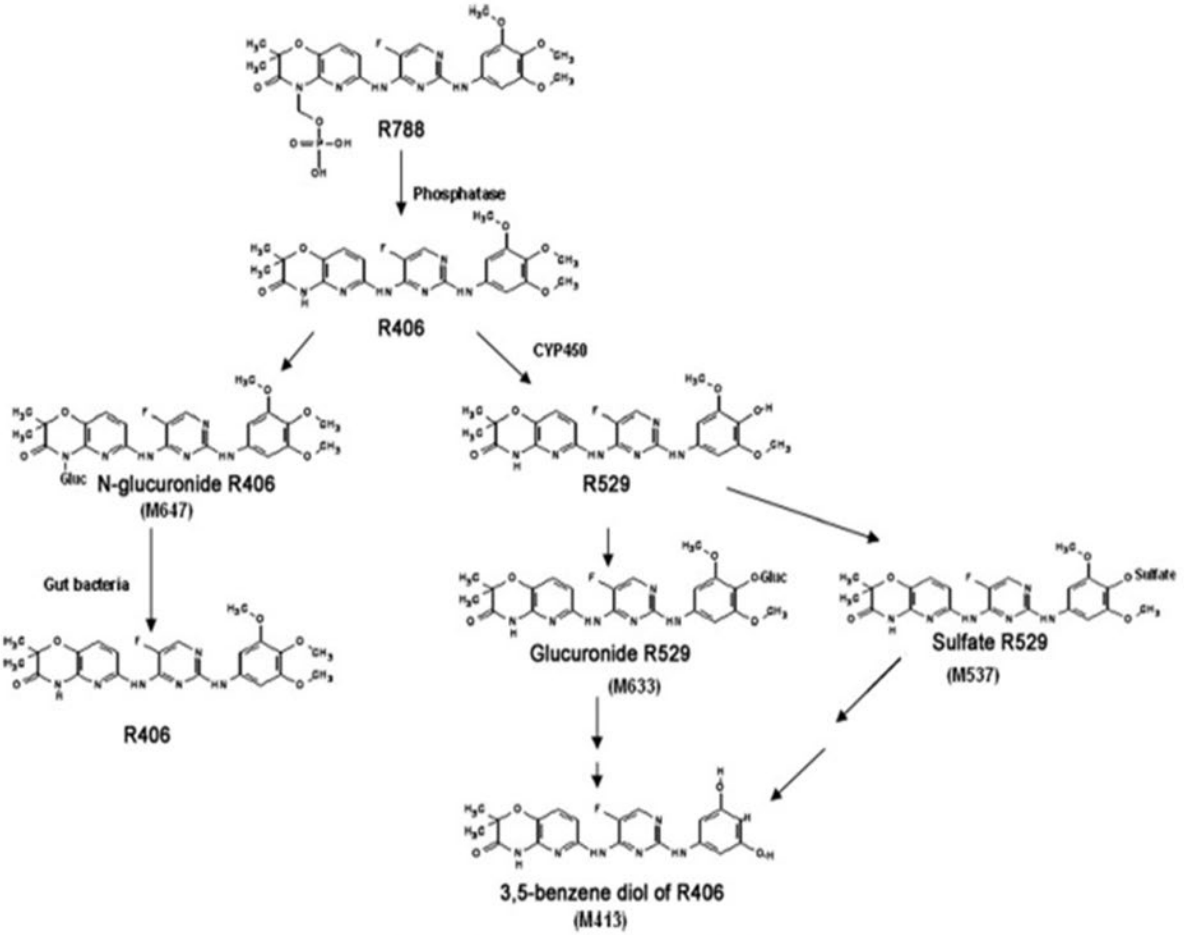
Excretion

The ADME study C788-014 confirmed the in vitro observation that R406 preferentially distributes to blood over plasma. Total radioactivity was excreted via urine and faeces until 192 hours postdose. Overall mean recovery of total radioactivity was 99.3%. Mean recovery of total radioactivity in the faeces and the urine was 80.0%, and 19.3%, respectively. This indicates that R406 is mainly excreted via the faecal route and that renal elimination is of minor importance.

Metabolism

In the mass balance study C788-014 which used [14C]-R788, the metabolism of fostamatinib was characterized. The majority of radioactivity in plasma was associated with R406. R788 was observed only sporadically in plasma. Low levels of metabolites were observed in plasma. These metabolites were identified as an O-glucuronide of a desmethyl R406 metabolite, R406-N-glucuronide, and R949529-sulfate. The radioactivity excreted in urine through 72 hours post-dose consisted of several metabolites and low levels of R788. R406-N-glucuronide was the major metabolite in urine and this urinary metabolite accounted for 13.9% of the administered dose.

The majority of the radioactivity excreted in feces was associated with the 3,5-benzene diol of R406 and R406, accounting for 30.6% and 29.8% of the resolved fecal radioactivity, respectively. No unchanged R788 was detected in feces. In summary, R406 was found to undergo both oxidation and direct glucuronidation with excretion in the faeces as the main elimination pathway.



SCHEME 1. Proposed scheme of R788 metabolism in humans.

Consequences of possible genetic polymorphism

Study D4300-007 evaluated the relationship between variations in the gene encoding UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) in Japanese and white male HV. UGT1A1 is

involved in the metabolism of fostamatinib, and mutations in the UGT1A1 gene has been identified in the literature.

Table 8 **Crosstabulation of UGT1A1 Risk Alleles Showing Number and Percentage of Subjects with each Genotype Result by Ethnicity Group Cohorts 1 to 7 (Safety Population)**

			UGT1A1*6			
	Ethnicity		*1*1	*1*6	*6*6	Total
UGT1A1*28	Japanese	*1*1	20 (50.0%)	13 (32.5%)	1 (2.5%)	34 (85.0%)
		*1*28	6 (15.0%)	0 (0.0%)	0 (0.0%)	6 (15.0%)
	N = 40	*28*28	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
		Total	26 (65.0%)	13 (32.5%)	1 (2.5%)	40 (100.0%)
UGT1A1*28	Non-Japanese	*1*1	5 (31.3%)	0 (0.0%)	0 (0.0%)	5 (31.3%)
		*1*28	8 (50.0%)	1 (6.3%)	0 (0.0%)	9 (56.3%)
	N = 16	*28*28	2 (12.5%)	0 (0.0%)	0 (0.0%)	2 (12.5%)
		Total	15 (93.8%)	1 (6.3%)	0 (0.0%)	16 (100.0%)

Denominator for each percent is the number of subjects observed in the given Ethnicity group.
Source: Section 11, Table 11.1.1.11

The effect of fostamatinib on genetic polymorphisms of UGT1A1 has not been fully established. The sparse data indicate that certain UGT1A1 genotypes may get elevated unconjugated bilirubin levels after long term use of fostamatinib. A warning is stated in the SmPC regarding increased risk of hyperbilirubinemia in patients with genetic polymorphisms of UGT1A1 e.g. Gilbert.

Dose proportionality and time dependencies

Fostamatinib appears to be dose proportional within the therapeutic range and up to doses of 200 mg bid. Higher doses lead to a greater than proportional exposure. Steady state is reached after 3-4 days.

Table 4: **Comparison of Dose-Normalized C_{max} and AUC/AUC_{ss} of Fostamatinib to Healthy Subjects**

Study	Doses	Doses (mg/mg)	Dose Ratio	C_{max} Ratio	AUC Ratio
Single dose					
C788-001	80, 250, and 400 mg suspension	400/80	5.0	4.0	4.3
	80, 250, and 400 mg suspension	250/80	3.1	3.7	4.4
C788-008	100, 200, and 300 mg white tablets	300/100	3.0	3.5	2.9
	100, 200, and 300 mg white tablets	200/100	2.0	2.5	2.7
D4300-007	50, 100, 150, and 200 mg BFC tablets	200/50	4.0	2.4	2.0
	50, 100, 150, and 200 mg BFC tablets	150/50	3.0	3.8	2.8
	50, 100, 150, and 200 mg BFC tablets	100/50	2.0	2.1	1.9
D4300-018	100 and 150 mg BFC tablets	150/100	1.5	1.5	1.5
D4300-020	100 and 150 mg OFC-I tablets	150/100	1.5	1.3	1.4
D4300-032	100 and 200 mg BFC tablets	200/100	2.0	2.0	1.9
Steady-state (*bid*)					
C788-013	100 and 300 mg BFC tablets *bid*	300/100	3.0	3.9	4.0
D4300-007	50, 100, and 200 mg BFC tablets *bid*	200/50	4.0	5.1	5.5
	50, 100, and 200 mg BFC tablets *bid*	100/50	2.0	1.8	1.8
D4300-032	100 and 200 mg BFC tablets *bid*	200/100	2.0	3.3	3.4

AUC: area under the plasma concentration versus time curve from time zero to infinity; AUC_{τ}: area under the plasma concentration versus time curve during one dosing interval; BFC: blue film-coated; C_{max}: maximum plasma drug concentration; CI: confidence interval.
Data derived from Appendix 1 or from m2.7.1, Appendix 1.

With a half-life about 16 hours and a dosing interval of 12 hours the expected AR would be around 2.3. In study D4300-007, the accumulation rate for the 200 mg BID dose was larger than expected, 6.55 probably due to a low Day 1 exposure. No time dependency was observed in the Pop PK analysis and no unexpected accumulation after long term use is expected.

Table 5: Summary of Geometric Mean R406 Accumulation Ratios (CV%)

Study	Race	Study Type	Dose	Accumulation Ratio
C788-001	White	Volunteer SAD/MAD	160 mg *bid*	2.54 (24.4)
C788-003	White	Volunteer MAD	250 mg *bid* Day 7	4.04 (40.0)
			250 mg *bid* Day 20	3.34 (58.2)
C788-004	White	Methotrexate DDI patients	100 mg *bid*	3.46 (38.7)
D4300-007	Japanese	SAD/MAD	50 mg *bid*	2.39 (35.4)
			100 mg *bid*	2.22 (18.1)
			200 mg *bid*	6.55 (52.1)
D4300-032	Japanese	J200	100 mg *bid*	2.06 (44.6)
			200 mg *bid*	3.54 (34.4)

DDI: drug-drug interaction; MAD: multiple ascending dose; SAD: single ascending dose.

Intra- and inter-subject variability

Intra- and inter-subject variability observed in both healthy volunteer as well as target patient studies is high. The typical inter-subject variability in exposure was ~ 35% coefficient of variation (CV) for AUC and ~ 50% – 60% CV for C_{max}, and intra-subject variability in exposure is ~ 18%–27% CV for AUC and ~ 31%–43% CV for C_{max} in the PK studies in healthy volunteers.

Pharmacokinetics in target population

In the Phase 3 clinical studies C788-047 and C788-048, PK blood samples were collected at Weeks 2, 6, and 24 visits. Table 11-10 shows PK data from CSR C788-047 with sampling at multiple time points.

Table 11-10: Mean R406 Plasma Concentrations (ng/mL) in ITP Subjects after BID Administration of Fostamatinib

	R406 Plasma Concentrations (ng/mL)					
	Week 2		Week 6		Week 24	
Time (h)	n	Mean (SD)	n	Mean (SD)	n	Mean (SD)
0	1	532 (nc)	2	430 (202)		na
1	6	476 (203)	8	775 (249)		na
2	6	334 (105)	5	518 (198)	2	1160 (430)
4	13	537 (238)	8	773 (537)	2	493 (412)
6	4	348 (62.1)	5	639 (398)	2	595 (137)
8	1	329 (nc)	1	406 (nc)	0	-
12	7	392 (178)	6	552 (276)	3	361 (166)
14	6	300 (246)	9	425 (343)	1	658 (nc)

Source: Table 14.3.13.
SD = standard deviation; nc = not calculable; na = not available
Note: Means and SDs expressed to three significant digits.

In clinical extension study (C788-049) pharmacokinetic parameters were estimated for R406 in ITP patients (Table 11-5). In this study, steady-state AUC and C_{max} estimates were within the range of exposure obtained in earlier healthy volunteer studies.

Table 11-5: Estimated Average Pharmacokinetic Parameters for R406 in ITP Patients Following 150 mg Dose of Fostamatinib

Variable	N	Average (± SD)	Geometric Mean
T_{max} (h)	12	2.17 ± 2.33	1.55
C_{max} (ng/mL)	12	810 ± 289	769
AUC_{0-8} (ng•h/mL)	12	4340 ± 1640	4090
AUC_{0-12} (ng•h/mL)	10[a]	5450 ± 2210	5120

Source: PK Report Study Number C-935788-049 (Appendix 16.5.1, Table 3).
Note: AUC_{0-8} = area under the curve from time of dosing to 8 hours; AUC_{0-12} = area under the curve from the time of dosing extrapolated to 12 hours; C_{max} = maximum observed concentration; ITP = immune thrombocytopenic purpura; SD = standard deviation; T_{max} = time of maximum observed concentration.
[a] Half-life could not be calculated for Subjects 447-460-003 and 447-486-001, therefore no AUC_{0-12} values were calculated for these two subjects.

The population PK model included data from 10 Phase I studies in healthy volunteers, four phase II studies and three phase III studies in patients with rheumatoid arthritis and finally, data from the three phase III studies in patients with ITP. The vast majority of data derives from earlier development stages, therefore it is expected that the addition of 332 observations from ITP patients would have limited influence on the model established using the available 17712 data points from healthy subjects and RA patients. Model-predicted fostamatinib average $DAUC_{ss}$ in ITP patients was 10232 ng*h/mL for the 100 mg bid and 15101 ng*h/mL for the 150 mg bid of fostamatinib (Table 4).

Table 4 Summary Statistics of Estimated R406 Selected Pharmacokinetic and Exposure Parameters in ITP Subjects

Treatment	Body Weight (kg)	CL (L/h)	V2 (L)	$DAUC_{ss}$ (ng*h/mL)
100 mg Twice Daily Dose				
Mean	80.4	21.7	544	10232
SD	21.3	7.05	188	3688
Min	47.2	7.15	279	4441
Median	80	21.1	516	9478
Max	163	45.0	1273	27961
150 mg Twice Daily Dose				
Mean	81.1	23.7	512	15101
SD	36.9	8.62	292	8372
Min	48	6.53	278	6970
Median	74.5	23.2	416	12942
Max	204	43.0	1523	45907

While it appears from the Pop PK model that clearance was comparable between healthy volunteers and RA patients, volume of distribution is 3-fold higher in RA patients.

Special populations

Impaired renal function

The dedicated study (D4300-009) in patients with renal impairment, including end stage renal disease demonstrated that AUC and C_{max} were lower in both groups with renal impairment compared to subjects with normal renal function. However, R406 is highly bound to plasma proteins, and AUC for the unbound fraction was similar across groups. Half-life and T_{max} were also similar and there was no relevant relationship between R406 PK and creatinine clearance identified. The amount of R406 N-glucuronide recovered in urine decreased with decreasing renal function at 14.7 mg, 7.56 mg, and 0.518 mg for normal, moderate, and ESRD groups, respectively, but urinary excretion was minimal across groups in line with what was also demonstrated in the mass-balance study. Less than 1% of the dose of R406 cleared by dialysis.

Table 8 **Statistical comparison of R406 key pharmacokinetic parameters between renal groups**

				Comparison to normal renal function group (Group 1)	
Parameter	**Renal group[a]**	**N**	**Geometric LS mean**	**Ratio (%)**	**90% CI**
AUC (ng*h/mL)	Group 1	8	7384		
	Group 3	6	5786	78.36	(52.40, 117.18)
	Group 5	8	5451	73.83	(50.86, 107.16)
C_{max} (ng/mL)	Group 1	8	693.9		
	Group 3	8	400.7	57.74	(35.81, 93.10)
	Group 5	8	429.8	61.94	(38.49, 99.69)

Source: Table 11.2.5.
RI renal impairment.
Treatment Period 2 for end stage was not included in this analysis. Results based on linear mixed effect analysis of variance model with renal group as fixed effects. Body mass index was included as a continuous effect only for the C_{max} parameter.
[a] Normal: Normal renal function (Group 1). CL_{CR} >=80 mL/min; 150 mg (3 x 50 mg tablets) fostamatinib on Day 1 of single treatment period;
Moderate: Moderate RI (Group 3). CL_{CR} >=30 mL/min but < 50 mL/min; 150 mg (3 x 50 mg tablets) fostamatinib on Day 1 of a single treatment period;
End stage: (Group 5). Currently requiring dialysis.
Treatment Period 1: Group 5, 150 mg (3 x 50 mg tablets) fostamatinib on Day 1, after completion of dialysis session.

Impaired hepatic function

Subjects enrolled in the dedicated hepatic impairment study (D4300-010) were 8 with mild hepatic impairment (Child-Pugh Class A), 8 with moderate hepatic impairment (Child-Pugh Class B), 8 with severe hepatic impairment (Child-Pugh Class C), and 8 with normal hepatic function.

Hepatic impairment have no consistent effect on PK of R406. As fostamatinib can cause elevation of liver enzymes and hepatotoxicity, fostamatinib should not be used in ITP patients with severe hepatic impairment and liver function should be monitored in patients with mild to moderate hepatic impairment as stated in the SmPC.

Table 8 Statistical comparison of R406 primary pharmacokinetic endpoints

Parameter	Hepatic group[a]	N	Geometric LS mean	Comparison to normal hepatic function group	
				Ratio (%)	90% CI
AUC (ng*h/mL)	Group 1	8	6387	71.21	(51.48, 98.49)
	Group 2	8	6858	76.46	(55.28, 105.75)
	Group 3	8	9490	105.80	(74.69, 146.33)
	Group 4	8	8970		
C_{max} (ng/mL)	Group 1	8	614.6	88.81	(60.63, 130.09)
	Group 2	8	602.3	87.02	(59.41, 127.48)
	Group 3	8	582.1	84.11	(57.42, 123.20)
	Group 4	8	692.1		

Results based on linear model with hepatic function group as a fixed effect. Fostamatinib 150 mg (three 50-mg tablets) was administered as a single oral dose with 240 mL of water.

[a] Group 1: mild hepatic dysfunction – Child-Pugh Category A.
Group 2: moderate hepatic dysfunction – Child-Pugh Category B.
Group 3: severe hepatic dysfunction – Child-Pugh Category C.
Group 4: normal hepatic function.

Source: Table 11.2.4.

Gender

Gender is not a significant covariate by itself, and the same dose is proposed for both men and women.

Race

Specific studies were conducted to assess the PK of R406 in Japanese male subjects compared with white male subjects. There was no consistent PK differences of R406 following fostamatinib dosing in Japanese and Western subjects. In the population PK analysis, race did not emerge as a significant factor for variability in exposure. The vast majority of subject in the Pop PK analysis were white, and only 70 subjects with Asian origin were included.

Weight

The thorough QT Study C788-013, included comparable numbers of males and females and included an analysis of gender effects. The data show slightly higher AUC_{ss} in females; however, when adjusted for body weight the exposure values are similar indicating that the exposure difference is primarily due to lower body weight in females.

Table 6: Mean (SD) PK Parameters of R406 on Day 4 by Gender – Study C788-013

PK Parameter	Fostamatinib 100 mg *bid*		Fostamatinib 300 mg *bid*	
	Female (n=22)	Male (n=28)	Female (n=23)	Male (=29)
AUC_{ss} (ng•h/mL)	12900 (3580)	10600 (2350)	54300 (19200)	40600 (14600)
AUC_{ss}/Dose/Weight	8610 (2380)	8520 (1860)	11700 (3440)	10900 (3540)

Note: AUC_{ss} is over 24 hours

The Pop PK analysis found body weight to be an important covariate and confirmed that R406 exposure decreases with increase in body weight. AUC_{ss} was almost halved in patients >90 kg compared to patients <50 kg. However, body weight was not significant in the exposure-response population model. It is concluded that body weight – though having an effect on exposure - seems to have little effect on the safety and efficacy of fostamatinib if a fixed dose paradigm is used.

Elderly

Elderly patients aged 65 or older accounted for 14% of the data set in the PK evaluation of fostamatinib; 5 subjects were aged 85 or older. From a PK point of view it is acceptable to use the same dose recommendations in all age groups.

Children

Fostamatinib is not intended for the pediatric population. No PK data in children has been included in the submission. Due to adverse effects on bone metabolism, the PDCO granted a waiver for the complete paediatric population below 18 years of age.

Pharmacokinetic interaction studies

The potential for DDI of fostamatinib and R406 was extensively examined in vitro. The potential interaction of R406 for CYP3A4 inhibition and induction, CYP2C8 induction, inhibition of BCRP and inhibition of P-gp was further investigated in clinical DDI studies. R406 was shown to be a potent inhibitor of human UGT1A1 in vitro. Data from clinical studies C788-047 and -048 indicated plasma bilirubin levels did increase by 22-64%, when ITP patients received fostamatinib. Even though R406 does not show inhibitory activity against UGT2B7, the effect on other UGTs such as UGT1A6 and UGT1A9 remains unclear. The potential of PK DDIs for co-administration with acetaminophen remains undetermined and a warning is included in the SmPC.

A total of 14 clinical interaction studies were performed. Table 8 gives a results summary of in vivo studies where fostamatinib was the victim of DDI evaluated by R406 exposure and table 9 gives a summary of in vivo studies where fostamatinib acts as perpetrator of DDI evaluated by exposure of the concomitant drug.

Table 8: Effect of Co-administered Drugs on Systemic Exposures of R406, Active Metabolite of Fostamatinib

Co-administered Drug	Dose of Co-administered Drug	Dose of Fostamatinib [a]	Geometric Mean Ratio [b] (90% CI)	
			AUC [c]	C_{max}
Ketoconazole	200 mg q12h x 3.5 d	80 mg	2.02 [d] (1.77, 2.30)	1.37 (1.23, 1.53)
Verapamil	80 mg q8h x 4 d	150 mg	1.39 (1.08, 1.80)	1.06 (0.78, 1.44)
Rifampicin	600 mg q24h x 8 d	150 mg	0.25 (0.19, 0.32)	0.41 (0.30, 0.56)
Ranitidine	150 mg single dose	150 mg	0.97 (0.80, 1.18)	0.98 (0.71, 1.34)
Rosuvastatin	20 mg single dose	100 mg *bid*	1.10 (1.04, 1.16)	1.13 (1.02, 1.25)
Simvastatin	40 mg single dose	100 mg *bid*	1.11 (1.01, 1.22)	1.11 (0.98, 1.27)

[a] Single dose unless otherwise noted.
[b] Ratio with/without co-administered drug.
[c] AUC = $AUC_{0-\infty}$.
[d] AUC = AUC_{ss}
q8h=every 8 h; q12h=every 12 h; q24h=every 24 h; d = days.

Table 9: Effect of Fostamatinib on Systemic Exposures of Co-administered Drugs

Co-administered Drug	Dose of Co-administered Drug [a]	Dose of Fostamatinib	Analyte	Geometric Mean Ratio [b] (90% CI)	
				AUC [c]	C_{max}
Methotrexate	Varying [d]	100 mg q12h x 5.5 d	methotrexate	1.12 (0.90, 1.40)	1.01 (0.85, 1.20)
			7-OH methotrexate	1.06 (0.83, 1.36)	1.06 (0.82, 1.35)
Midazolam	7.5 mg	100 mg q12h x 6.5 d	midazolam	1.23 (1.11, 1.37)	1.09 (0.95, 1.25)
Microgynon (Oral Contraceptive)	ethinyl estradiol 30 µg [e]	100 mg q12h x 20.5 d	ethinyl estradiol	1.28 (1.22, 1.36)	1.34 (1.26, 1.43)
	levonorgestrel 150 µg [e]		levonorgestrel	1.05 (0.98, 1.13)	0.97 (0.90, 1.04)
Warfarin	25 mg	100 mg q12h x 13.5 d	R-warfarin	1.18 (1.13, 1.23)	1.02 (0.97, 1.08)
			S-warfarin	1.13 (1.07, 1.19)	0.99 (0.92, 1.06)
Pioglitazone	30 mg	100 mg q12h x 8 d	Pioglitazone	1.18 (1.08, 1.28)	0.83 (0.64, 1.07)
			hydroxyl-pioglitazone	0.90 (0.79, 1.02)	0.91 (0.79, 1.05)
Digoxin	0.25 mg q12h x 1d; then 0.25 mg q24h x 14d	100 mg q12h x 7 d	digoxin	1.37 (1.30, 1.46)	1.70 (1.46, 1.98)
Rosuvastatin	20 mg	100 mg q12h x 9 d	rosuvastatin	1.95 (1.77, 2.15)	1.88 (1.69, 2.09)
Simvastatin	40 mg	100 mg q12h x 7 d	simvastatin	1.64 (1.33, 2.02)	2.12 (1.64, 2.74)
			simvastatin acid	1.66 (1.46, 1.89)	1.83 (1.57, 2.13)

[a] Single dose unless otherwise noted.
[b] Ratio with/without co-administered drug.
[c] $AUC_{0-\infty}$ for midazolam, warfarin, and pioglitazone; AUC_{tt} for ethinyl estradiol, levonorgestrel and digoxin, rosuvastatin, and simvastatin, and AUC_{0-48h} for methotrexate.
[d] Methotrexate doses were individualized (actual dose range 8 to 23 mg/week).
[e] Subjects were using Microgynon at least 3 months prior to study and continued on prescribed 28 day cycles throughout study period.
q12h = every 12 hours; q24h = every 24 h; d = days.

No clinical effects considered relevant for change of posology were demonstrated when fostamatinib was given concomitantly with either verapamil, ranitidine, methotrexate, midazolam, microgynon (contraceptive), warfarin or pioglitazone.

With ketoconazole, a potent CYP3A4 inhibitor, R406 plasma exposure increased 2-fold (average increases in C_{max} and AUC of 37% and 102%, respectively) when subjects received a single 80 mg dose of fostamatinib on top of ketoconazole given 200 mg twice daily for 3.5 days. A warning that concomitant administration of fostamatinib and a strong CYP3A4 inhibitor may warrant reduction in dose frequency (BID to QD) is stated in the SmPC.

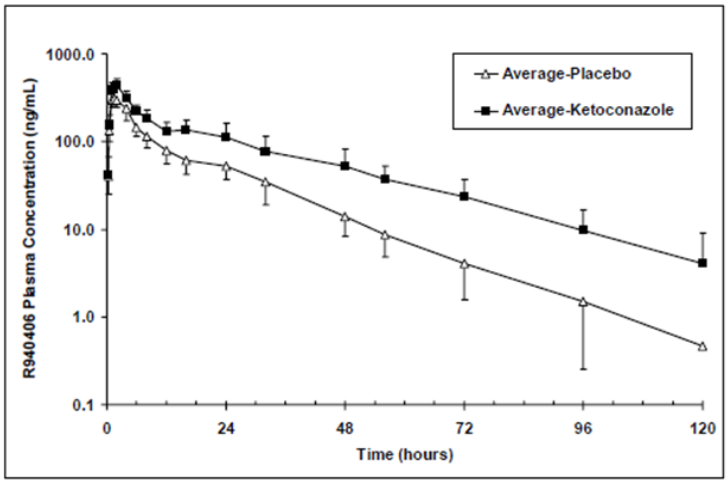
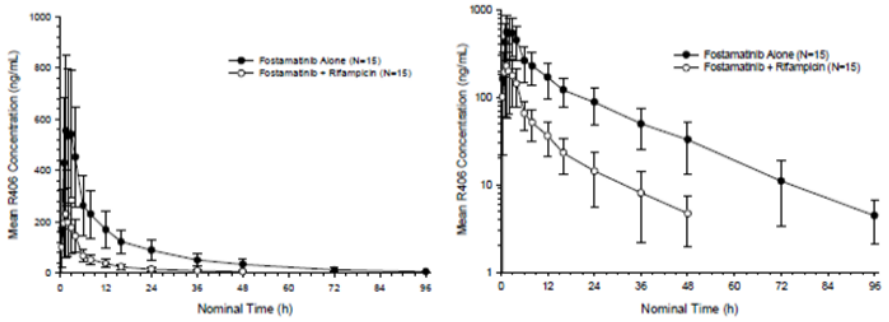


Figure 5: Average R940406 Plasma Concentrations (ng/mL) Following Co-Administration of 80 mg R935788 With Ketoconazole or Ketoconazole Placebo in Healthy Normal Volunteers (mean ± SD, n = 8)

A single dose of 150 mg fostamatinib was administered alone and in combination with the strong CYP3A4 inducer, rifampicin 600 mg given qd for 8 days. R406 exposure (as AUC) was reduced by 75% in combination with rifampicin. Concomitant use of fostamatinib with strong CYP3A4 inducers is not recommended.

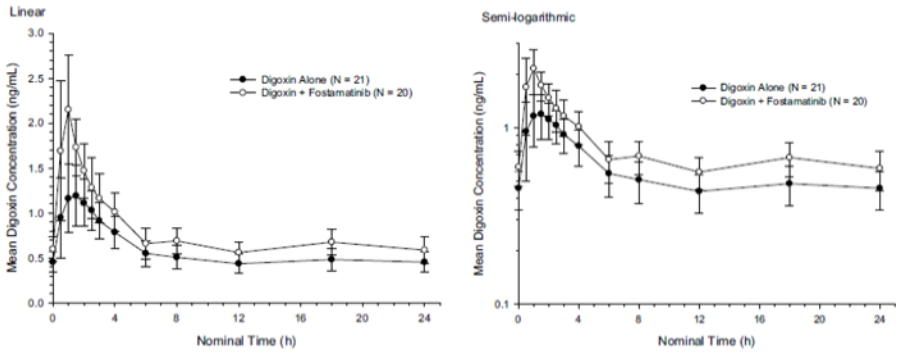
Figure 1 **Arithmetic mean (±SD) R406 plasma concentration time profiles by treatment on linear and semi-logarithmic scales**



Source: Table 11.2.1

Fostamatinib was an inhibitor of the human P-gp efflux transporter in Caco-2 cells. Digoxin, a P-gp substrate, dosed 0.25 mg qd for 15 days was given alone or co-administered with fostamatinib 100 mg bid for 7 days. Co-administration with fostamatinib increased digoxin exposure by 34% (Ae0-24) in urine and by 37% (AUC) and 70% (C_{max}) in plasma.

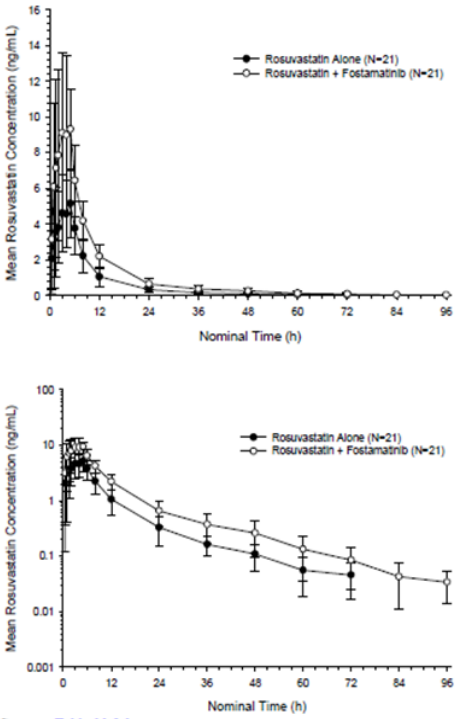
Figure 2 **Arithmetic mean (±SD) digoxin concentration-time profiles by treatment on linear and semi-logarithmic scales**



Source: Table 11.2.1

The potential of multiple doses of 100 mg bid fostamatinib for interaction with two statins rosuvastatin (a BCRP substrate) and simvastatin (a CYP3A4 substrate) was investigated in two separate groups each consistent of 21 healthy subjects. A single dose of 20 mg rosuvastatin or 40 mg simvastatin was dosed with or without fostamatinib. Steady-state PK of R406 was also assessed. In the rosuvastatin group multiple dosing with fostamatinib resulted in increased AUC and C_{max} of rosuvastatin with 96% and 88%, respectively.

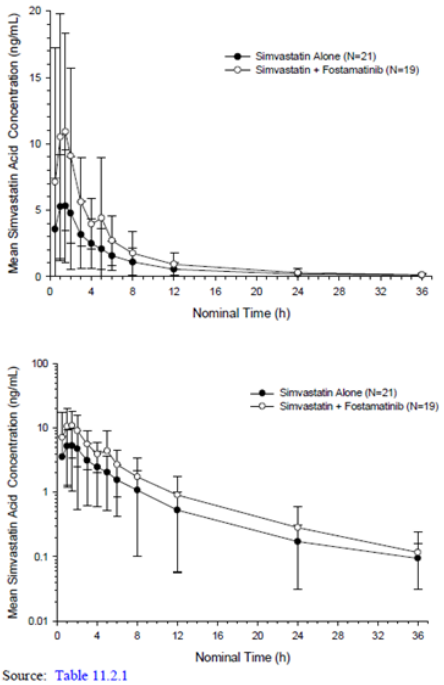
Figure 2 **Arithmetic mean (±SD) rosuvastatin plasma concentration-time profiles by treatment on linear and semi-logarithmic scales**



Source: Table 11.2.1

In the simvastatin group, multiple dosing with fostamatinib increased simvastatin exposure both in its lactone and acid forms. AUC increased by 64% and Cmax by 113% for simvastatin while AUC increased by 74% and C_{max} 83% for simastatin acid.

Figure 6 **Arithmetic mean (±SD) simvastatin plasma concentration-time profiles by treatment on linear and semi-logarithmic scales**



Source: Table 11.2.1

R406 exposures were slightly higher when fostamatinib was combined with rosuvastatin or simvastatin.

Drug reduction of CYP3A4 substrates may be warranted when given concomitantly with fostamatinib. For rosuvastatin, shift to another treatment should be considered and for digoxin additional therapeutic drug monitoring could be necessary.

2.4.3. Pharmacodynamics

Mechanism of action

Fostamatinib is a pro-drug of the biologically active metabolite R406. R406 inhibits signaling from receptors systems mediated by immunoreceptor tyrosine-based activation motifs (ITAM) that are dependent on SYK. Its inhibition of the FcR, BCR, and C-type lectin receptors (CLR) signaling pathways makes it a potentially broadly applicable anti-inflammatory and immunomodulatory agent. In ITP, R406 appears to ameliorate platelet destruction by interrupting the FcR signaling mediated by SYK und preventing undesired cell clearance and is expected to lead to an increase in platelet counts. Several ITP mouse model studies showed that pretreatment with fostamatoinib significantly protected mice from antibody-induced thrombocytopenia. Increase in platelet counts is the primary pharmacodynamic target of interest in the targeted population of ITP patients. In the phase 3 confirmatory studies conducted in ITP patients, the primary endpoint was achievement of a stable platelet response by Week 24 defined as a platelet count of at least 50,000/µL on at least 4 of the 6 visits between Weeks 14-24.

Dose selection

The 100 mg dose twice daily was supported by data generated from study C788-001 conducted in healthy subjects, for which a biomarker assay measuring the activation of peripheral blood basophils following ex vivo anti-IgE stimulation was developed. Basophils degranulate upon activation (a Syk-dependent process), an event that coincides with increased surface expression of CD63. Measuring the percentage of CD63+ basophils in blood samples obtained after R406 dosing, normalized to predose samples, may provide an indicator for the inhibitory effect of R406 on the Syk signaling pathway. The clinical relevance of the PD marker in relation to ITP has not been established. PK profiles of R406 were obtained in healthy human subjects, following single oral doses at 80-600 mg and multiple doses at 100-300 mg, bid. A sigmoidal E_{max} equation was used to model the plasma R406 concentrations and the PD effects of R406. The R406 plasma concentration that produced a 50% reduction of the PD effect was 496 ± 42.2 ng/mL (~ 1.06 µM). This would translate to a daily AUC requirement of approximately 12,000 ng×h/mL (~ 496 ng/mL×24h) and would correspond to the average R406 exposure at the 100 mg dose in healthy volunteers (ranged between 4,400 to 7,020 ng×h/mL per dose interval, i.e. corresponding to daily exposure of 8,800 and 14,000 ng×h/Ml). While the model is to be considered exploratory only, as it is not clear whether the employed biomarker of CD63 expression is an accurate surrogate of the effect of R406 on platelet counts, it nevertheless supports the use of the bid 100 mg dose regimen. Use of the bid 100 mg dose was furthermore justified by results gained in RA patients:

a) the bid 50 mg dose did not result in significant improvement in the ACR score and

b) did not result in significantly decreases from baseline of two biomarkers (MMP-3 and IL-6) of inflammation measured after 12 weeks of treatment (study C788-006).

A higher dose of 250 mg bid for 21 days investigated in healthy subjects (Study C788-003), was considered to be above the maximum tolerated dose. More specifically, the study duration was reduced to 20 days due to the negative safety profile and, overall, 50% of the subjects in the fostamatinib treatment group discontinued due to adverse events (elevated transaminases, leukopenia, nausea/vomiting/dizziness and rash).

From the escalating phase 2 study conducted in ITP patients where doses between 75 and 175 mg were investigated (Study D4300-022), no robust conclusions can be drawn regarding efficacy/safety response. Further analyses of dose exposure response in terms of efficacy and safety employing a PK/PD model approach did not provide any further insight compared to the separate study results.

Summarizing, the 100 mg dose administered twice daily seems to have been selected based on the assumption of the best benefit risk balance, thereby allowing a dose increase to 150 mg bid or a decrease to 100 mg sid, depending on the observed platelet response and the occurrence of side effects.

Primary and Secondary pharmacology

Effect on the immune system

A reduction of CD63+ basophils was observed in healthy subjects and was attributed to SYK-inhibition. A clear trend for a reduction in monocytes bearing CD14 was also shown, but the mechanism behind this phenomenon could not be fully elucidated. It is however postulated to be an effect of R406 on survival, shedding or internalization of the marker or compartmentalization and not to be a result of an effect on production of these cells. It is also suggested that SYK kinase inhibition in resting monocytes does not

interfere with Fc receptor (CD64) expression. Overall, it is considered that the reduction of monocytes, although at times shown to be substantial (up to 65% in study C406-001), „unlikely to affect the immune system due to functional redundancy and the immune system's resilience to all but most drastic changes in cell numbers". A further effect of R406 was suggested on T cell responses based on the modest effect on the level of expression of CD86 (mfi) on the CD14+ cells in study C406-001. The clinical relevance thereof remains however unclear. What seems to be the most relevant effect on the immune system is the clear trend for a decrease in neutrophils (with a corresponding increase in lymphocytes) that was observed across the healthy volunteers' studies, especially in the higher dose cohorts (studies C406-001 and C788-003), and which was confirmed in the clinical studies conducted in ITP patients. The potential mechanism behind neutropenia may be related in part to the off-target effect inhibitory effect on some kinases to be involved in haemotopoiesis such as VEGF, but is not entirely clear. In RA patients, a significant decrease from baseline for two biomarkers, namely mean MMP-3 and IL-6 concentrations, was furthermore demonstrated for the 100 and 150 mg bid treatment groups after 12 weeks of treatment, further underpinning the broad action on the immune system.

Overall, the clinical relevance of these broad effects on the immune system seems uncertain. Higher incidences in infections in the fostamatinib group compared to placebo have been observed in ITP and RA patients and a potential causal relationship of fostamatinib treatment with the occurrence of infections cannot be entirely ruled out at the current stage. Results from non-clinical studies do however not point to a significant effect of fostamatinib on the immune system. Based on the animal models provided, Fostamatinib does not appear to have immunosuppressive effects. No increase in tumor incidence was noted in the carcinogenicity studies and there was no evidence for increases in opportunistic infections in any of the species in the toxicology program (rodents, rabbits, and monkeys).

In conclusion, while it is agreed that short term administration might not impact on the immune system to a clinically relevant extent in ITP patients, as shown by the reversibility of effects after termination of therapy, effects of long-term administration do not seem to be as well characterised, with remaining open questions on the mechanism behind the reduction of monocytes and neutrophils and on a potential causal relationship with the occurrence of infections.

Effect on platelet function

R406 selectively inhibited SYK-dependent platelet aggregation induced by collagen-related peptide and collagen. In a Phase 1 study of fostamatinib in healthy human subjects (study C406-001) that achieved supratherapeutic concentrations of R406, there was no effect on collagen- or adenosine diphosphate (ADP)-induced platelet aggregation at any time-point measured (single dose part A: Day 1 pre-dose, 2 and 4 hours post-dose; multiple dose part B: Day 1 pre-dose and 4hours post-dose and Day 7 pre-dose and 4 hours post-dose). Reference is however made to the non-clinical results, where the combination of ASA and R406 strongly increased the RTBF at all doses tested and similar data was also observed with time to occlusion (TTO).

Effect on QT prolongation

In a dedicated QT/QTc study (C-935788-013), which was a randomized, double-blind, double-dummy, comparative, placebo and active controlled parallel study, the effect of 100 and 300 mg twice daily administration of Fostamatinib for 4 days on the duration of QT intervals was evaluated. Assay sensitivity was adequately established. The response of QTcF at the two doses was comparable, except for the late observation period, where the 300 mg group had slightly higher mean values. For all observations, for both doses, the upper bounds of the 95% one-sided confidence intervals were however below 10 msec.

The maximum placebo-subtracted change in QTcF increase at any observation for either R788 dose group was 5.83 msec and the largest upper confidence bound was 8.72 msec, both in the 300 mg group at 23.5 hours post dose. Considering that the largest QTcF increase from baseline was observed at 23.5 hours, a late effect of a slowly increasing metabolite could have been assumed and was discussed by the Applicant. As this was the only observation of higher values in the whole sampling period of Day 4, a late effect of a potential metabolite's concentration that would be slowly increasing seems however unlikely.

A mild HR reduction was noted (statistically significant after placebo subtraction). For the 100 mg group, the maximum placebo-subtracted HR change was -3.99 bpm and for the 300 mg group -6.64 bpm, both at 3.5 hours. This was consistent with pre-clinical data, where a slight reduction in heart rate and increase in RR interval was noted at 50 mg/kg in the cardiovascular study. Overall, this is not considered to be of significant clinical impact.

There was no evident exposure-response relationship between placebo-subtracted changes in QTcF and serum concentration of R406. Females showed higher concentration levels compared to male. This was however attributed to the lower body weight and a higher weight-normalized dose received by females. Results of further analyses provided no indication that R788 has a clinically meaningful effect on QTcF among females compared to males.

Based on the results from this study, it is concluded that a twice daily administration of fostamatinib up to 300 mg (supratherapeutic dose) is not expected to prolong the QT interval at therapeutic doses to a clinically significant degree. Of note, also the clinical phase 3 studies did not show any cardiovascular safety signals.

Tyrosin kinase inhibitors class effects

R406 was profiled in broad kinase panels utilizing different biochemical assays indicating a range of potential activities, some of which were confirmed or qualified by relevant cell-based assays. Using cell-based assays, R406 inhibits the kinase activity of RET proto-oncogene (RET), vascular endothelial growth factor receptor-2 (VEGFR-2), FMS-related tyrosine kinase 3 (FLT3), Janus kinase (JAK)1/3, and KIT proto-oncogene receptor tyrosine kinase (KIT) within 5-fold of R406 activity against the SYK assay. Bearing these results in mind, it is noteworthy that a class effect of tyrosine kinase inhibitors on bone metabolism has been suggested (*Effects of tyrosine kinase inhibition on bone metabolism: untargeted consequences of targeted therapies; Endocrine-Related Cancer 21, 3; R247–R259*). By targeting a broad range of TKIs (all of which are involved to some extent in the bone metabolism with either potentially deleterious or favourable effects), it is difficult to accurately estimate the risk that is related to bone metabolism, especially for long term administration in patients at risk (e.g. elderly, patients with concomitant steroid treatment, patients with osteoporosis/osteopenia, patients with fractures or young adults where epiphyseal fusion may not have entirely occurred); this has been capture in the imposed PASS included in the annex II.

Chondrodystrophy/growth plate dysplasia and ovarian changes (VEGFR inhibition)

Chondrodystrophy/growth plate dysplasia was observed in juvenile animals (1-month study in juvenile rabbits showed growth plate dysplasia in the proximal femur and femoro-tibial joint; chondrodystrophy of the femoral head in rats in toxicity studies), which seems attributable to be likely related to the off-target inhibition of VEGFR.

A further observed non-clinical finding was the increased occurrence of degenerate/necrotic ovarian follicles in juvenile rabbits. This was also argued to be consistent with an off-target anti-angiogenic effect (VEGFR inhibition). In the developmental toxicity study in adult rabbits (G-935788-0006), the mean number of corpora lutea and implantations compared favourably with the control across all groups. There was no

evidence, for degenerate/necrotic ovarian follicules at necropsy in this rabbit-study. Furthermore, these ovarian follicular changes were not reported in any other study in rodents or in primates included in the chronic and carcinogenicity studies up to 2 years in duration.

It is therefore concluded that, from a clinical perspective, an absolute risk on fertility for women (and girls) with childbearing potential who may desire to have children in the future seems to be rather unlikely.

These findings of chondrodystrophy/growth plate dysplasia should not be an issue in adults, as these would be limited to actively growing bones (before growth plate closure). Therefore subjects < 18 years of age are excluded for treatment of fostamatinib. Epiphyseal fusion of the femoral head and the pelvic bone may also occur as late as 18 years of age or even later and should be considered in this regard. Since fostamatinib was shown *in vitro* to target also other tyrosine kinases that are involved in the bone metabolism (e.g., VEGFR, RET), any potential untargeted effects on bone remodelling or formation remain undetermined, especially in patients with osteoporosis, patients with fractures or young adults where epiphyseal fusion has not yet occurred. Closer monitoring in these patients is therefore recommended. The benefit risk of continuing therapy during the healing of a bone fracture should be thoroughly evaluated by the physician.

Hypertension (VEGFR inhibition)

R406 was shown to potently inhibit the auto-phosphorylation of VEGFR-2 kinase. VEGF plays a role in blood pressure regulation by causing vasorelaxation via nitric oxide (NO) release from the endothelium, and inhibition of VEGFR-2 has been shown to elevate BP both in nonclinical species and in humans. At this time, it is however not known if VEGFR inhibition is the sole mechanism behind BP elevation, given that R406 also inhibits other kinases that are potentially involved in BP regulation.

Changes in blood pressure have been evaluated in an ambulatory blood pressure (BP) monitoring study in 135 RA patients following 100 mg bid dosing of fostamatinib for 28 days (study D4300-033). Increases in systolic and diastolic BP were observed after 28 days with a mean treatment-related increase of 2.93 (95% CI of 0.40 to 5.45) and 3.53 mm Hg (95% CI of 2.04 to 5.03) over placebo changes, respectively. In the fostamatinib group, mean changes from baseline were evident by Day 8, and subsequently plateaued up to Day 29. No patients had clinic BP ≥180/110 mmHg. The BP effect appeared to be reversible within 1 week following discontinuation of dosing.

Consistent with the results from this study, comparable increases in blood pressure were observed in healthy volunteers and in patients with ITP, the latter population showing in several cases a category two or three shift in blood pressure. Available data suggest that subjects already suffering from pre-existing hypertension or receiving oral steroids be more likely susceptible for an increase in blood pressure. Adequate justification has been provided that the effect on changes in blood pressure of R406 appears to be dose-dependent, and therefore, a dose reduction is appropriate if blood pressure increases during treatment.

RET inhibition

R406 was shown a potent inhibitor of RET kinase in vitro and in cells, and inhibition of this protein has been linked to urogenital and major vessel defects in developmental toxicity studies in both rabbits and rodents. Based on the reproductive and/or developmental effects seen in rats and rabbits, conclusion indicate that administration of fostamatinib early in human pregnancy or during lactation may pose a risk to the fetus/child, which is also included in the SmpC/PL.

Other tyrosinkinase inhibitors class effects such as gastrointestinal effects (nausea, diarrhea) and transaminase elevations (ALT and AST) were also observed for Fostamatinib. Interpretation of the significance of transaminase elevations may be hampered due to the drug's off-target pharmacological

activity on bilirubin conjugation. R406 is a potent UDP glucuronosyltransferaseform 1A1 (UGT1A1) inhibitor (see below), therefore, administration of fostamatinib may result in increases of unconjugated bilirubin levels. An isolated increase in blood bilirubin (without an increase in another liver function test) may represent the enzyme inhibition activity of the drug, and thus should allow continued dosing with close monitoring. Concomitant medication with drugs that are metabolized by UGT1A9/A1 (such as paracetamol, propofol or levothyroxine) may result in clinically relevant drug interactions and warrant specific safety monitoring as reported in the SmPC. Potent Activity against non-kinase targets (adenosine A3 receptor, UDP glucuronosyltransferase UGT1A1, phosphodiesterase PDE5, adenosine transporter) was shown on a non-clinical level. The physiological significance of pharmacological modulation of human adenosine A3 receptors was not elucidated and remains unclear.

Potentially important covariates

Gender analysis: In the thorough QT study, it has been evaluated whether there was a difference in the effect of fostamatinib on the QTc intervals in female compared to male subjects. The results of these analyses did not indicate that fostamatinib has a clinically meaningful effect on QTcF among females compared to males. In an ambulatory blood pressure monitoring study in 135 RA subjects following 100 mg bid dosing of fostamatinib for 28 days, most patients were female and no robust conclusions can be drawn regarding potential gender differences. With a view on the safety profile, AEs seem to occur more frequently in female subjects, which is probably related to a lower body weight.

Pharmacodynamic (PD) interactions with other medicinal products or substances

A dedicated DDI study investigating the effect of multiple dose administration of fostamatinib 100 mg twice daily on warfarin exposure (single dose 25 mg) and PD (evaluated in terms of INR) was conducted (study D4300C00013). The primary statistical comparison of INR parameters following administration of a single dose of warfarin 25 mg concomitantly with multiple dose fostamatinib dosed to steady-state show a geometric LS mean Ratio of 89.7% (90%CI: 84.6-95.2). Co-administration with fostamatinib thus resulted in a decrease of INR, which seems counterintuitive considering the increase in exposure of warfarin, therefore monitoring of anticoagulant activity is warranted when anticoagulants with narrow therapeutic index such as warfarin are co-administered with fostamatinib.

R406 have substantial off-target activity, and close monitoring of AEs emerging in a real life setting if fostamatinib is administered to patients with comorbidities and concomitant medication for other conditions will be required. Co-administration with fostasmatinib and immunomodulating agents have not been thoroughly investigated. Co-administration with corticosteroids is safe. Concomitant use with NSAIDSs in RA did not identify any safety concerns. Use of NSAIDs is not recommended in ITP.

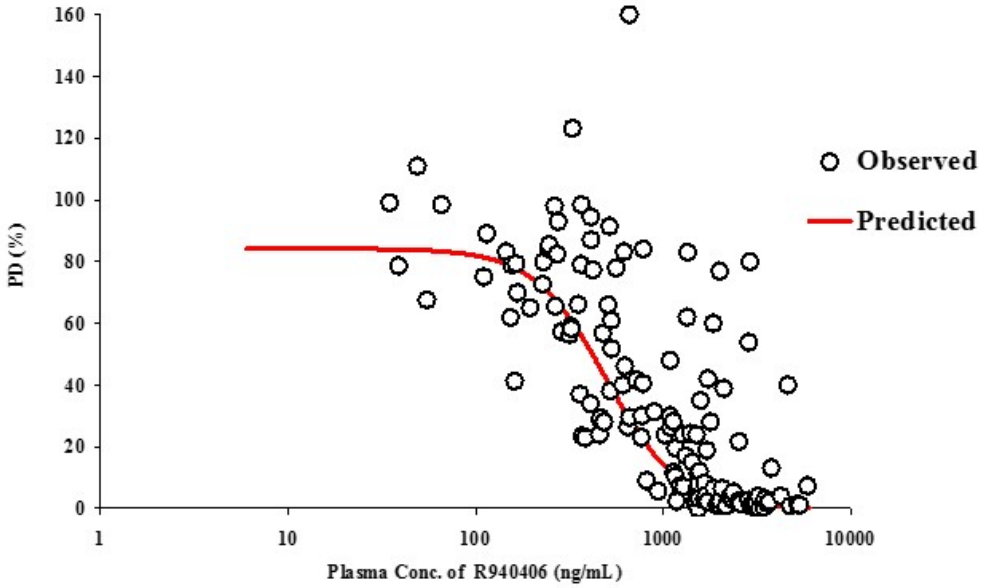
Genetic differences in pharmacodynamic response

In study D4300C00007, the relationship between variations in the gene encoding UDP glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) was investigated. The results from this study indicate that regulation of bilirubin levels is partly dependent on genotype at UGT1A1 and that the slight increases in total bilirubin can be in part explained by UGT1A1*6 and UGT1A1*28 genotype, in both placebo and fostamatinib treated subjects. UGT1A1*6 or UGT1A1*28 genotype did however not appear to be a factor in the incidence of AEs for Japanese or White subjects.

Relationship between exposure and effect

The PD marker, percentage change in CD63+ basophils, was related to the plasma concentration of R406. A sigmoidal E_{max} equation was used to model the plasma R406 concentrations and the PD effects of R406. The R406 plasma concentration that produced a 50% reduction of the PD effect was 496 ± 42.2 ng/mL (~ 1.06 µM). This would translate to a daily AUC requirement of approximately 12,000 ng×h/mL (~ 496 ng/mL×24h) (figure 1).

Figure 2: Correlation Between Plasma R940406 Concentrations and Percent Change of CD63+ Basophils in Normal Human Volunteers After Single and Multiple Oral Doses of R940406



Effect

A population PK/PD analysis was conducted to explore the relationship between fostamatinib exposure, as measured by its metabolite R406, and efficacy. The exposure-efficacy analysis was based on data from 2 Phase 3 studies in ITP patients. The population PK/PD analysis did not demonstrate an exposure-efficacy relationship. Higher exposure on average was evident in responders compared to non-responders only for Week 12, not between Weeks 14 – 24 or Week 24. The variability in response to fostamatinib in the ITP patients is not attributed to PK variability.

Safety

The population PK/PD analysis were also used to explore the relationship between fostamatinib exposure, as measured by its metabolite R406, and safety. The exposure-safety analysis was based on data from 5 Phase 2 and 3 studies in patients with RA and 2 Phase 3 studies in patients with ITP. R406 exposure had little to no effect on increases in ALT, AST, and bilirubin. R406 increased blood pressure with a maximal effect of about 10 mmHg. The DAUC required to achieve half of E_{max} (EC_{50}) is comparable to the average DAUC achieved at a 300 mg daily dose. Neutrophil counts tended to decrease with higher exposure of R406. However, the maximum effect was relatively small and likely of no clinical consequence.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

A two-compartment Pop PK model with simultaneous first- and zero-order delayed absorption and first order elimination best described the PK of fostamatinib in RA and ITP patients with bodyweight and population identified as significant covariates. Predicted daily area under the curve at steady state was the exposure metric carried forward for E-R analyses of safety variables BP, ALT, BILI and ANC with blood platelet count as the efficacy variable. Of the 2535 subjects included in the PK/PD data set, were 1675 subjects on active treatment, of these were 102 subjects (6%) ITP patients with 3 blood samples taken per study at weeks 2, 6, and 24. Only PD data from ITP patients were included in the blood pressure analysis.

Fostamatinib is rapidly converted into the highly permeable R406 metabolite in the gut through the action of gut alkaline phosphatase. R406 is a substrate of P-gp in vitro. The mean absolute bioavailability of R406 is 55% with high variability (30% to 85%). T_{max} is approximately 1.5 hours regardless of single or multiple dosing. Several tablet formulations were used throughout development with bioequivalence established. Large variability was observed for all formulations. The effects of food on exposure of R406 was modest and not considered clinically relevant. R406 distributed to extravascular sites with volume of distribution of 256 L. The half-life of R406 is 16 hours and the clearance 15.7 L/h. R406 is highly bound to plasma proteins and distributes into red blood cells with a ratio of 2.6.

A mass balance study showed predominately R406 is circulating in plasma with the majority excreted in feces and 20% excreted in urine as R-406 glucuronide. R406 is mainly cleared via CYP3A4 metabolism. R406 exposure is close to dose proportional in the therapeutic dosing range 100 to 150 mg bid fostamatinib. The expected AR is 2.3. PK samples were collected in ITP patients in both Phase 3 studies, 047 + 048. The intra- and inter-subject variability is considerable. Pop PK analyses indicated that PK is comparable in healthy volunteers and ITP patients.

The dose of fostamatinib should not be adjusted in subjects with renal impairment. Use of fostamitinib in ITP patients with severe hepatic impairment is not recommended. PK is similar in men and women when adjusted for body weight. R406 exposure decreases with increase in body weight. Body weight was not significant in any of the variables in the exposure-response population model. A study in Japanese and white male healthy subjects did not identify any PK differences between the groups. Fostamatinib metabolism is not expected to be affected by genetic polymorphisms of UGT1A1. However, there could be increased risk of hyperbilirubinemia in patients with genetic polymorphisms of UGT1A1 e.g. Gilbert. No dose adjustments have been proposed in elderly patients. Fostamatinib is not intended for use in children due to safety concerns.

Drug Interactions

In vitro, R406 was an inhibitor of UGT1A1 (IC50 143 nM), could cause time-dependent inhibition of CYP3A4 (KI = 1 to 2.3 µM, kinact 0.022 to 0.024 min-1) and induce CYP2C8. Fostamatinib was an inhibitor of P-gp (IC50 3.2 µM) and R406 was a substrate of P-gp up to 10 µM. Both fostamatinib and R406 were inhibitors of BCRP in vitro (0.050 and 0.031 µM, respectively).

The DDI potential of R406 for CYP3A4 inhibition and induction, CYP2C8 induction, inhibition of BCRP and inhibition of P-gp was investigated in clinical DDI studies.

Concomitant administration of fostamatinib with strong CYP3A4 inhibitors may warrant dose reductions. Concomitant use of fostamatinib with strong CYP3A4 inducers e.g. rifampicin is not recommended. Ranitidine did not have a clinically relevant impact on fostamatinib exposure. Repeat dose administration of

fostamatinib did not seem to affect exposure of methotrexate in RA subjects but the results are difficult to interpret. Concomitant use of fostamatinib may increase systemic exposure of some CYP3A4 substrate drugs and toxicities of CYP3A4 substrate drugs that may require dosage reduction should be monitored. Anticoagulant activity (e.g. INR) monitoring is recommended with concomitant use of fostamatinib and anticoagulants with narrow therapeutic index. Fostamatinib had a minor effect on CYP2C8 mediated metabolism of pioglitazone. Concomitant use of fostamatinib may increase concentrations of P-gp substrates (e.g., digoxin) and BCRP substrates (e.g., rosuvastatin). Toxicities of these drugs that may require dose reduction should be monitored. A study investigating ethinyl estradiol (a substrate of UGT1A1) did indicate possible UGT1A1 inhibition. PK/PD analysis of safety variables indicated that increase of R406 exposure had little effect on unconjugated bilirubin levels, a marker for UGT1A1 inhibition in vivo. The potential of PK DDIs for co-administration of fostamatinib with acetaminophen remain undetermined.

Pharmacodynamics

Fostamatinib is a pro-drug converted to the pharmacological active R406 in the gut. R406 inhibits SYK, a kinase involved in the intracellular signalling of multiple cell types involved in inflammation and tissue degradation. The pathogenesis of ITP is incompletely understood, but primary ITP is considered due to autoimmune mechanisms leading to platelet destruction and platelet underproduction. A murine model of ITP showed that fostamatinib had modifying effect of antibody-induced thrombocytopenia. Several clinical studies in healthy subjects and ITP patients showed a consistent reduction in monocytes and neutrophils with a corresponding increase in lymphocytes. Careful hematology monitoring is therefore warranted when administering fostamatinib in patients. While it is agreed that short term administration might not impact the immune system to a clinically relevant extent in ITP patients, effects of long-term administration do not seem to be as well characterised, with remaining open questions on the mechanism behind the reduction of monocytes and neutrophils and on a potential causal relationship with the occurrence of infections. A 50 % reduction of basophil activation was seen in the plasma concentrations achieved at therapeutic doses, i.e. 100 mg and 150 mg fostamatinib bid. R406 did not have effect on platelet function.

Fostamatinib was active against a broad range of other tyrosine kinases, especially, of RET proto-oncogene (RET), vascular endothelial growth factor receptor-2 (VEGFR-2), FMS-related tyrosine kinase 3 (FLT3), Janus kinase (JAK)1/3 and KIT proto-oncogene receptor tyrosine kinase (KIT). By targeting a broad range of TKIs (all of which are involved to some extent in the bone metabolism with either potentially deleterious or favourable effects), it is difficult to accurately estimate the risk that is related to bone metabolism, especially for long term administration in patients at risk of osteoporosis (e.g. elderly, patients with concomitant steroid treatment, patients with fractures or young adults where epiphyseal fusion may not have entirely occurred). Genetic differences in PD response are possible but the small numbers and high heterogeneity make the issue difficult to investigate.

Dose exposure response was addressed by a population PK/PD approach, which is however not considered to add high value to the separate study assessments. The use of the bid 100 mg dose of fostamatinib in the confirmatory phase 3 studies in ITP patients was in part justified based on a PD analysis. A lower dose of 50 mg bid was postulated to show lack of efficacy, as demonstrated in RA patients. Study C406-001 investigating 3 weeks of administration of a 250 mg bid in healthy subjects resulted in a high discontinuation rate due to adverse events. Overall, a positive relationship between exposure and efficacy has not been demonstrated.

Exposure-safety analysis was based on all available data from 5 Phase 2 and 3 studies in patients with RA and 2 Phase 3 studies in patients with ITP. Within the therapeutic exposure ranges achieved in the clinical studies, exposure had minimal effect on safety endpoints, besides blood pressure. R406 exposure in the

therapeutic range increase blood pressure with a maximal predicted effect of about 10 mm Hg. There appear to be a linear PK/PD relationship for this outcome.

Results from a QT study conducted ten years ago, but adherent to current guidelines, demonstrated that R406 does not prolong the QTc interval.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of fostamatinib (R788) and/ or its active metabolite R406 were evaluated extensively in clinical pharmacology and biopharmaceutic studies. PK in the target patient population is limited but appears comparable to PK characteristics observed in healthy volunteers and patients with rheumatoid arthritis.

The pharmacodynamics of Fostamatinib shows a broad range of activities against other tyrosine kinases and non-tyrosin kinase targets as well as a broad anti-inflammatory and immunomodulatory action (with partly uncertain clinical relevance).

The investigation of pharmacokinetics and pharmacodynamics of fostamatinib is considered adequate.

2.5. Clinical efficacy

2.5.1. Dose response study

Study D43000C00022: A Phase II, Open-Label, Efficacy and Safety, Ascending Dose, Pilot Study of R935788 for the Treatment of Adult Refractory Immune Thrombocytopenic

Objectives: The primary objective of this pilot study was to assess the preliminary efficacy of R788 in the treatment of chronic refractory immune thrombocytopenic purpura (ITP) as measured by platelet response. The secondary objective of this pilot study was to assess the safety of R788 in the treatment of chronic refractory ITP using standard safety tests.

Study Design and Methodology: This study was designed to include patients with chronic refractory ITP who were eligible for a 6- to 12 week dose exploration therapeutic trial, and were eligible to continue on study if an investigator defined response was observed.

In order to be eligible for study participation, patients had to have ITP defined as a platelet count <30,000/mm3 consistently for 3 months. In some cases, the baseline platelet count could have been >30,000/mm3 but the platelet count history 3 months prior to study entry met the ITP inclusion criterion.

During the course of the study all patients were to visit the study site on as few as 9 occasions and as many as 39 occasions over a period of approximately 2 months to 25.5 months (with dosing from 6 weeks up to 2 years). After 24 months, patients who continued to demonstrate a sustained response, in the investigator's judgment, were to be offered the opportunity to receive continued ongoing therapy, provided that there were no contraindications.

The investigator considered a patient to have had a response based on the protocol defined criteria of a baseline platelet count increase by at least 20,000/mm3 to a total count of 30,000/mm3 or more while being treated with R788 and the patient had not received a dose of intravenous immunoglobulin G (IVIg), or other concomitant therapy known to increase platelet counts, within 2 weeks of the increase in platelet count.

Secondary endpoints included the percentage of patients who achieved a platelet count of 50,000/mm3 or greater and the percentage of patients who achieved a platelet count of 150,000/mm3 or greater.

Up to 18 patients (in dose cohorts of 3 to 6 patients) were to be treated with R788 in this study, at doses from 75 mg orally (PO) twice daily (bid) up to a maximum of 225 mg PO bid. At least 3 patients must have been enrolled at a given dose cohort, and have completed 4 weeks of treatment, and the Independent Safety Reviewer must have provided consent, before any patient could be enrolled into the next higher dose cohort. If 2 or more patients demonstrated a sustained response at a given dose, an additional 3 patients may have been enrolled at that dose. If 4 or more patients demonstrated a sustained response at a given dose, an additional 6 patients could be enrolled to confirm the response and the tolerability.

For any given patient, the dose may have been increased by 25 mg PO bid after 2 weeks of treatment at a specific dose, provided that the previous dose had been without significant adverse effects (alanine aminotransferase [ALT] > 3 x upper limit of normal [ULN], polymorphonuclear neutrophils [PMN] <1000/mm3, and/or other significant National Cancer Institute-Common Toxicity Criteria [NCI-CTC] AE Grade 2 toxicity). The dose may have been increased further in increments of 25 mg PO bid no more frequently than every 2 weeks; however, increases beyond Week 4 required the consent of the Independent Safety Reviewer.

Patients who did not experience a response to any dose by Week 6 were to be withdrawn from treatment. Patients who demonstrated a sustained response by Week 12 were eligible to continue therapy for up to an additional 9 to 21 months at the dose at which the patient sustained the response, provided that there were no contraindications.

Statistical Methods: All data collected in this study were to be documented with the help of patient data listings, summary tables, and graphical displays. Descriptive statistics were to be provided by observation time (visit) of interest and treatment group. The statistics for continuous variables were to include the sample size, mean, standard deviation, median (where applicable), and range. The mean and median statistics were to be presented with 1 decimal beyond the accuracy of collection. The standard deviation was to be presented with 2 decimals beyond the accuracy of collection. The range was to be presented using the same accuracy of collection.

Results:

A total of 18 patients were enrolled; 4 (22.2%) discontinued the study due to 'other' (2 patients failed to respond, 1 patient was withdrawn at Week 20 due to failure to respond, and 1 patient withdrew from the study on his own), 3 (16.7%) due to AEs (however, 2 additional patients are reported in AE tables as having withdrawn due to an AE including 1 patient that died and 1 patient that withdrew consent, below), 2 (11.1%) discontinued at the investigators discretion, 1 patient died, 1 patient discontinued due to being a non-responder at Week 12, and 1 patient withdrew consent.

The mean age of patients was 61.9 years (range: 30 to 81 years), the majority of patients were female (55.6%), and 77.8% of patients were Caucasian. All patients reported using an acceptable method of contraception. All subjects tested negative for HIV, HBV, and HCV. A total of 5 (27.8%) patients had an ITP bleeding history that was severe or life-threatening, 7 (38.9%) patients had been previously hospitalized due to a bleeding event, and 14 (77.8%) patients had a blood or platelet transfusion due to a bleeding event. Medical history included splenectomy for 9 (50.0%) patients) and 11 (61.1%) of patients were classified as hypertensive at study entry by either having hypertension recorded on medical history or by having a supine blood pressure greater than or equal to 140/90 mmHg recorded at screening or the baseline visit. Mean platelet count at baseline was 42,222/mm3 (range: 6,000 to 155,000/mm3).

Table 14.1.5
Summary of Treatment Duration
Safety Population

Parameters	R788 PO Total (N=18)
Treatment Duration (a)	18
Mean (Std Dev)	538.72 (449.612)
Median	452.50
Range	28.0 - 1192.0
Initial dosage of R788, N(%)	
R788 75 MG BID	3 (16.7%)
R788 100 MG BID	5 (27.8%)
R788 125 MG BID	6 (33.3%)
R788 150 MG BID	4 (22.2%)
Highest achieved dosage of R788, N(%)	
R788 100 MG BID	1 (5.6%)
R788 125 MG BID	2 (11.1%)
R788 275 MG QD	1 (5.6%)
R788 150 MG BID	6 (33.3%)
R788 175 MG BID	8 (44.4%)

(a) Treatment duration = last dosing date - first dosing date + 1. If patient was continuing dosing with R788 at the time of database lock, then the last visit date will be assumed to be the last available dosing date.

Table 11-3 Summary of Patients whose Platelet Count Increased by at least 20,000/mm^3 from Baseline to a Total of 30,000/mm^3 or More

Time Point	R788 PO N=18
Week 2, n (%)	8/17 (47.1)
Week 6, n (%)	5/15 (33.3)
Week 12, n (%)	5/10 (50.0)
Week 24, n (%)	4/7 (57.1)
Month 12, n (%)	5/10 (50.0)
Month 24, n (%)	2/7 (28.6)

Source: Table 14.2.1
Denominator represents the number of patients with data available at the specific time point.

Concomitant Medication (excerpt): According to protocol all concomitant medication must be recorded in the CRF. No further information is provided in the protocol (e.g. regarding allowed/prohibited ITP specific concomitant medication).

The following excerpts from tables illustrate a comparison of selected pre-study medication and concomitant medication during study.

From Table 14.1.6: Summary of Pre Study Medications, Safety Population

CORTICOSTEROIDS FOR SYSTEMIC USE	11(61.1%)
PREDNISONE	8(44.4%)
METHYLPREDNISOLONE SODIUM SUCCINATE	4(22.2%)
METHYLPREDNISOLONE	1(5.6%)
ANTIHEMORRHAGICS	7(38.9%)
AMINOCAPROIC ACID	7(38.9%)
IMMUNE SERA AND IMMUNOGLOBULINS	5(27.8%)
IMMUNOGLOBULINS	5(27.8%)

From Table 14.1.7 Summary of Concomitant Medications, Safety Population

CORTICOSTEROIDS FOR SYSTEMIC USE	16(88.9%)
PREDNISONE	12(66.7%)
METHYLPREDNISOLONE SODIUM SUCCINATE	7(38.9%)
METHYLPREDNISOLONE	1(5.6%)
ANTIHEMORRHAGICS	14(77.8%)
AMINOCAPROIC ACID	12(66.7%)
ELTROMBOPAG	2(11.1%)
IMMUNE SERA AND IMMUNOGLOBULINS	10(55.6%)
IMMUNOGLOBULINS	9(50.0%)
IMMUNOGLOBULIN HUMAN ANTI-RH	1(5.6%)
IMMUNOGLOBULIN HUMAN NORMAL	1(5.6%)

The main drawback of this uncontrolled phase II open label study is the missing definitions of ITP specific concomitant medication used during the study as well as any consideration in the analyses. As illustrated above by excerpts from the relevant tables of the CSR, an obviously higher number of patients received ITP medication during the study than pre-study. Consequently, it is not considered feasible to evaluate any (add-on) effect of fostamatinib. Therefore, this study is rather a proof-of-concept study and provides preliminary data for dose selection. Main evidence for efficacy derives from the pivotal phase III studies with supportive evidence from the open-label extension study.

2.5.2. Main study(ies)

C788 047 and **C788 048**: A Phase 3, Multicenter, Randomized, Double Blind, Placebo-Controlled Study of Fostamatinib Disodium in the Treatment of Persistent/Chronic ITP

Master Protocol Versions 2.0 dated April 8 2014 for both studies 047 and 048 were the last versions effective before recruitment started. The protocols were revised several times. Changes to the protocol that were added after start of recruitment include changes to inclusion/exclusion criteria as well as clarifications regarding prior medication and definition of inclusion and baseline counts.

Methods

Study Participants

The in- and exclusion criteria are in general endorsed and include the recommendations in the EMA "Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia" (EMA/CHMP/153191/2013).

Inclusion Criteria

Subjects had to have met all of the following to be included in the study:

1. Subject had to be willing and able to give written informed consent by signing an IRB-approved ICF before undergoing any study-specific procedures.

2. Subject had to have a diagnosis of ITP for at least 3 months and no known etiology for thrombocytopenia. *[Hungary- and Italy-specific: chronic only.]*
3. Subject's platelet count averaged < 30,000/μL (and none > 35,000 unless a result of rescue therapy) from at least 3 qualifying counts within the preceding 3 months. At least 2 of the qualifying counts must have been taken during the screening period.
4. Subject must have received at least 1 typical regimen for the treatment of ITP. The typical regimen included such approved agents as:
    - a thrombopoietin (romiplostim, eltrombopag)
    - corticosteroids with or without splenectomy
    - intravenous immunoglobulin

[Italy-specific: at least 2 regimens.] [Hungary- and Italy-specific: must have included splenectomy, unless subject refused or not a candidate.]

5. Male or female at least 18 years of age. [Italy-specific: added upper age limit of 70.]
6. Performance status on KPS scale ≥ 70.
7. Subject's concurrent treatment for ITP consisted of either glucocorticoids (< 20 mg prednisone equivalent per day), or azathioprine, or danazol. The dose of the concurrent medication had to have been stable for 14 days before baseline and must have been expected to remain stable throughout the study. No other concurrent medications for ITP were permitted.
8. Subject's other therapeutic agents for ITP had to have been discontinued in accordance with the protocol-required washout periods.

Exclusion Criteria

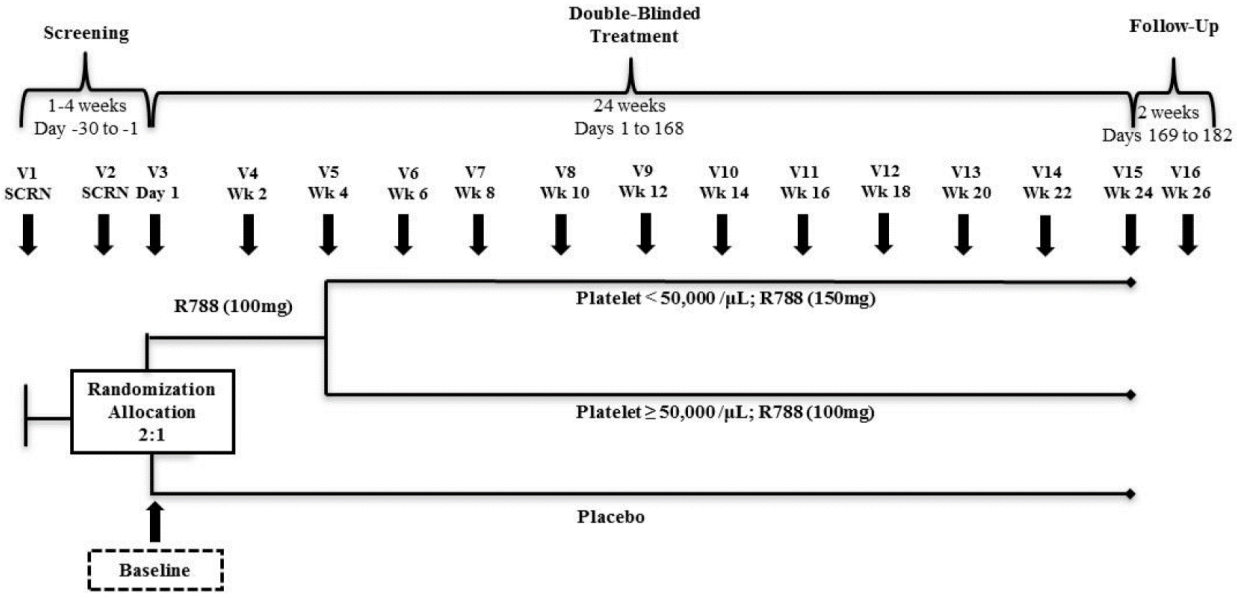
Subjects could not have had any of the following to be eligible for the study:

1. Subject with ITP associated with lymphoma, chronic lymphocytic leukemia, viral infection, autoimmune disorders, thyroid disease, HIV, or hepatitis or induced or alloimmune thrombocytopenia, or thrombocytopenia associated with myeloid dysplasia. *[Italy-specific: included any other neoplasia.]*
2. Subject with autoimmune hemolytic anemia.
3. Subject had a history of or active, clinically significant respiratory, gastrointestinal (pancreatitis), renal, hepatic, neurological, psychiatric, musculoskeletal, genitourinary, dermatological, or other disorders that, in the investigator's opinion, could have affected the conduct of the study or the absorption, metabolism, or excretion of the study drug.
4. Subject had any major cardiovascular event within the 6 months before randomization, including but not limited to: myocardial infarction, unstable angina, cerebrovascular accident, pulmonary embolism, or New York Heart Association class III or IV heart failure.
5. Subject had uncontrolled or poorly controlled hypertension, defined as systolic blood pressure (SBP) ≥ 140 mmHg, or diastolic blood pressure (DBP) ≥ 90 mmHg, whether or not the subject was receiving antihypertensive treatment. Subjects could have been rescreened if their blood pressure was successfully and promptly controlled (within 30 days) using conventional antihypertensive

therapy to achieve optimal blood pressure control (< 140/90 mmHg). *[Australia- and Italy-specific: rescreened if blood pressure was within 60 days and blood pressure (BP) stable for at least 30 days.]*

6. Subject had a history of coagulopathy, including prothrombotic conditions such as Factor V Leiden, activated protein C resistance, antithrombin III deficiency and lupus anticoagulant, or arterial or DVT within 6 months before randomization. [Italy-specific: added protein C deficiency and protein S deficiency.]
7. In subjects with DVT greater than 6 months before randomization, anticoagulants had to be discontinued for at least 30 days and subsequent D-dimer had to be within normal limits for the site's local laboratory.
8. Subject had a bleeding assessment score of grade 2 at any site by IBLS.
9. Subject had 1 or more of the following laboratory abnormalities: leukocyte count < 2,500/µL, neutrophil count < 1,500/µL, lymphocyte count < 750/µL, hemoglobin < 10 g/dL without ongoing transfusion support, or transaminase levels (ALT, AST) > 1.5 times upper limit of normal (ULN), total bilirubin > 2.0 mg/dL, or estimated glomerular filtration rate (eGFR) < 30 mL/minute at the time of screening.

Treatments



The initial dose was 100mg bid of fostamatinib or placebo. If platelet count remained low at week 4 and the study drug has been well tolerated, dose was to be increased to 150mg bid. Comprehensive guidance was provided for dose adjustments due to adverse events. Subjects could have been withdrawn from the study due to lack of response after 12 weeks of treatment or if rescue treatment was required after week 10.

Subjects receiving doses twice daily self-administered 1 tablet in the morning and 1 in the evening. For once daily dosing, subjects self-administered 1 tablet daily in the morning. Tablets were taken with or without food.

Dose adjustment to as low as 100 mg qd was recommended/performed in the event of intolerability or AEs. Four patients maintained their response on 100 mg/day after achieving a response at a higher dose. From a practical point of view this is acceptable, as the treating physician would be expected to end treatment, if there is a lack of response to this dose.

Certain therapeutic regimens for ITP were permitted for subjects with platelet counts < 50,000/μL who needed "rescue" support for the platelet count. Allowed therapeutic regimens included:

IVIg: up to 1 g/kg × 1 to 3 days, or

- IV anti-D IgG: up to 50 μg to 75 μg/kg × 1 to 2 days, or
- IV methylprednisolone up to 1 g/day for 1 to 3 days or oral dexamethasone up to 40 mg/day for 1 to 2 days or oral prednisone up to 1 mg/kg/day for 1 to 3 days.

The investigator was required to discuss all instances of "rescue therapy" with the sponsor's medical monitor in advance of initiating the therapy whenever possible. Subjects receiving rescue therapy after Week 10 were deemed non-responders and were considered for study withdrawal.

In the two placebo-controlled studies concomitant ITP medication could not be changed during the study whereas in extension study 049 this medicine could be tapered when a stable platelet count ≥50,000/μL had been reached. In the pivotal studies the TPO-RA's tapering and/or discontinuation as the patients had effect was performed. Continuation of concomitant medication may provide an add-on effect and thereby making it difficult to assess the sole fostamatinib effect clearly. It is argued that a pre-planned analysis of the secondary endpoint "reduction of concomitant medication" was dropped from the SAP (study 049), because the incidence of dose reductions was low and the time on study too brief for analysis. Considering that Study 049 was an uncontrolled open-label study, presented arguments imply that the potential dose reduction achieved by treatment with Fostamatinib was limited. Arguments why such a result would preclude analysis cannot be followed. It should be stressed, that omission of pre-planned analyses due to unfavourable outcomes is not considered appropriate. The Applicant provided the requested analysis. The majority of subjects had to maintain their concomitant ITP medication:

Table 1: Subjects with a Reduction in the Dose of Concomitant ITP Therapy in Study 049 – All Subjects Who Took Concomitant ITP Therapy (Treated Subjects in 049 Study)

Parameter	Statistic	Prior Study Treatment Group in study 047/048		Total (N=80
		Fostamatinib (N=50)	Placebo (N=30)	
Achieving a Reduction in the Dose of Concomitant ITP Therapy				
Yes	n (%)	10 (20.0)	3 (10.0)	13 (16.3)
No	n (%)	40 (80.0)	27 (90.0)	67 (83.7)

Note: Percentages are based on N

Certain therapeutic regimens for ITP were permitted for subjects with platelet counts < 50,000/μL who need "rescue" support of the platelet count. The Applicant provided explanations and discussed the differences in terms of rescue treatment between both phase III studies. As the rate for rescue medication between fostamatinib and placebo patients is comparable in both studies, no further issue is made.

Objectives

The primary objective of the studies was to establish the efficacy of fostamatinib as compared with placebo in achieving a stable platelet response in subjects with persistent/chronic ITP (superiority).

Secondary objectives included assessment of the incidence of bleeding complications in subjects receiving fostamatinib as compared with placebo, and assessment of the overall safety and tolerability of fostamatinib versus placebo in subjects with persistent/chronic ITP.

Outcomes/endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was achievement of a stable platelet response by Week 24 defined as a platelet count of at least 50,000/μL on at least 4 of the last 6 scheduled visits between Weeks 14 and 24 inclusive.

According to the protocol measurements of platelet count for the primary endpoint were to be performed at the local laboratory. Considering the reliability of the routine, standard measurements of platelet counts was supported by certification according to the local regulations and is consistent with standard clinical practice. The small number of subjects at each study site made the risk of a corresponding center effect low.

Secondary Efficacy Endpoints

The secondary efficacy endpoints of this study were as follows:

- Achievement of a platelet response (a platelet count of at least 50,000/μL) at Week 12.
- Achievement of a platelet response (a platelet count of at least 50,000/μL) at Week 24.
- Among subjects with a baseline platelet count < 15,000/μL, achievement of a count ≥30,000/μL and at least 20,000/μL above baseline at Week 12.
- Among subjects with a baseline platelet count < 15,000/μL, achievement of a count ≥30,000/μL and at least 20,000/μL above baseline at Week 24.
- Frequency and severity of bleeding according to the IBLS over the 24-week study period.
- Frequency and severity of bleeding according to the WHO bleeding scale over the 24-week study period.

Safety Outcomes

The safety outcomes of this study include the change from baseline in blood pressure, liver function, and absolute neutrophil count (ANC); and the incidence and severity of GI complaints, (nausea, vomiting, diarrhea, abdominal pain), and infections, as well as the overall incidence of adverse events.

Pharmacokinetic (PK) Endpoints

The PK endpoint of this study will be a preliminary assessment of the kinetics of fostamatinib in subjects with ITP.

Sample size

For both studies, the sample size was determined to be a total of 75 patients (50 fostamatinib and 25 placebo). This was based on providing 90% power for the primary efficacy endpoint of achieving a stable platelet response using a 2-sided, Fisher's Exact Test with an alpha level of 0.05 and a 2:1 (fostamatinib:placebo) allocation, assuming a true proportion for fostamatinib of 0.40 and a true proportion for placebo of 0.05. Clinical justification for these estimates has not been presented. The observed effect of fostamatinib is approximately 20 %. Drop-outs and other intercurrent events were not taken into account in the sample size calculations. The size of the confidence interval will be used as a measure of the uncertainty in the presented results.

Randomisation and blinding (masking)

In both main studies, subjects were randomized (2:1, active:placebo) to receive fostamatinib or matching placebo for 24 weeks using permuted block randomization. Randomization was stratified to ensure that active and control populations have relatively equal representation of subjects with respect to prior splenectomy (yes/no) and severity of thrombocytopenia (platelets < 15,000/μL or ≥ 15,000/μL).

Both studies were double-blinded, as recommended by the current guideline on thrombocytopenia (EMA/CHMP/153191/2013). Administrative measures were in place to protect the treatment allocation.

Statistical methods

Analysis populations

The Intent-to-Treat (ITT) population includes all randomized subjects. All efficacy endpoints were analyzed based on the ITT population, and subjects were analyzed according to their randomized treatment assignment. The efficacy analyses based on the ITT population were considered the primary efficacy analyses.

The Per-Protocol (PP) population included all subjects in the ITT population who had no major protocol violations. Major protocol violations included:

- Not receiving any study treatment.
- Not receiving the correct study treatment.
- Failing to meet key (predefined) eligibility criteria.
- Other major protocol violations, as determined by a blinded review of the data before database lock.

The analyses based on the PP population were considered secondary analyses of efficacy.

The Safety Population included all randomized subjects who received any amount of randomized study drug. All analyses of safety were performed on the Safety Population, and subjects were analyzed according to the actual treatment they received.

Placebo-Controlled Efficacy Population (ISE) was the same as a pooling of the ITT study populations used for the individual study analyses. Data obtained after subjects transitioned from Study C788 047 or C788 048 to the long-term open label extension was not included.

Primary endpoint

The primary efficacy endpoint is achievement of a stable platelet response by Week 24, defined as having a platelet count of at least 50,000/μL on at least 4 of the last 6 scheduled visits over Weeks 14-24. The comparison of proportions of responders and non-responders between the fostamatinib and the placebo arm was tested using a 2-sided Fisher's Exact Test conducted with a significance level of 0.05. The exact (Clopper-Pearson) confidence intervals has been used.

Intercurrent events and missing data

- Subjects who discontinue treatment prior to Week 24 due to lack of efficacy were considered non-responders.
- Subjects who discontinue treatment prior to Week 24 due to AE were considered non-responders.
- Subjects who receive rescue treatment after 10 weeks were considered non-responders.
- Subjects who left the study due to other reasons were considered to have the same level of platelets as in the latest measurement (LVCF): For the primary and 4 platelet-related secondary endpoints imputation rules for missing values were applied. The imputation of missing values as non-responders for patients discontinuing due to AE or perceived lack of efficacy or for receiving rescue medication after week 10 is considered conservative. The use of LOCF for patients that discontinued the study drug due to other reasons is not endorsed, since this method has methodological disadvantages and is not necessary conservative.

It was unclear how platelet levels of patients receiving rescue treatment or who had to pause treatment due to AE were handled for the analysis (e.g. how long after rescue medication were platelet counts considered related to rescue medication). However, the Applicant adequately clarified how corresponding platelet counts were handled for analysis.

Sensitivity analyses

A sensitivity analysis was planned for the primary efficacy endpoint using multiple imputation methods. For the non-monotone missing data, a Markov chain Monte Carlo procedure was planned while chained equations were planned for monotone missing data. The imputed data sets were analyzed using a logistic regression model with a term for treatment and summarized using Rubin's multiple imputation strategy. Only patients with evaluations in the efficacy period (Weeks 14 to 24) were going to be imputed with MI. Patients with missing primary endpoint and without observations in the efficacy period would be imputed as non-responders: The approach is considered adequate, however it will be difficult to implement in case too few patients remain in the placebo part of the study. A post-hoc sensitivity analysis was performed where all LVCF imputed subjects were considered non-respondent. This is endorsed.

A post-hoc analyses were all subjects with missing values were considered non-responders was also presented.

Secondary endpoints

The secondary efficacy endpoints related to proportions of patients with a certain platelet count were analysed in the same manner as the primary endpoint. The rules for intercurrent events were the same as those used for the primary endpoint.

The difference in means between treatments for the IBLS scores across visits was tested using a two-sided, two-sample t-test. The mean of the WHO bleeding scale scores across visits during the 24-week treatment period was analyzed in the same manner.

Multiplicity control for the primary and secondary endpoints

The secondary efficacy endpoints will only be analysed if the null hypothesis for the primary efficacy endpoint is rejected in favour of fostamatinib. According to the SAPs version 2, the secondary efficacy endpoints were to be analyzed using the fixed sequence testing procedure to control the type I error. However, this was not implemented because the sequence specified did not follow the usual ordering conventions for such an approach.

Pooling of data

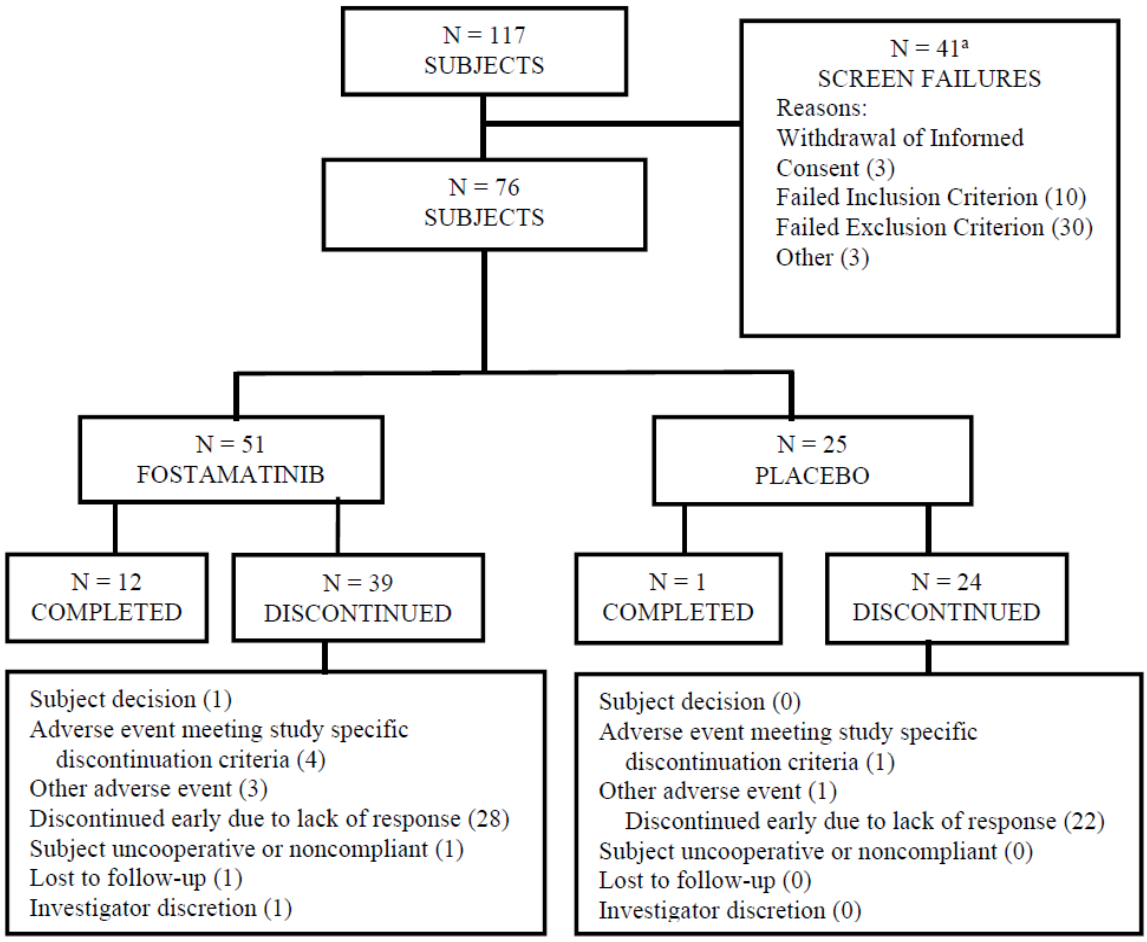
The submission presented the results for each study separately and for the pooled data.

Results

Participant flow

Study 047:

Figure 10-1: Disposition of Subjects

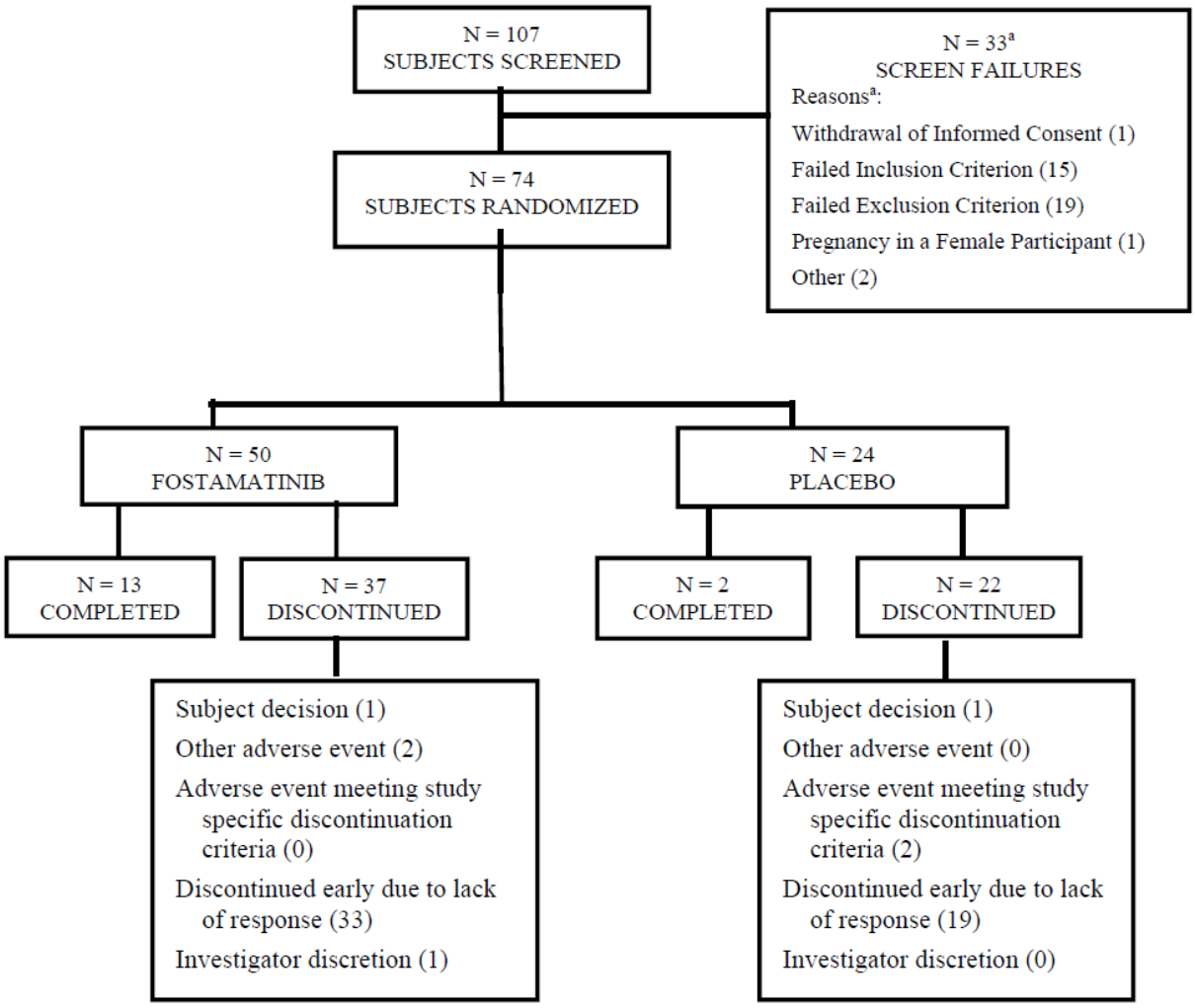


Sources: Tables 14.1.1 and 14.1.2

[a] A subject may have had more than one reason for screen failure.

Study 048:

Figure 10-1: Disposition of Subjects



[a] A subject may have had more than one reason for screen failure.
Source: Tables 14.1.1 and 14.1.2

The number of screen failures is approximately the same in the two pivotal studies. The main exclusion failures were related to violation of various laboratory criteria, hypertension and wash-out period violations. The main failed inclusion criterion was related to the platelet count measurements.

It remains uncertain whether the following inclusion criterion was fulfilled for all subjects: *"Subject's platelet count averages < 30,000/µL (and none > 35,000 unless as a result of rescue therapy) from at least 3 qualifying counts within the preceding 3 months. At least 2 of the qualifying counts must have been taken during the screening period."*

Based on spot checks in the respective listings some patients were identified, who seem to deviate from this inclusion criterion: patient 047-470-0001 had a platelet count of 54500 at screen visit A and 19500 at screen visit B initially by the Applicant described as not being associated with rescue medication although later changed to being caused by rescue medication. This patient was counted as a responder to fostamatinib.

Table 1: Subject 047-470-001 prior, rescue, and concomitant ITP medications

Date (Start – Finish)	Name of Treatment	Category of Treatment	Platelet Count
– 27Feb2015	Revolade®	Prior	NC
06Mar2015 – 08Mar2015	20 mg dexamethasone	Rescue	06Mar – 0/µL
09Mar2015	10 mg dexamethasone	Rescue	NC
10Mar2015	32 mg Medrol®	Rescue	NC
11-Mar2015 – 16Mar2015	16 mg Medrol®	Rescue	12Mar (ScrA) – 54,500/µL 15Mar (ScrB) – 19,500/µL
17Mar2015 – 18Mar2015	12 mg Medrol®	Concomitant	17Mar – 6,300/µL 18Mar – 4,900/µL
19Mar2015	125 mg methylprednisolone	Rescue	2,300/µL
20Mar2015	64 mg methylprednisolone	Rescue	5,500/µL
21Mar2015 –	12 mg Medrol®	Concomitant	

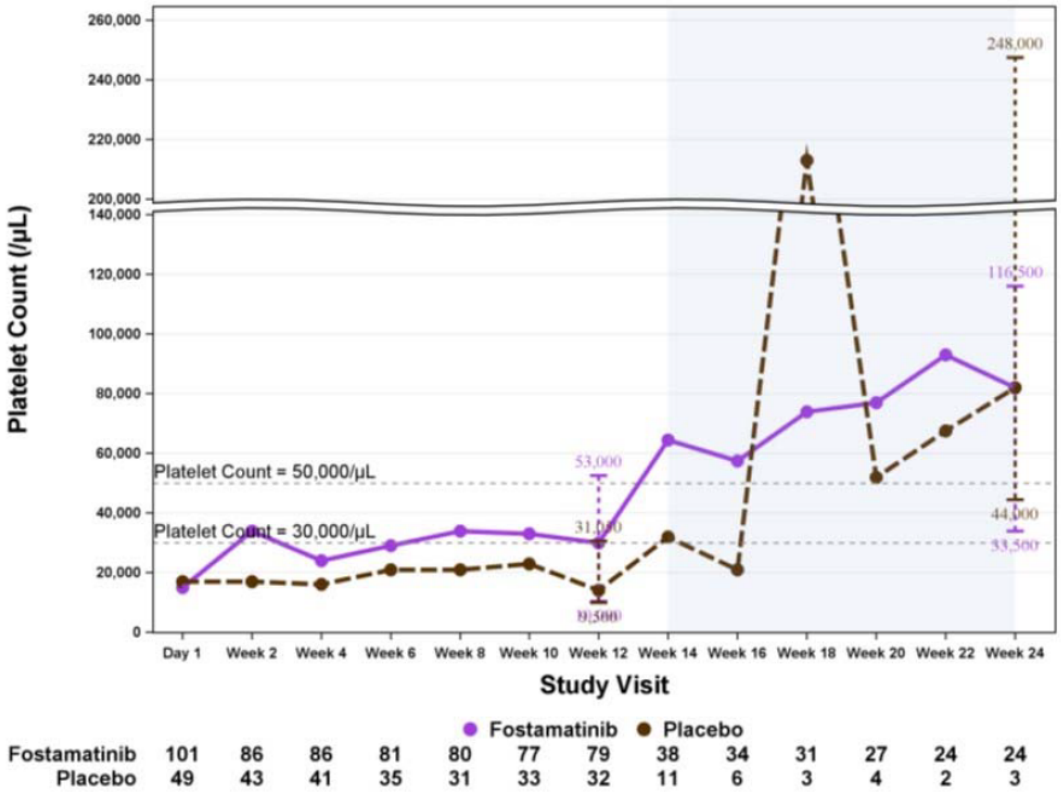
NC = not collected; ScrA = Screen A; ScrB = Screen B

Some additional subjects were identified with platelet counts >35,000 during screening: 047-490-001 (41000 Screen B), 048-570-001 (71000 Screen A), 048-570-002 (68000 Screen A), 048-570-001 (43000 Screen A) and 048-473-006 (109000 Unscheduled Visit Screening Phase). Clarifications were provided that these subjects had platelet counts of >35.000 during screening due to rescue medication. An additional analysis of the primary endpoint excluding all patients who did not fulfil all inclusion and exclusion criteria has been provided. The result of the primary endpoint remained statistically significant in study 047, whereas the result of the primary endpoint remained being not statistically significant in study 048. No new concerns arise from these data.

A sensitivity analysis excluding patients with deviations from eligibility has been performed and there is no change to the conclusion of the study. The number of screening visits did not have impact on the baseline platelet count used for randomization.

Figure 1 (*below*) indicates by week available subjects measurements of platelet counts. The numbers reported are adjusted, according to participant flow presented in Study Reports of Trial 047 and 048, considering 20 subjects who discontinued treatment due to reasons other than lack of efficacy at week 12 or later and patients receiving rescue medication having been removed.

Figure 1: Median Platelet Count by Study Visit for Each Treatment Group (Placebo-Controlled Efficacy Population)



The interquartile range (Q1-Q3) for each treatment group is displayed at Week 12 and Week 24.
Note: At each visit, those subjects whose platelet counts were impacted by rescue medication (i.e., within 28 days of rescue medication use) were are not included for that visit in the figure above.

Baseline data

Table 3: Demographics and Baseline Characteristics (Placebo--Controlled Efficacy Population)

Variable	Study C788-047		Study C788-048		Randomized Studies		All Subjects (N=150)
	Placebo (N=25)	Fostamatinib (N=51)	Placebo (N=24)	Fostamatinib (N=50)	Placebo (N=49)	Fostamatinib (N=101)	
Age at baseline (years)							
Median	57.0	57.0	49.5	49.5	53.0	54.0	53.5
Range	26, 77	20, 88	20, 78	21, 82	20, 78	20, 88	20, 88
≥ 65 years, n (%)	7 (28.0)	19 (37.3)	4 (16.7)	9 (18.0)	11 (22.4)	28 (27.7)	39 (26.0)
≥ 75 years, n (%)	3 (12.0)	9 (17.6)	1 (4.2)	2 (4.0)	4 (8.2)	11 (10.9)	15 (10.0)
Gender, n (%)							
Male	8 (32.0)	21 (41.2)	11 (45.8)	19 (38.0)	19 (38.8)	40 (39.6)	59 (39.3)
Female	17 (68.0)	30 (58.8)	13 (54.2)	31 (62.0)	30 (61.2)	61 (60.4)	91 (60.7)
Race, n (%)							
White	21 (84.0)	44 (86.3)	24 (100.0)	50 (100.0)	45 (91.8)	94 (93.1)	139 (92.7)
Non-White	4 (16.0)	7 (13.7)	0 (0.0)	0 (0.0)	4 (8.2)	7 (6.9)	11 (7.3)
Asian	2 (8.0)	3 (5.9)	0 (0.0)	0 (0.0)	2 (4.1)	3 (3.0)	5 (3.3)
Black African American	2 (8.0)	2 (3.9)	0 (0.0)	0 (0.0)	2 (4.1)	2 (2.0)	4 (2.7)
Other	0 (0.0)	2 (3.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	2 (1.3)
Height (cm)							
Median	167.60	164.50	169.00	169.50	168.00	168.00	168.00
Range	147.9, 194.0	143.3, 188.0	152.0, 186.0	156.0, 190.0	147.9, 194.0	143.3, 190.0	143.3, 194.0
Weight at baseline (kg)							
Median	82.00	71.10	85.00	79.00	83.00	78.00	79.60
Range	58.1, 204.1	47.2, 163.2	45.0, 107.0	48.7, 124.0	45.0, 204.1	47.2, 163.2	45.0, 204.1

Variable	Study C788-047		Study C788-048		Randomized Studies		All Subjects (N=150)
	Placebo (N=25)	Fostamatinib (N=51)	Placebo (N=24)	Fostamatinib (N=50)	Placebo (N=49)	Fostamatinib (N=101)	
Body mass index at baseline (kg/m^2)							
Median	26.03	25.89	29.01	26.67	27.89	26.54	26.71
Range	18.6, 72.7	19.2, 63.8	16.9, 42.3	17.3, 38.4	16.9, 72.7	17.3, 63.8	16.9, 72.7
Baseline platelet count (/µL)							
Median	16000	15000	21000	16000	17000	15000	16000
Q1, Q3	6000, 23000	7000, 25000	10000, 28000	8000, 22000	7000, 26000	8000, 23000	7000, 25000
Range	1000, 48000	1000, 51000	1000, 156000	1000, 33000	1000, 156000	1000, 51000	1000, 156000
< 15,000/µL, n (%)	12 (48.0)	25 (49.0)	9 (37.5)	22 (44.0)	21 (42.9)	47 (46.5)	68 (45.3)
≥ 15,000/µL, n (%)	13 (52.0)	26 (51.0)	15 (62.5)	28 (56.0)	28 (57.1)	54 (53.5)	82 (54.7)
Type of ITP, n (%)							
Persistent	3 (12.0)	3 (5.9)	1 (4.2)	3 (6.0)	4 (8.2)	6 (5.9)	10 (6.7)
Chronic	22 (88.0)	48 (94.1)	23 (95.8)	47 (94.0)	45 (91.8)	95 (94.1)	140 (93.3)
Time since ITP diagnosis (years)							
Median	5.50	7.50	10.80	8.80	7.80	8.70	8.45
Range	0.4, 45.0	0.6, 53.0	0.9, 29.1	0.3, 50.2	0.4, 45.0	0.3, 53.0	0.3, 53.0
≥ 3 years, n (%)	17 (68.0)	38 (74.5)	18 (75.0)	38 (76.0)	35 (71.4)	76 (75.2)	111 (74.0)
Splenectomy, n (%)	10 (40.0)	20 (39.2)	9 (37.5)	14 (28.0)	19 (38.8)	34 (33.7)	53 (35.3)
Time since splenectomy (months)							
n	10	20	9	14	19	34	53
Median	88.60	193.92	152.97	171.45	113.70	186.60	159.37
Range	2.3, 474.5	15.6, 633.5	23.2, 220.5	17.7, 556.5	2.3, 474.5	15.6, 633.5	2.3, 633.5
≥ 6 months since splenectomy, n	9	20	9	14	18	34	52

Variable	Study C788-047		Study C788-048		Randomized Studies		All Subjects (N=150)
	Placebo (N=25)	Fostamatinib (N=51)	Placebo (N=24)	Fostamatinib (N=50)	Placebo (N=49)	Fostamatinib (N=101)	
Number of unique prior ITP medications[a]							
Median	5.0	3.0	3.0	3.0	3.0	3.0	3.0
Range	1, 10	1, 9	1, 10	1, 13	1, 10	1, 13	1,13
Number of prior ITP medications[a]							
Median	6.0	5.0	4.0	4.0	5.0	4.0	5.0
Range	1, 20	1, 15	1, 41	1, 31	1, 41	1, 31	1,41
Currently on ITP medication, n (%) Yes	11 (44.0)	23 (45.1)	10 (41.7)	26 (52.0)	21 (42.9)	49 (48.5)	70 (46.7)

Source: Appendix 2, Table 2.1.1
ITP = immune thrombocytopenia; N = number of subjects in the Placebo-Controlled Efficacy Population; Q1 = first quartile; Q3 = third quartile; TPO-RA = thrombopoietin receptor agonist.
[a] Does not include splenectomy as a prior therapy. "Unique" refers to the number of unique prior ITP medications; each medication was counted once, regardless of whether the subject received more than 1 series of treatment with the same medication.

Vaccination history was not captured as part of the medical history prior to initiation of the ITP studies.

Numbers analysed

047:

Table 10-1: Subject Disposition – All Randomized Subjects

Status	Fostamatinib (N=51) n (%)	Placebo (N=25) n (%)	All Subjects (N=76) n (%)
Number of randomized subjects (ITT Population)	51 (100.0)	25 (100.0)	76 (100.0)
Number of subjects in the PP Population	51 (100.0)	25 (100.0)	76 (100.0)
Number of subjects in the Safety Population	51 (100.0)	25 (100.0)	76 (100.0)

048:

Table 10-1: Subject Disposition – All Randomized Subjects

Status	Fostamatinib (N=50) n (%)	Placebo (N=24) n (%)	All Subjects (N=74) n (%)
Number of randomized subjects (ITT population)	50 (100.0)	24 (100.0)	74 (100.0)
Number of subjects in the PP population	49 (98.0)	23 (95.8)	72 (97.3)
Number of subjects in the Safety Population[a]	51 (102.0)	23 (95.8)	74 (100.0)

[a] *One patient randomized to the placebo group was assigned the wrong treatment kit by mistake, and was treated with fostamatinib for 2 weeks. This patient's efficacy data were analyzed with the placebo arm, but his safety data were analyzed with the Fostamatinib arm.*

One patient in the placebo arm of study C788-048 achieved a stable platelet response according to the primary endpoint. Looking at lab values for this patient, fluctuating platelet counts are observed. Based on these observations, it is likely that this patient seems to have cyclic thrombocytopenia, and should not have been included in the study.

Outcomes and estimation

Primary endpoint

The primary efficacy endpoint was achievement of a stable platelet response by Week 24 defined as a platelet count of at least 50,000/μL on at least 4 of the last 6 scheduled visits between Weeks 14 and 24 inclusive.The efficacy seem to be approximately 16-18%: The percentage of responders in the fostamatinib arms in both studies was 16.8 %(95 % CI: 9.5%, 24.1%).

Post-hoc analyses

The use of Last Observation carried Forward (LOCF):

In study 048, there were 2 patients in the fostamatinib arm and 1 in the placebo arm who were imputed using LOCF. In the fostamatinib arm, one patient was considered responder and the other non-responder. The "responder" patient (subject 048-428-006) left the study due to relocation due to work/study-related reasons and may have been a responder given the patient's platelet count (>50,000/μL week 8-16). However, it is more conservative to assume that this patient is a non-responder. Since a patient was imputed as responder in the active arm (non-conservative approach), the results of the sensitivity analysis is very

important. The primary analysis was repeated using MI for the mentioned subject and considering all subjects as non-responders. The results are concordant with those of the primary analysis:

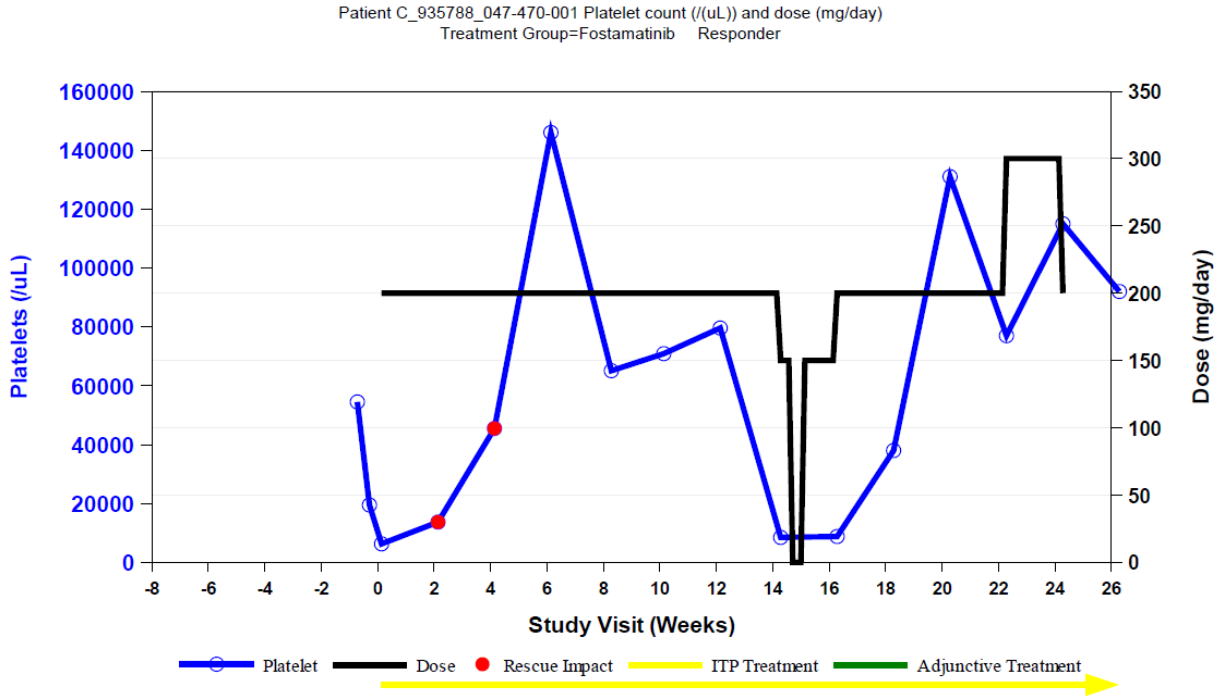
Table 11-3: Primary Efficacy Endpoint – ITT Population

Parameter	Fostamatinib (N=50)	Placebo (N=24)	Difference in % Yes (Fostamatinib - Placebo) and 95% CI[a]
Achieved a stable platelet response (count of ≥50,000/μL on at least 4 of the last 6 scheduled visits between Weeks 14 and 24, inclusive)			
Primary Analysis (LOCF):			
Yes, n (%)	9 (18.0)	1 (4.2)	13.8 (0.5, 27.1)
No, n (%)	41 (82.0)	23 (95.8)	
p-value[b]			0.1519
Sensitivity Analysis (Multiple Imputation):			
% Yes[c]	18.00	4.34	13.66 (0.16, 27.16)
% No[c]	82.00	95.8	
p-value[c]			0.0474

LOCF = Last Observation Carried Forward.
[a] Confidence interval based on the normal approximation.
[b] p-value is from Fisher's Exact Test, testing for a difference in proportions between treatments.
[c] Missing platelet count values were imputed using multiple imputation methods. SAS MIANALYZE procedure was used to combine estimates across imputations. Reported percentages and p-value are based on the average of 10,000 iterations.

Source: Table 14.2.1, Table 14.2.3

Listings of platelet counts for all patients give the impression that these are rather variable at least in some patients. In study 047 The most notable patient is 047-470-001 (Figure below).



Adjunctive Treatment is defined as WHO Standardized Medication Name(CMDECOD) in ('AMINOCAPROIC ACID','TRANEXAMIC ACID','ABSORBABLE GELATIN SPONGE','ETAMSILATE').
Data Cutoff Date: 08MAR2018

It is not considered comprehensible why this patient was counted as responder, as 3/6 platelet counts were below 50,000 between weeks 14-24. There seems to be a discrepancy between weeks and dates/study days in the respective listing 16.2.6.1 (listing of platelet count). From the dates/study days it seems that the

graphical illustration reflects the platelet counts correctly, whereas the designated weeks in the listing are wrong. In addition, this patient did not fulfill the criteria to continue treatment with fostamatinib after week 12, as the platelet count at week 12 according to Listing 16.2.6.1 was 8,500/µl) and apparently had declined before dose reduction (see graph above; this is due to the fact that randomization date and treatment date/Day 1, are not the same, as they should be, see below). The site randomized patient 047-470-001 on 17 March 2015, and the platelet count was 6,300/µL. However, to fulfill the protocol requirement for stable steroid dose less than 20 mg daily (prednisone equivalent), the subject's actual start date for study drug/fostamatinib was 31 March 2015 and not on the randomization date. The Applicant has considered Day 1 for this patient as the date of first dose of fostamatinib, and not the randomization date, which is not acceptable. The first day in the study is the randomization date. The fact that the subject was randomized without fulfilling the inclusion criterion is a protocol violation and not a reason to move the start date of the study. It is important to assure that the start date is consistently defined to avoid immortal bias. When the randomization date is considered Day 1, this patient is a non-responder (only 3/6 instead of 4/6 platelet counts were ≥ 50,000 between weeks 14-24). The Applicant presented two supplementary analysis to evaluate the effect of this patient on the results. In one case, this patient was removed, in the other case this patient was considered a non-responder. When removing this patient of the dataset, the stable responder proportion for fostamatinib is 16.00 % (95 % CI 0.13 %; 29.13%), which is lower than that reported for the primary analysis (17.6 %). When considering this patient a non-responder, the stable responder proportion for fostamatinib is 15.69 % (95 % CI 0.29 %; 28.66%), which is lower than that reported for the primary analysis (17.6 %). Both sensitivity analyses were in line with the results reported on the primary analysis and showed a statistical significance difference compared to placebo, although the CI were very wide and the lower end almost included 0 difference. It is acknowledged, that the sensitivity analyses still showed a statistically significant difference compared to placebo. Patient 047-470-001 has been moved from the responder into the non-responder population and the Effects Table in section 3.6 has been updated accordingly.

Three patients had their first fostamatinib dose after the day of randomization (8, 1, and 1 day). As they were all non-responders there is no impact on efficacy.

Secondary endpoints

The secondary efficacy endpoints of platelet count ≥50,000/µL at week 12 and 24 for the entire population (Table 13) and for patients with at low baseline platelet count (Table 14) are considered supportive of the primary efficacy endpoint. A hierarchal testing to control for the type I error in the SAPs was not implemented and therefore it is concluded that the confidence intervals and p-values from the secondary endpoints are not meaningful.

Table 13: Platelet Count ≥ 50,000/µL at Week 12, at Week 24 in C788-047 and C788-048 (ITT Population)

Parameter Statistic	C788-047		C788-048	
	Fostamatinib (N=51)	Placebo (N=25)	Fostamatinib (N=50)	Placebo (N=49)
Platelet count ≥ 50,000/µL at:				
Week 12				
Yes, n (%)	11 (21.6)	0 (0.0)	12 (24.0)	3 (12.5)
No, n (%)	40 (78.4)	25 (100.0)	38 (76.0)	21 (87.5)
Difference in % for Yes (Fostamatinib - Placebo) and 95% CI[a]	21.6 (10.3, 32.9)		11.5 (-6.3, 29.3)	
Week 24				
Yes, n (%)	8 (15.7)	0 (0.0)	8 (16.0)	1 (4.2)
No, n (%)	43 (84.3)	25 (100.0)	42 (84.0)	23 (95.8)
Difference in % for Yes (Fostamatinib - Placebo) and 95% CI[a]	15.7 (5.7, 25.7)		11.8 (-1.1, 24.8)	

Source: m5, C788-047 Table 14.2.10; m5, C788-048 Table 14.2.10.
CI = confidence interval.
[a] Confidence interval calculated based on the normal approximation.

Table 14: Secondary Efficacy Endpoints – Platelet Count ≥ 30,000/µL and ≥ 20,000/µL above Baseline at Week 12 and at Week 24 – ITT Subjects with Baseline Platelet Count < 15,000/µL

Parameter Statistic	C788-047		C788-048	
	Fostamatinib (N=25)	Placebo (N=12)	Fostamatinib (N=22)	Placebo (N=9)
Week 12				
Yes, n (%)	4 (16.0)	0 (0.0)	6 (27.3)	1 (11.1)
No, n (%)	21 (84.0)	12 (100.0)	16 (72.7)	8 (88.9)
Difference in % for Yes (Fostamatinib - Placebo) and 95% CI[a]	16.0 (1.6, 30.4)		16.2 (-11.5, 43.9)	
p-value[b]	0.2823		0.6395	
Week 24				
Yes, n (%)	4 (16.0)	0 (0.0)	3 (13.6)	0 (0.0)
No, n (%)	21 (84.0)	12 (100.0)	19 (86.4)	9 (100.0)
Difference in % for Yes (Fostamatinib - Placebo) and 95% CI[a]	16.0 (1.6, 30.4)		13.6 (-0.7, 28.0)	
p-value[b]	0.2823		0.5375	

Source: m5, C788-047 Table 14.2.10; m5, C788-048 Table 14.2.10.
CI = confidence interval.
[a] Confidence interval calculated based on the t-distribution for continuous variables and on the normal approximation for categorical variables.
[b] p-value from Fisher's Exact Test, testing for a difference in proportions between treatments

IBLS and WHO Bleeding Scales

Bleeding symptoms were assessed at each visit using two bleeding score scales, the IBLS and WHO bleeding scales. For each scale, the mean subject scores across visits were secondary endpoints. For each scale, mean scores across visits were numerically somewhat lower in the fostamatinib group (IBLS: 0.04 versus 0.06 for fostamatinib and placebo, respectively [95% CI -0.05, 0.02]; WHO: 0.26 versus 0.38 [95% CI -0.32, 0.09]) compared to the placebo group. For these two endpoints, the results based on the PP population were similar to the results based on the ITT population.

There was no difference between arms for the secondary endpoint of bleeding-score (Table 15). This is not unexpected given that patients with a high IBLS were excluded from the study. Of note is the difference in IBLS between the two identical studies: in study 047 IBLS was higher (in both arms) than in study 048. One difference between the two studies is the mean age with patients in study 047 being on average 7.5 years older than in study 048.

Table 15: Summary of Bleeding Scores in C788-047 and C788-048 (ITT Population)

Parameter	C788-047		C788-048	
	Fostamatinib (N=51)	Placebo (N=25)	Fostamatinib (N=50)	Placebo (N=24)
IBLS – Mean score at baseline				
N	51	25	50	24
Mean	0.14	0.12	0.07	0.06
Minimum – Maximum	0.0 - 0.4	0.0 - 0.3	0.0 - 0.3	0.0 - 0.3
IBLS – Efficacy Endpoint: Mean score across 9 anatomical sites and across visits during the 24-week treatment period[a]				
N	51	25	50	24
Mean	0.13	0.14	0.04	0.06
Median	0.09	0.12	0.01	0.02
SD	0.12	0.10	0.08	0.07
Minimum – Maximum	0.0 - 0.5	0.0 - 0.3	0.0 - 0.4	0.0 - 0.2
Difference in Means (Fostamatinib - Placebo) and 95% CI[b]	-0.01 (-0.1, 0.0)		-0.01 (-0.05, 0.02)	
p-value[c]	0.6642		0.4927	
WHO – Efficacy Endpoint: Mean of WHO Bleeding Scale scores across visits during the 24-week treatment period[d]				
N	51	25	50	24
Mean	0.61	0.46	0.26	0.38
Median	0.33	0.17	0.00	0.13
SD	0.66	0.56	0.38	0.47
Minimum – Maximum	0.0 - 2.8	0.0 - 2.0	0.0 - 1.1	0.0 - 1.7
Difference in Means (Fostamatinib - Placebo) and 95% CI[b]	0.15 (-0.2, 0.5)		-0.12 (-0.3, 0.1)	
p-value[c]	0.3365		0.2499	

Source: m5, C788-047 CSR: Table 14.2.10, Table 14.3.14; m5, C788-048 CSR: Table 14.2.10, Table 14.3.14,
CI = confidence interval; IBLS = ITP bleeding scale; SD = standard deviation; WHO = World Health Organization.

[a] IBLS: At each visit for each subject, 9 anatomical sites were each graded from 0 (none) to 2 (marked bleeding). At baseline the parameter summarized is the subject's average score across the 9 sites (note: the source table for the baseline values summarizes the total score at baseline, which is divided by 9 to obtain the average score). The efficacy endpoint summarized is the average across visits of the subject's average score across sites.

[b] Confidence interval calculated based on the t-distribution.

[c] p-value from a two-sided two-sample t-test, testing for a difference in means between fostamatinib and placebo.

[d] WHO bleeding scale: At each visit, each subject's symptoms were graded from 0 (no bleeding) to 4 (debilitating blood loss). For each subject, the efficacy endpoint summarized is the average score across visits.

Ancillary analyses

047:

Table 20: Study C788-047: Subgroup Analyses of Primary Efficacy Endpoint by Age, Sex, Previous TPO Receptor Agonist, Prior Splenectomy, and Baseline Platelet Count (ITT Population)

Parameter	Fostamatinib (N=51)	Placebo (N=25)	Difference (95% CI)[a]	Fostamatinib (N=51)	Placebo (N=25)	Difference (95% CI)[a]
Age	**< median (57 years)**			**≥ median (57 years)**		
Total, n	23	12	21.7 (4.9, 38.6)	28	13	14.3 (1.3, 27.2)
Yes, n (%)	5 (21.7)	0		4 (14.3)	0	
Sex	**Male**			**Female**		
Total, n	21	8	19.0 (2.3, 35.8)	30	17	16.7 (3.3, 30.0)
Yes, n (%)	4 (19.0)	0		5 (16.7)	0	
Prior TPO-RA	**Previous TPO-RA**			**No Previous TPO-RA**		
Total, n	26	15	15.4 (1.5, 29.3)	25	10	20.0 (4.3, 35.7)
Yes, n (%)	4 (15.4)	0		5 (20.0)	0	
Prior splenectomy	**Prior Splenectomy**			**No Prior Splenectomy**		
Total, n	20	10	15.0 (-0.6, 30.6)	31	15	19.4 (5.4, 33.3)
Yes, n (%)	3 (15.0)	0		6 (19.4)	0	
Baseline platelets	**< 15,000/µL**			**≥ 15,000/µL**		
Total, n	25	12	16.0 (1.6, 30.4)	26	13	19.2 (4.1, 34.4)
Yes, n (%)	4 (16.0)	0		5 (19.2)	0	

Source: m5, C788-047 Table 14.2.4, Table 14.2.5, Table 14.2.7, Table 14.2.8, and Table 14.2.9
Yes = primary efficacy endpoint responder
[a] Confidence interval based on the normal approximation.

Table 14.3.12.1

ITP CONCOMITANT MEDICATIONS BY PRIMARY EFFICACY RESPONDER STATUS AND TREATMENT
ITT POPULATION

ATC Class 3/Preferred Term	Fostamatinib Responder (N=9) n (%)	Fostamatinib Non-Responder (N=42) n (%)	Placebo (N=25) n (%)	Total (N=76) n (%)
ANABOLIC STEROIDS	1 (11.1)	0 (0.0)	0 (0.0)	1 (1.3)
DANAZOL	1 (11.1)	0 (0.0)	0 (0.0)	1 (1.3)
BLOOD AND RELATED PRODUCTS	0 (0.0)	2 (4.8)	1 (4.0)	3 (3.9)
PLATELETS	0 (0.0)	2 (4.8)	1 (4.0)	3 (3.9)
CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN	5 (55.6)	14 (33.3)	14 (56.0)	33 (43.4)
DEXAMETHASONE	1 (11.1)	4 (9.5)	3 (12.0)	8 (10.5)
METHYLPREDNISOLONE	1 (11.1)	1 (2.4)	2 (8.0)	4 (5.3)
PREDNISOLONE	1 (11.1)	8 (19.0)	6 (24.0)	15 (19.7)
PREDNISONE	4 (44.4)	5 (11.9)	6 (24.0)	15 (19.7)
IMMUNOGLOBULINS	1 (11.1)	14 (33.3)	7 (28.0)	22 (28.9)
ANTI-D IMMUNOGLOBULIN	0 (0.0)	1 (2.4)	0 (0.0)	1 (1.3)
IMMUNOGLOBULIN G HUMAN	1 (11.1)	1 (2.4)	0 (0.0)	2 (2.6)
IMMUNOGLOBULIN HUMAN NORMAL	1 (11.1)	11 (26.2)	6 (24.0)	18 (23.7)
IMMUNOGLOBULINS	0 (0.0)	3 (7.1)	1 (4.0)	4 (5.3)
IMMUNOSUPPRESSANTS	0 (0.0)	2 (4.8)	1 (4.0)	3 (3.9)
AZATHIOPRINE	0 (0.0)	2 (4.8)	1 (4.0)	3 (3.9)

Program Name: F:\RIGEL\ITP\047\PROGRAMS\TABLES\T14031201.SAS Creation Date, Time: 14JAN17 22:18
Source: Listing 16.2.8.12
Note: ITP concomitant medications include all ITP medications used after the first dose of study drug.
Subjects are counted at most once for an ATC class, even if they took the same medication on multiple occasions or more than one medication in the same ATC class. Similarly, subjects are counted at most once for a preferred term, even if they took the same medication on multiple occasions or more than one medication with the same preferred term. Subjects may fall into more than one category, so the percentages may sum to more than 100%.

048:

Table 22: Study C788-048: Subgroup Analyses of Primary Efficacy Endpoint by Age, Sex, Previous TPO Receptor Agonist, Prior Splenectomy, and Baseline Platelet Count (ITT Population)

Parameter	Fostamatinib (N=50)	Placebo (N=24)	Difference (95% CI)[a]	Fostamatinib (N=50)	Placebo (N=24)	Difference (95% CI)[a]
Age	**< median (49.5 years)**			**≥ median (49.5 years)**		
Total, n	25	12	24.0 (7.3, 40.7)	25	12	3.7 (-16.5, 23.8)
Yes, n (%)	6 (24.0)	0		3 (12.0)	1 (8.3)	
Sex	**Male**			**Female**		
Total, n	19	11	12.0 (-13.0, 37.0)	31	13	16.1 (3.2, 29.1)
Yes, n (%)	4 (21.1)	1 (9.1)		5 (16.1)	0	
Prior TPO-RA	**Previous TPO-RA**			**No Previous TPO-RA**		
Total, n	20	10	15.0 (-0.6, 30.6)	30	14	12.9 (-6.8, 32.5)
Yes, n (%)	3 (15.0)	0		6 (20.0)	1 (7.1)	
Prior splenectomy	**Prior Splenectomy**			**No Prior Splenectomy**		
Total, n	14	9	21.4 (-0.1, 42.9)	36	15	10.0 (-7.5, 27.5)
Yes, n (%)	3 (21.4)	0		6 (16.7)	1 (6.7)	
Baseline platelets	**< 15,000/µL**			**≥ 15,000/µL**		
Total, n	22	9	9.1 (-2.9, 21.1)	28	15	18.3 (-2.1, 38.7)
Yes, n (%)	2 (9.1)	0		7 (25.0)	1 (6.7)	

Source: m5, C788-048 Table 14.2.4, Table 14.2.5, Table 14.2.7, Table 14.2.8, and Table 14.2.9
Yes = primary efficacy endpoint responder; TPO = thrombopoietin.
[a] Confidence interval based on the normal approximation.

Table 14.3.12.1

ITP CONCOMITANT MEDICATIONS BY PRIMARY EFFICACY RESPONDER STATUS AND TREATMENT
ITT POPULATION

ATC Class 3/Preferred Term	Fostamatinib Responder (N=9) n (%)	Fostamatinib Non-Responder (N=41) n (%)	Placebo Responder (N=1) n (%)	Placebo Non-Responder (N=23) n (%)	Total (N=74) n (%)
ANABOLIC STEROIDS	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	1 (1.4)
DANAZOL	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	1 (1.4)
BLOOD AND RELATED PRODUCTS	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.4)
PLATELETS, CONCENTRATED	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.4)
CORTICOSTEROIDS FOR SYSTEMIC USE, PLAIN	3 (33.3)	19 (46.3)	0 (0.0)	15 (65.2)	37 (50.0)
DEXAMETHASONE	0 (0.0)	2 (4.9)	0 (0.0)	5 (21.7)	7 (9.5)
HYDROCORTISONE	0 (0.0)	2 (4.9)	0 (0.0)	0 (0.0)	2 (2.7)
METHYLPREDNISOLONE	0 (0.0)	2 (4.9)	0 (0.0)	4 (17.4)	6 (8.1)
PREDNISOLONE	0 (0.0)	1 (2.4)	0 (0.0)	1 (4.3)	2 (2.7)
PREDNISONE	2 (22.2)	13 (31.7)	0 (0.0)	5 (21.7)	20 (27.0)
PREDNISONE ACETATE	1 (11.1)	1 (2.4)	0 (0.0)	2 (8.7)	4 (5.4)
IMMUNOGLOBULINS	1 (11.1)	5 (12.2)	0 (0.0)	6 (26.1)	12 (16.2)
IMMUNOGLOBULIN HUMAN NORMAL	1 (11.1)	5 (12.2)	0 (0.0)	5 (21.7)	11 (14.9)
IMMUNOGLOBULINS	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	1 (1.4)
IMMUNOSUPPRESSANTS	0 (0.0)	4 (9.8)	0 (0.0)	0 (0.0)	4 (5.4)
AZATHIOPRINE	0 (0.0)	4 (9.8)	0 (0.0)	0 (0.0)	4 (5.4)

Program Name: F:\RIGEL\ITP\048\PROGRAMS\TABLES\T14031201.SAS Creation Date, Time: 17JAN17 11:19
Source: Listing 16.2.8.12
Note: ITP concomitant medications include all ITP medications used after the first dose of study drug.
Subjects are counted at most once for an ATC class, even if they took the same medication on multiple occasions or more than one medication in the same ATC class. Similarly, subjects are counted at most once for a preferred term, even if they took the same medication on multiple occasions or more than one medication with the same preferred term. Subjects may fall into more than one category, so the percentages may sum to more than 100%.

The efficacy of fostamatinib in splenectomised patients compared to non-splenectomised patients is higher in study 048 whereas the opposite is the case for study 047, mainly illustrating the fact that the number of patients is too low to conclude anything with regards to the various subgroups.

In study 047 only 1/9 (11.1%) responders previously received rituximab compared to 25/42 (59.5%) non-responders whereas in study 048 3/9 (33.3%) of responders and 5/41 (12.2%) of non-responders previously received rituximab.

The issues with the small number of patients is also evident for concomitant steroid treatment (Tables 14.3.12.1 above). Other subgroups of particular interest, besides splenectomised patients and patients receiving concomitant ITP treatment, are the elderly (>65, >70, >75 years of age) and whether the patients had received prior TPO-RA treatment or not. Nevertheless, due to the limited data no conclusions as to the impact of concomitant treatment and the effect of age, prior splenectomy or TPO-RA treatment can be drawn.

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections). The pivotal studies 047 and 048 are merged, as study design was identical. Results from 047 is written in black (and updated primary endpoint results in **bold**) and 048 in blue.

Table XXX: Summary of efficacy for trial C788-047 (in black and in bold after removing pt. 047-470-001 for the primary efficacy endpoint) and C788-048 (in blue)

Title: A PHASE 3, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF FOSTAMATINIB DISODIUM IN THE TREATMENT OF PERSISTENT/CHRONIC IMMUNE THROMBOCYTOPENIC PURPURA (ITP)			
Study identifier	C788-047 / C788-048		
Design	This was a Phase 3 multicenter, randomized, double-blind, placebo-controlled, parallel group study to investigate the efficacy of 24 weeks of treatment with fostamatinib versus placebo in achieving a stable platelet count in subjects with persistent/chronic ITP.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	24 weeks 1 to 4 weeks 3 weeks follow-up; extension into Study C788-049	
Hypothesis	Superiority		
Treatments groups	Fostamatinib		Fostamatinib 100 or 150 mg, 1 tablet bid over24 weeks, 51 randomized patients
	Placebo		Placebo (matching 100 or 150 mg), 1 table bid. over 24 weeks, 25 randomized patients
Endpoints and definitions	Primary Endpoint	Stable platelet response by Week 24	Defined as a platelet count of at least 50,000/µL on at least four of the last six scheduled visits over Weeks 14 to 24. Subjects who discontinued treatment before Week 24 because of lack of efficacy or an AE, or who received rescue treatment after Week 10, were considered primary efficacy endpoint non-responders.
	Secondary Endpoint	Platelet response (a platelet count of at least 50,000/µL) at Week 12 and at Week 24	Proportion of Subjects with a Platelet Count ≥ 50,000/µL at Week 12 and at Week 24
	Secondary Endpoint	Subjects with Low Baseline Platelet Count (< 15,000/µL)	Proportion of Subjects with a Platelet Count of ≥ 30,000/µL and ≥ 20,000/µL above Baseline at Week 12 and at Week 24
	Secondary Endpoint	IBLS and WHO Bleeding Scales	Frequency and severity of bleeding according to the ITP Bleeding Score (IBLS) and World Health Organization (WHO) bleeding scale over the 24-week study period
Database lock	16 August 2016 / 04 October 2016		

Results and Analysis				
Analysis description	**Primary Analysis (LOCF)**			
Analysis population and time point description	ITT population: Study 047 / Study 048 *A platelet count of at least 50,000/µL on at least four of the last six scheduled visits over weeks 14 to 24.*			
Descriptive statistics and estimate variability	Treatment group		Fostamatinib	Placebo
	Number of subjects		51 / 50	25 / 24
Stable platelet response by Week 24	Yes, n(%) **(when removing pt. that had Day1 14 days after randomisation and was thus considered a non-responder)**		9 (17.6) **8 15.7)**/ 9 (18.0)	0 (0.0) / 1 (4.2)
	No, n(%)		42 (82.4) / 41 (82.0)	25 (100) / 23 (95.8)
	Difference (fostamatinib – placebo) in % Yes	17.6 **(15.7%)** / 13.8		
	CI*	3.1, 30.5 **(5.7, 25.7)**/ -6.1, 27.9		
	p-value #	0.0261 **(0.0462)**/ 0.1519		
Notes	CI= Confidence Interval *Confidence interval based on the normal approximation. #p-value is from Fisher' s Exact Test, testing for a difference in proportions between treatments			

Analysis description	**Sensitivity Analysis (Multiple Imputation) Study 048**			
Analysis population and time point description	ITT population *A platelet count of at least 50,000/µL on at least four of the last six scheduled visits over Weeks 14 to 24.*			
Descriptive statistics and estimate variability	Treatment group		Fostamatinib	Placebo
	Number of subject		50	24
Stable platelet response by Week 24	Yes, n(%) $		18.00	4.34
	No, n(%)$		82.00	95.8
	Difference fostamatinib - placebo in % Yes	13.66		
	CI*	0.16, 27.16		
	p-value#	0.0474		
Notes	CI= Confidence Interval *Confidence interval based on the normal approximation. #p-value is from Fisher's Exact Test, testing for a difference in proportions between treatments $, Missing platelet count values were imputed using multiple imputation methods. SAS MIANALYZE procedure was used to combine estimates across imputations. Reported percentages and p-value are based on the average of 10,000 iterations.			

Analysis description	**Secondary Analysis:** *Proportion of Subjects with a Platelet Count ≥ 50,000/µL at Week 12 and at Week 24*			
Analysis population and time point description	ITT population: Study 047 / Study 048			
Descriptive statistics and estimate variability	Treatment group		Fostamatinib	Placebo
	Number of subjects		51 / 50	25 / 24
Platelet response (a platelet count of at least 50,000/µL) at Week 12 and at Week 24	Week 12 Yes, n (%)		11 (21.6) / 12 (24.0)	0 (0.0) / 3 (12.5)
	Week 12 No, n (%)		40 (78.4) / 38 (76.0)	25 (100.0) / 21 (87.5)
	Week 12 (Difference fostamatinib – placebo) in % Yes (CI*)	21.6 (10.3, 32.9) / 11.5 (-6.3, 29.3)		
	Week 24 Yes, n(%)		8 (15.7) / 8 (16.0)	0 (0.0) / 1 (4.2)
	Week 24 No, n(%)		43 (84.3) / 42 (84.0)	25 (100.0) / 23 (95.8)
	Week 24 (Difference fostamatinib – placebo) in % Yes (CI*)	15.7 (5.7, 25.7) / 11.8 (-1.1, 24.8)		
Notes	CI= Confidence Interval *Confidence interval based on the normal approximation.			

Analysis description	**Secondary Analysis:** *Platelet Count ≥30,000/µL and ≥ 20,000/µL above baseline, at week 12 and at week 24 in subjects with a low (< 15,000/µL) baseline platelet count.*			
Analysis population and time point description	ITT population: Study 047 / Study 048 Thirty-seven subjects (25 subjects in the fostamatinib group and 12 subjects in the placebo group) had a baseline platelet count less than 15,000/µL in study 047. Twenty-nine (22 subjects in the fostamatinib group and 9 subjects in the placebo group) had a baseline platelet count less than 15,000/µL in study 048.			
Descriptive statistics and estimate variability	Treatment group		Fostamatinib	Placebo
	Number of subjects		25 / 22	12 / 9
Subjects with Low Baseline Platelet Count (< 15,000/µL)	Week 12 Yes, n(%)		4 (16.0)	0(0.0)
	Week 12 No, n(%)		21 (84.0)	12(100.0)
	Week 12 (Difference fostamatinib – placebo) in % Yes (CI*)	16.0 (1.6, 30.4) / 16.2 (-11.5, 43.9)		
	Week 24 Yes, n (%)		4 (16.0) / 3 (13.6)	0 (0.0) / 0 (0.0)
	Week 24 No, n (%)		21 (84.0) / 19 (86.4)	12 (100.0) / 9 (100.0)
	Week 24 (Difference fostamatinib – placebo) in % Yes (CI*)	16.0 (1.6, 30.4) / 13.6 (-0.7, 28.0)		
Notes	CI= Confidence Interval *Confidence interval based on the normal approximation.			

Analysis description	**Secondary Analysis:** *Bleeding symptoms according to the IBLS and WHO bleeding scales*. Study 047 / Study 048		
Analysis population and time point description	ITT population		
Descriptive statistics and estimate variability	Treatment group	Fostamatinib	Placebo
	Number of Subjects	51 / 50	25 / 24
IBLS Bleeding Scale Efficacy Endpoint: Mean score across 9 anatomical sites and across visits during the 24-week treatment period	Mean	0.13 / 0.04	0.14 / 0.06
	Median	0.09 / 0.01	0.12 / 0.02
	Difference fostamatinib - placebo in % Yes (CI*)	-0.01 (-0.1, 0.0) / 0.01 (-0.05, 0.02)	
	SD	0.12 / 0.08	0.10 / 0.07
	95% CI for mean	0.1, 0.2 / 0.02, 0.07	0.1, 0.2 / 0.03, 0.09
	p-value#	0.6642 / 0.4927	
WHO Bleeding Scale Efficacy Endpoint: Mean of WHO Bleeding Scale scores across visits during the 24-week treatment period	Mean	0.61 / 0.26	0.46 / 0.38
	Median	0.33 / 0.00	0.17 / 0.13
	Difference fostamatinib - placebo in % Yes (CI*)	0.15 (-0.2, 0.15) / -0.12 (-0.3, 0.1)	
	SD	0.66 / 0.38	0.56 / 0.47
	95% CI for mean	0.4, 0.8 / 0.15, 0.36	0.2, 0.7 / 0.18, 0.57
	p-value#	0.3365 / 0.2499	
Notes	CI= Confidence Interval *CI calculated based on the t-distribution for continuous variables and on the normal approximation for categorical variables. #p-value from a two-sided two-sample t-test, testing for a difference in means between fostamatinib and placebo.		

Analysis performed across trials (pooled analyses and meta-analysis)

Table 7: Platelet Response: Protocol-specified Primary Endpoints and ISE SAP-specified Endpoints

Protocol/SAP		Comparison with Placebo	Endpoint Summary Definition	Complete Definition	Notes
Protocol-Specified Primary Endpoints:					
Phase 3 Controlled Studies C788-047, C788-048	[1]	Yes	Platelet count ≥ 50,000/μL on ≥ 4 of 6 visits, Weeks 14-24.	Section 2.2.1	• Primary analysis: Imputation by LOCF. • Sensitivity analysis: Imputation by multiple imputation methodology.
Open-Label, Long-Term Extension Study C788-049	[2]		Long-Term Stable Platelet Response (Endpoint Version 1): Platelet count ≥ 50,000/μL within 12 weeks of beginning treatment that was subsequently sustained for a period of 12 months.	Section 2.3.1	• Analyzed based on interim data
	[3]	Yes (Crossover)	Stable Platelet Response in Placebo Crossover Subjects (Endpoint Version 2): Platelet count ≥ 50,000/μL within 12 weeks of beginning treatment that was subsequently sustained for a period of 12 weeks.	Section 2.3.1	• Analyzed based on interim data
Phase 2 Study D4300-022	[4]		Platelet count increase from baseline of ≥ 20,000/μL to a platelet count ≥ 30,000/μL.	Section 2.1.1	• Endpoint assessed at each follow-up visit based on available data.
ISE SAP-Specified Endpoints (analyses performed by study and pooled across study):					
ISE SAP	[5]	Yes	Same as primary endpoint in placebo-controlled studies ([1] above).	Appendix 1: SAP for ISE	• Imputation by multiple imputation methodology. • Sensitivity analysis: Imputed all subjects with missing response as non-response.
	[6]		(1) For subjects who initiated fostamatinib in one of the placebo-controlled studies: Same as primary endpoint ([1] above). (2) For subjects who were randomized to placebo in the Phase 3 studies and rolled over to the extension study: Platelet count ≥ 50,000/μL on ≥ 2 of 3 visits, Month 4-6.	Appendix 1: SAP for ISE	• Post-hoc definition. • Purpose: Estimate fostamatinib stable platelet response rate during first 6 months across all fostamatinib exposure.
	[7]		Treatment with fostamatinib for ≥ 6 months (180 days) and ≥ 2/3 of monthly platelet counts ≥ 50,000/μL after Month 3.	Appendix 1: SAP for ISE	• Post-hoc definition. • Purpose: Estimate stable platelet response rate across all fostamatinib subjects treated for ≥ 6 months.

Table 5: Study Drug Exposure and Compliance (Placebo-Controlled Efficacy Population)

	Study C788-047		Study C788-048		Randomized Studies	
	Placebo (N=25)	Fostamatinib (N=51)	Placebo (N=24)	Fostamatinib (N=50)	Placebo (N=49)	Fostamatinib (N=101)
Duration of Exposure (weeks)						
Median	12.14	12.14	12.14	12.71	12.14	12.29
Q1, Q3	12.00, 14.57	11.71, 21.43	11.93, 12.57	12.00, 23.71	12.00, 13.00	12.00, 21.43
Range	2.9, 24.7	1.1, 26.1	2.3, 24.1	2.6, 24.6	2.3, 24.7	1.1, 26.1
< 4 weeks	1 (4.0)	3 (5.9)	2 (8.3)	1 (2.0)	3 (6.1)	4 (4.0)
≥ 4 weeks	24 (96.0)	48 (94.1)	22 (91.7)	49 (98.0)	46 (93.9)	97 (96.0)
≥ 8 weeks	24 (96.0)	45 (88.2)	21 (87.5)	48 (96.0)	45 (91.8)	93 (92.1)
≥ 12 weeks	20 (80.0)	36 (70.6)	18 (75.0)	42 (84.0)	38 (77.6)	78 (77.2)
≥ 16 weeks	5 (20.0)	13 (25.5)	3 (12.5)	22 (44.0)	8 (16.3)	35 (34.7)
≥ 20 weeks	2 (8.0)	13 (25.5)	3 (12.5)	16 (32.0)	5 (10.2)	29 (28.7)
≥ 24 weeks	1 (4.0)	11 (21.6)	1 (4.2)	9 (18.0)	2 (4.1)	20 (19.8)
Total Daily Dose (mg)						
Median	259.01	254.82	258.28	263.04	258.93	259.15
Range	131.3, 270.2	140.0, 389.7	40.0, 268.7	146.2, 283.3	40.0, 270.2	140.0, 389.7
Treatment Compliance (%)						
Median	99.49	97.22	100.00	100.00	100.00	100.00
Range	70.2, 102.3	50.0, 115.7	67.2, 101.2	89.7, 102.7	67.2, 102.3	50.0, 115.7

Source: Appendix 2: Table 3.1
N = number of subjects in the Placebo-Controlled Efficacy Population; Q1 = first quartile; Q3 = third quartile

Table 6: Fostamatinib Exposure in Phase 3 Studies (Fostamatinib Efficacy Population)

	Fostamatinib Initiated in			
	Randomized Study		Extension Study	
	C788-047 (N=51)	C788-048 (N=50)	C788-049 (N=44)	All Subjects (N=145)
Total Subject Exposure (weeks)	2234.0	3648.3	2622.9	8505.1
Duration of Exposure (weeks)				
Median	24.29	52.79	30.07	29.14
Q1, Q3	12.86, 41.71	24.57, 120.14	12.93, 106.21	17.14, 103.57
Range	1.1, 179.6	2.6, 165.1	6.6, 146.6	1.1, 179.6
< 4 weeks, n (%)	3 (5.9%)	1 (2.0%)	0 (0.0%)	4 (2.8%)
≥ 4 weeks, n (%)	48 (94.1%)	49 (98.0%)	44 (100.0%)	141 (97.2%)
≥ 12 weeks, n (%)	41 (80.4%)	47 (94.0%)	37 (84.1%)	125 (86.2%)
≥ 24 weeks, n (%)	32 (62.7%)	42 (84.0%)	24 (54.5%)	98 (67.6%)
≥ 48 weeks, n (%)	12 (23.5%)	25 (50.0%)	21 (47.7%)	58 (40.0%)

Source: Appendix 2: Table 3.2
N = number of subjects in the Fostamatinib Analysis Population; Q1 = first quartile; Q3 = third quartile.

Final results considering pooled data and the refractory patient population are reported in the table below

Table 4: Study outcomes from placebo-controlled clinical studies

Study Outcomes	Statistical Parameters	Study C788-047		Study C788-048		Pooled studies		Refractory population[6]	
		Fosta (N=51)	PBO (N=25)	Fosta (N=50)	PBO (N=24)	Fosta (N=101)	PBO (N=49)	Fosta (N= 72)	PBO (N=33)
Stable platelet response[1,2]	n (%)	8 (16)	0 (0)	9 (18)	1 (4)	17 (17)	1 (2)	10 (14)	0 (0)
	CI 95%	(5.7, 25.7)	(0, 0)	(7.4, 28.7)	(0, 12.2)	(9.5, 24.1)	(0, 6.0)	(5.9, 21.9)	(0.0, 0.0)
	p-value	$p^3 = 0.0471$		NS		$p^3=0.0071$		$P^3=0.0287$	
Eligible for C788-049[4] at Week 12[5]	n (%)	28 (55)	22 (88)	33 (66)	19 (79)	61 (60)	41 (84)	43 (60)	29 (88)
Completed study (Week 24)	n (%)	12 (24)	1 (4)	13 (26)	2 (8)	25 (25)	3 (6)	16 (22)	1 (3)

[1] Includes all patients with platelet counts and excludes patients whose platelet counts were measured following rescue therapy after Week 10.

[2] Stable platelet response was prospectively defined as a platelet count of at least 50,000/μL on at least 4 of the 6 visits between Weeks 14 and 24.

[3] p-value from Fisher Exact test

[4] C788-049: open label extension study

[5] Patients who did not respond to treatment after 12 weeks were eligible to enrol in open-label extension study.

[6] Refractory patient population defined as the subgroup of patients who had received three or more prior ITP therapies

Fosta = fostamatinib; PBO = placebo; NS = Did not demonstrate a statistically significant difference between treatment arms

Table 18: Analyses of Secondary Efficacy Endpoints, Data Pooled Across Studies (Placebo-Controlled Efficacy Population)

Parameter	Fostamatinib (N=101)	Placebo (N=49)	Treatment Difference (95% CI)[a]
Achievement of a platelet response (a platelet count ≥ 50,000/μL)			
At Week 12:			
n (%)	23 (22.8)	3 (6.1)	16.6 (6.1, 27.2)
At Week 24:			
n (%)	16 (15.8)	1 (2.0)	13.8 (5.7, 21.9)
Among subjects with baseline platelet count < 15,000/μL, achievement of a platelet count ≥ 30,000/μL and ≥ 20,000/μL above baseline			
At Week 12:			
n/N (%)	10/47 (21.3)	1/21 (4.8)	16.5 (1.7, 31.3)
At Week 24:			
n/N (%)	7/47 (14.9)	0/21 (0.0)	14.9 (4.7, 25.1)
IBLS scores across visits during the 24-week treatment period			
Mean	0.09	0.10	-0.01 (-0.05, 0.02)
Median	0.06	0.09	
SD	0.106	0.095	
Minimum – Maximum	0.0 - 0.5	0.0 - 0.3	
Mean of WHO Bleeding Scale scores across visits during the 24-week treatment period			
Mean	0.43	0.42	0.02 (-0.17, 0.20)
Median	0.17	0.17	
SD	0.564	0.515	
Minimum – Maximum	0.0 - 2.8	0.0 - 2.0	

Source: Appendix 2: Table 5.7
Note: The baseline platelet count measurement is the last platelet count measurement prior to the first randomized dose.
CI = confidence interval; IBLS = ITP bleeding scale; SD = standard deviation; WHO = World Health Organization.
[a] Treatment difference = fostamatinib % - placebo %. Confidence interval calculated based on the t-distribution for continuous variables and on the normal approximation for categorical variables.

Clinical studies in special populations

The age distribution between the two treatment arms in both placebo controlled studies is similar:

Table 1 Number and Proportion of Subjects 65 Years of Age or Older in Fostamatinib ITP Studies

	Placebo			Fostamatinib			All		
	Age 65-74 Years (n/N)	Age 75-84 Years (n/N)	Age ≥ 85 Years (n/N)	Age 65-74 Years (n/N)	Age 75-84 Years (n/N)	Age ≥ 85 Years (n/N)	Age 65-74 Years (n/N)	Age 75-84 Years (n/N)	Age ≥ 85 Years (n/N)
Controlled Trials									
047	4/25	3/25	0/25	10/51	5/51	4/51	14/76	8/76	4/76
048	3/24	1/24	0/24	7/50	2/50	0/50	10/74	3/74	0/74
047/048	7/49	4/49	0/49	17/101	7/101	4/101	24/150	11/150	4/150
Non-controlled Trials									
049	7/44	2/44	0/44	14/79	4/79	2/79	21/123	6/123	2/123

047 = Study C788-047; 048 = Study C788-048; 022 = Study D4300C00022
Source: q166_t_demog.sas (05 February 2019

Supportive study(ies)

C788 049: A Phase 3 Open-Label Extension Study of Fostamatinib Disodium in the Treatment of Persistent/Chronic Immune Thrombocytopenic.

A total of 123 subjects from Studies C788-047 and C788-048 enrolled in this extension study (Table 2). Approximately 34.1% of subjects remained in the study at the time of the interim data cutoff.

Of the 76 subjects randomized in Study C788-047, 59 subjects rolled over to Study C788-049. Nine subjects (7 subjects treated with fostamatinib and 2 subjects in the placebo group) had discontinued from Study C788-047 (and did not enter Study C788-049) because of AEs (C788 047, Table 14.1.1). One subject treated with fostamatinib in Study C788-047 was a screen failure for Study C788-049.

Of the 74 subjects randomized in Study C788-048, 64 subjects rolled over to Study C788-049. Four subjects (2 subjects treated with fostamatinib and 2 subjects in the placebo group) had discontinued from Study C788-048 (and did not enter Study C788-049) because of AEs (C788 048 Table 14.1.1).

Table 2: Subjects from Studies C788-047 and C788-048 Rolling Over into Extension Study C788-049

Status	Total n (%)
Number of subjects signing informed consent	124
Number of screen failures	1[a]
Number of subjects in the Treated Population	123 (100.0)
Rollover from Study C788-047	59 (48.0)
Originally randomized to fostamatinib	36
Originally randomized to placebo	23
Rollover from Study C788-048	64 (52.0)
Originally randomized to fostamatinib	43
Originally randomized to placebo	21

Source: C788-049 Table 14.1.1 and Listing 16.2.4.1
[a] Subject was from Study C788-047 (fostamatinib group)

Five patients from study 047 and eight patients in study 048 in the fostamatinib arms (and only 1 placebo patient in 047 and 0 in 048) did not enter extension study 049 (Table 1 below) despite not having an AE (and they should still be blinded to the given treatment):

Table 1 Subjects in the Placebo-Controlled Studies Who did not Enter Extension Study 049 for Reasons Other Than Adverse Events

Subject Identifier	Subject Disposition
Study 047	
047-063-007	Discontinued Study 047 early (84 days from first dose) Reason for Early Discontinuation: Lost to Follow-Up
047-443-001	Completed Study 047; did not enter Study 049 due to screen failure
047-443-006	Discontinued Study 047 early (76 days from first dose)* Reason for Early Discontinuation: Withdrawal by Subject
047-461-002	Discontinued Study 047 early (85 days from first dose) Reason for Early Discontinuation: Lack of Efficacy
047-465-001	Discontinued Study 047 early (94 days from first dose) Reason for Early Discontinuation: Lack of Efficacy
047-486-002	Completed Study 047 but elected not to enter Study 049
047-497-002	Discontinued Study 047 early (73 days from first dose)* Reason for Early Discontinuation: Physician Decision
047-561-002	Discontinued Study 047 early (82 days from first dose) Reason for Early Discontinuation: Non-Compliance with Study Drug
Study 048	
048-427-002	Discontinued Study 048 early (119 days from first dose) Reason for Early Discontinuation: Lack of Efficacy
048-428-006	Discontinued Study 048 early (113 days from first dose) Reason for Early Discontinuation: Withdrawal by Subject
048-431-001	Completed Study 048 but elected not to enter Study 049
048-435-002 (PLB)	Discontinued Study 048 early (34 days from first dose)* Reason for Early Discontinuation: Withdrawal by Subject
048-438-004	Discontinued Study 048 early (57 days from first dose)* Reason for Early Discontinuation: Physician Decision
048-565-001	Completed Study 047 but elected not to enter Study 049

Study 047 = Study C788-047; Study 048 = Study C788-048; Study 049 = Study C788-049

Source: Q167_1_rsn_not_enter049_q132; Study 047 Listing 16.2.4.15 and Study 048 Listing 16.2.4.15

Note: Subjects who discontinued the placebo-controlled study in which they were participating prior to Week 12 were not eligible to enter the extension study (049).

* Discontinued prior to Week 12

The reason "Lack of Efficacy" (3 patients) after week 12 is puzzling given that neither the patients nor the treating physicians should know if the patients received fostamatinib or placebo. The patients should therefore have entered study 049 after week 12, unless they opted not to, but not for Lack of Efficacy. Furthermore, there were four "Withdrawal by Subject/Physician Decision" in the fostamatinib arms, but only one in one placebo arm.

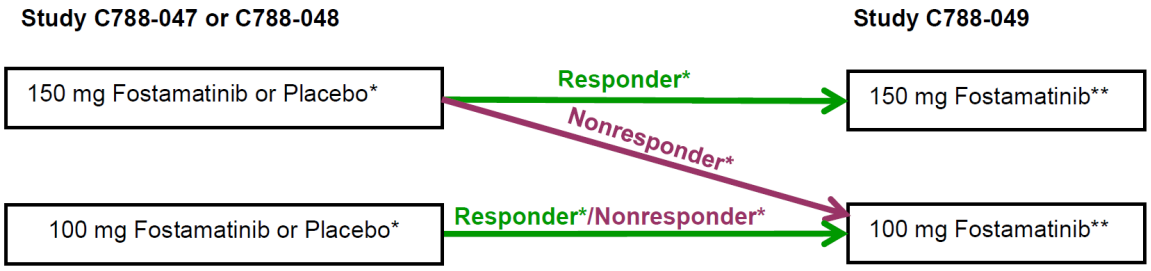
Certain therapeutic regimens for ITP were permitted for subjects with platelet counts < 50,000/μL who needed rescue support of the platelet count.

Allowed therapeutic ITP rescue regimens included:

- Intravenous (IV) IgG (IVIg): up to 1 g/kg × 1 to 3 days, or
- IV anti-rho [D] immunoglobulin (anti-D IgG): up to 50 to 75 μg/kg for 1 to 2 days, or

- IV methylprednisolone up to 1 g/day for 1 to 3 days, oral dexamethasone up to 40 mg/day for 1 to 2 days or oral prednisone up to 1 mg/kg/day for 1 to 3 days.

Figure 9-1: Initial Treatment Allocation



Note: Dose was administered *bid* unless dose reduction to *qd*.
*: Treatment assignment and dose from the previous study.
** At Month 1, subjects receiving fostamatinib 100 mg *bid* had the dose escalated to fostamatinib 150 mg *bid* if the platelet count was < 50,000/μL and fostamatinib was well tolerated.

The **primary objective** of this study was to assess the long-term safety of fostamatinib in subjects with persistent/chronic ITP.

The **secondary objectives** of this study were to establish the long-term efficacy of fostamatinib in achieving and maintaining a stable platelet count in subjects who completed the treatment phase of Study C788-047 or C788-048, and to assess the PK profile of fostamatinib in subjects with persistent/chronic ITP.

Primary Efficacy Endpoints

Long-Term Stable Platelet Response (Endpoint Version 1) – Satisfaction of this endpoint required meeting both of the following criteria:

Achievement of a platelet count ≥ 50,000/μL within 12 weeks of beginning active treatment.

Achievement of a sustained stable platelet response; defined as no 2 visits, at least 4 weeks apart, with a platelet count of < 50,000/μL, without an intervening visit with a platelet count of ≥ 50,000/μL unrelated to rescue therapy, within a period of 12 months following initial achievement of the target platelet count (see above).

Subjects who discontinued treatment (for any reason) or received rescue medication within 12 months following the initial achievement of a platelet count of at least 50,000/μL were considered non-responders with respect to this endpoint.

All 123 enrolled subjects were included in the analysis of this endpoint.

Based on this analysis, 19 subjects (15.4%) achieved platelet response within 12 weeks and maintained stable platelet response for at least 12 months (95% CI: 9.6%, 23.1%) (Table 14.2.1.1).

Database Cutoff Date: 08MAR2018

Table 14.2.1.1

PRIMARY EFFICACY ENDPOINT VERSION 1
TREATED POPULATION

Parameter	Statistic	Fostamatinib (N=123)
Achievement by 12 weeks and maintenance for 12 months of a stable platelet response		
Yes	n (%)	19 (15.4)
No	n (%)	104 (84.6)
	95% CI for % Yes (1)	(9.6, 23.1)

Stable Platelet Response in Placebo Crossover Subjects (Endpoint Version 2) – Satisfaction of this endpoint required meeting both of the following criteria:

1. Achievement of a platelet count of at least 50,000/μL within 12 weeks of beginning treatment (placebo treatment in C788-047 or C788-048 and fostamatinib treatment in C788-049).
2. Achievement of a sustained stable platelet response; defined as no two visits, at least 4 weeks apart, with a platelet count < 50,000/μL, without an intervening visit with a platelet count of ≥ 50,000/μL, unrelated to rescue therapy, within a period of 12 weeks following initial achievement of the target platelet count (see above).

The definition of response according to version 2 is different to that in the prior studies. This is due to the differences in study visit schedule of visits every 2 weeks in the Studies 047/048 to every 4 weeks in the Study 049.

Subjects who discontinued treatment or subjects who received rescue medication within 12 weeks following achievement of a platelet count of ≥ 50,000/ μ L, were considered non-responders.

A considerable number of unscheduled visits occurred during this study. In Studies 047 and 048, unscheduled visits were not taken into consideration for the analysis of the primary endpoint. Only platelet counts measured at scheduled visits contributed to the evaluation of the primary endpoint. However, in Study 049, schedule and unscheduled visits were used. The reason is that in Study 049, the endpoints are time dependent and not visit dependent. Forty-four (44) subjects (randomized to placebo in the prior study) were included in the analysis of this endpoint. Ten subjects (22.7%) achieved a stable platelet response (C788-049, Table 11-2), including one subject who had achieved this endpoint during treatment with placebo in the prior study.

Table 11-2: Responders: Subjects Treated with Placebo in Prior Studies – Version 2

Placebo in 047/048 Study	Fostamatinib in 049 Study		Total n (%)	95% CI for Total % Responder[a]	Difference in Total % Responder (Fostamatinib – Placebo) and 95% CI[b]
	Responder n (%)	Nonresponder n (%)			
Responder (placebo)	1 (2.3)	0 (0.0)	1 (2.3)	(0.1, 12.0)	20.5 (8.5, 32.4)
Nonresponder	9 (20.5)	34 (77.3)	43 (97.7)	---	
Total	10 (22.7)	34 (77.3)	44 (100.0)	---	
95% CI for Total % Responder	(11.5, 37.8)	---	---	---	p = 0.0039[c]

Source: Table 14.2.1.2
Note: 047 = C788-047; 048 = C788-048; 049 = C788-049.
Note: Primary efficacy endpoint Version 2, achievement by 12 weeks and maintenance for 12 weeks of a stable platelet response among subjects randomized to placebo in either Study C788-047 or C788-048.
[a] Clopper-Pearson exact confidence interval for a binomial proportion.
[b] CI based on normal approximation.
[c] p-value is from an exact two-sided McNemar's test, testing for a difference in proportions for Yes between treatments.

The primary objective of study 049 was safety. Secondary objectives were related to long-term efficacy (version 1 of the primary efficacy objective) and stable platelet response in placebo crossover subjects (version 2 of the primary efficacy objective). The sample size was not selected to detect a predefined difference, and the endpoints were not adjusted for multiplicity. The study is considered relevant during this assessment since it provides information regarding the product efficacy and long-term use. However, the results are only considered supportive. Bearing in mind that study 049 is an open-label study with a low number of participants (44 placebo patients from the double-blinded studies) the results of the efficacy endpoint v2 of this study (Table 11-2) supports the efficacy of around 18% from the placebo-controlled studies. 19/123 (15.4%) had a stable platelet response for at least a year (Table 14.2.1.1).

4/17 responders from the placebo-controlled trials lost their response in extension study 049 according to the primary efficacy endpoint version 1 (see Table 11-4 below).

Table 11-4: Duration of Treatment Response Based on Platelet Count and Rescue Medication (Treated Population)

Duration of Platelet Response (months)	Statistic
Subjects with any Platelet Response[a]	
n	57
Kaplan-Meier Estimated Median	6.1
95% CI for True Median	(2.4, 16.1)
Minimum – Maximum	0.3 - 38.3
Fostamatinib Subjects in 047/048 who were 049 Primary Efficacy Endpoint Version 1 Responders[b]	
n	13
Kaplan-Meier Estimated Median	38.3
95% CI for True Median	(16.1, 38.3)
Minimum – Maximum	14.2 - 38.3
Placebo Subjects in 047/048 who were 049 Primary Efficacy Endpoint Version 1 Responders[b]	
n	6
Kaplan-Meier Estimated Median	> 33.0
95% CI for True Median	(–, –)
Minimum - Maximum	23.1, > 33.0
All 049 Primary Efficacy Endpoint Version 1 Responders[b]	
n	19
Kaplan-Meier Estimated Median	38.3
95% CI for True Median	(–, –)
Minimum - Maximum	14.2, 38.3
Placebo Subjects in 047/048 who were 049 Primary Efficacy Endpoint Version 2 Responders[c]	
n	10
Kaplan-Meier Estimated Median	> 33.0
95% CI for True Median	(–, –)
Minimum - Maximum	6.5, > 33.0

Source: Table 14.2.3.1

Note: 047 = C788-047; 048 = C788-048; 049 = C788-049; CI = confidence interval.

Note: Duration of platelet response is defined as the time from when the subject first achieves a platelet count of at least 50,000/μL until either 1) the first of two visits with platelet counts < 50,000/μL that are at least 4 weeks apart without an intervening visit with a platelet count ≥ 50,000/μL unrelated to rescue therapy, or 2) rescue therapy, whichever occurred earlier. Subjects who have achieved and are maintaining a platelet response but who discontinued because of an AE were censored at the study discontinuation date. Subjects who dropped out for other reasons or completed the study or remained in the study at interim data cut while still maintaining a platelet response were censored as of the time of the last platelet measurement.

[a] Achievement of a platelet count of at least 50,000/μL unrelated to rescue therapy by 12 weeks following active treatment.

[b] Achievement by 12 weeks and maintenance for 12 months of a stable platelet response

[c] Achievement by 12 weeks and maintenance for 12 weeks of a stable platelet response

Table 2 Dose Adjustments and Platelet Counts for Subjects Who Experienced Temporary Loss of Response Followed by Ongoing Response at the Time of Data Cut-Off for Study 049

Subject Identifier	Fostamatinib Dose Adjustments	Platelet Count (/μL)
047-063-006 (Stable Responder)	↑ from 100 mg bid to 150 mg *bid* due to PC < 50,000/μL at Month 2 No dose adjustment ↓ from 150 mg bid to 100 mg *bid* due to neutropenia at Month 22 ↑ from 100 mg bid to 150 mg *bid* due to PC < 50,000/μL at Month 23 ↓ from 150 mg bid to 100 mg *bid* due to liver toxicity/injury at Month 24 No further dose adjustments	49,000 (Month 2) 44,000 (Month 15); 34,000 (Month 17); 46,000 (Month 19); 40,000 (Month 21) 44,000 (Month 22) 25,000 (Month 23) 65,000 (Month 24) 108,000 (Month 26); 116,000 (Month 28); 133,000 (Month 30); 95,000 (Month 32)*
047-554-005	No dose adjustment when PC < 50,000/μL at Month 6 (100 mg *bid*) ↓ from 100 mg *bid* to 150 mg QD due to PC > 250,000 at Month 12 per protocol ↑ from 150 mg QD to 100 mg *bid* due to PC normalized at Month 13 No further dose adjustments	33,000 (Month 6) 308,000 (Month 12) 190,000 (Month 13) > 50,000 (Months 14-20); 99,000 (Month 22)*
048-428-003	↑ from 100 mg *bid* to 150 mg *bid* due to PC < 50,000/μL at Month 1 No further dose adjustments	23,000 (Month 1); 51,000 (Month 2) 35,000 (Months 3 and 4) > 50,000 (Months 5-19) 33,000 (Month 20) > 50,000 (Months 21-30) 96,000 (Month 32)*
048-429-003	↑ from 100 mg *bid* to 150 mg *bid* due to PC < 50,000/μL at Month 2 No further dose adjustments	37,000 (Month 2) ≥ 50,000 (Months 3-14) 45,000 (Month 15) ≥ 50,000 (Months 16-20) 77,000 (Month 22)*
048-432-003	↑ from 100 mg *bid* to 150 mg *bid* due to PC < 50,000/μL at Month 10 No further dose adjustments	47,000 (Month 10) 45,000 (Month 11) 71,000 (Month 12) > 50,000 (Months 13-18) 52,000 (Month 20)*
048-439-002	↑ from 100 mg *bid* to 150 mg *bid* due to PC < 50,000/μL at Month 1 No further dose adjustments	46,000 (Month 1) 50,000 (Month 2) 48,000 (Month 3) > 50,000 (Months 4-28) 86,000 (Month 30)*
048-468-010 (Stable Responder)	↑ from 100 mg *bid* to 150 mg *bid* due to PC < 50,000/μL at Month 1 No further dose adjustments	29,000 (Month 1) > 50,000 (Months 2-10) 28,000 (Month 11) 48,000 (Month 12) > 50,000 (Months 13-15) 40,000 (Month 16) > 50,000 (Months 17-20) 103,000 (Month 22)*
048-473-006	No dose adjustment (150 mg *bid*) ↓ from 150 mg *bid* to 100 mg *bid* due to PC > 250,000 at Month 5 per protocol ↑ from 100 mg *bid* to 150 mg *bid* due to PC < 50,000/μL at Month 5** No further dose adjustments	296,000 (Month 4) 275,000 (Month 5) 428,000 (Month 6) > 50,000 (Months 7-24) 371,000 (Month 26)*
048-473-008	↑ from 100 mg *bid* to 150 mg *bid* due to PC < 50,000/μL at Month 1 No further dose adjustments	36,000 (Month 1) > 50,000 (Months 2-17) 131,000 (Month 18)*

↑ = dose increase; *bid* = twice daily; PC = platelet count
Note: Month refers to visit
* Last available value
** Unscheduled dose adjustment later in Month 5 visit window following SAE (rescue therapy).
Source: C788-049, Listings 16.2.5.1 and 16.2.6.1

Two deviations from the protocol not listed in the deviation listing have been noticed regarding rescue medication (i.e. IVIG and romiplostim) and patients receiving these treatments should have been considered non responders. Nevertheless, none of the responders received any non-allowed concomitant or rescue medication and subjects receiving rescue therapy after week 10 were treated in the analysis in an identical manner to that used for studies 047 and 048. Platelet counts observed within 4 weeks after any rescue medication, including any increase in concomitant steroid doses were not included in assessment of response. Study 049 is considered supportive only and main evidence for efficacy needs to be derived from the pivotal studies 047 and 048.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The indication pursued for Fostamatinib is for the treatment of thrombocytopenia in adult patients 18 years of age and older with persistent or chronic ITP who have had an insufficient response to one or more therapies. Fostamatinib is for oral administration.

The efficacy of fostamatinib for the treatment of chronic immune thrombocytopenia in ITP has been evaluated in four clinical studies:

- a Phase 2 study (D4300-022) (dose-finding)
- two Phase 3, double-blind, randomised, placebo-controlled studies (C788 047 and C788 048) (pivotal studies)
- an ongoing Phase 3, open-label, long-term extension study (C788 049) (supportive)

In the dose-finding study (022) pharmacokinetic and pharmacodynamic analyses could not be performed because of sample size limitations and thus do not comply with the recommendations in the EMA ITP guideline that doses should be evaluated for a platelet target level and range. Data are scarce with regards to a dose-response relationship and are based on PK data and Phase 2 results from the RA and ITP programs. The dose-response relationship issue is resolved as well as possible given the scarcity of data in ITP patients.

The design of the placebo-controlled phase 3 studies are in line with the EMA ITP guideline (EMA "Guideline on the clinical development of medicinal products intended for the treatment of chronic primary immune thrombocytopenia", EMA/CHMP/153191/2013). This includes accruing from multiple centres including Europeans, the double-blinded design and stratification according to splenectomy status. The pooling of these two studies is acceptable and in agreement with previous studies in ITP. The design of the studies is also in line with previous studies in ITP (romiplostim, eltrombopag). The EMA ITP guideline covers chronic ITP. There were 6/101 (6%) patients in the two placebo-controlled studies combined that had persistent (3-12 months since diagnosis) ITP. The applied indication for persistent ITP has been withdrawn.

Dose adjustment to as low as 100 mg qd was recommended/performed in the event of intolerability or AEs. Four subjects, who had a continuous response on 100 mg QD, have been presented to justify the use of this dose in case of high platelet counts or poor tolerability. From a practical point of view this is acceptable, as the treating physician would be expected to end treatment, if there is a lack of response to this dose.

The in- and exclusion criteria are in general endorsed. An exception is potentially inadequate wash-out times for prior treatment with IVIGs as well as rituximab. Partial agreement could be given to the argumentation

that efficacy assessment was done in week 14-24 and therefore any potentially inadequate wash-out time can be considered negligible. Furthermore, the mean duration of response to rituximab is about 10 months. Consequently, a wash-out period of 6 weeks is considered rather short. Nevertheless, as prior rituximab treatment commenced in 4 responders > 1 year ahead of fostamatinib treatment it is not considered having an impact on the platelet counts.

Specific concurrent ITP therapies were allowed during the study. According to the GL corticosteroid dependent or other treatment dependent patients excluding the experimental drug will be considered as non-responders. This was not applied in the trials. Clarification has been provided indicating that patients in studies 047 and 048 did not meet the definition of corticosteroid dependence. Of note, according to the inclusion criteria, patients have to receive stable doses of ITP concurrent medication for at least 14 days prior baseline. In contrast, the GL requires stable doses for at least 1 month. One patient (047-470-001) received concomitant steroid treatment before baseline and at the same time rescue steroid treatment, and is therefore not considered to have had a stable concomitant treatment ahead of baseline.
Patients testing positive for H. pylori were highly likely to have received antibiotic eradication treatment, although this has not been specified further. One was a placebo treated patient and two were fostamatinib treated non-responders.

The primary efficacy endpoint was achievement of a stable platelet response by Week 24 defined as a platelet count of at least 50,000/μL on at least 4 of the last 6 scheduled visits between Weeks 14 and 24 inclusive. This is in line with the EMA ITP guideline of a composite endpoint including a clinical meaningful platelet count remaining stable over a specified time period. One patient (047-470-001) did not commence treatment at the day of randomization but 2 weeks later; when considering randomization day as Day 1, this patient is a non-responder.

The GL proposes to include bleeding signs/symptoms, time to response, duration of response, concomitant treatment reduction and need for rescue treatment as secondary endpoints. This is only sparsely covered by the submitted phase III trials. In case of bleeding other scores/scales were used than that recommended by the GL. Overall, provided data do not allow clear conclusions regarding bleeding risk of included patients and of the effect of fostamatinib on the bleeding risk. Assessment of efficacy of fostamatinib needs to be based on the surrogate parameter platelet counts.

Study C788-049 was a phase III, open-label, extension study. Patients from studies C788-047 and C788-048 were to be enrolled in this extension study either those who successfully completed the 24 week treatment period or who were withdrawn early as non-responder. This extension study is still ongoing and two interim reports were provided, the latest was considered for assessment.

The primary measurement in this open-label extension study was platelet count done at every study visit. The first version of the primary efficacy endpoint was for the purpose of assessing efficacy among all subjects while they were on active treatment in one of the prior studies, in the current extension study, or in both, i.e. 1) achievement of a platelet count of at least 50,000/μL within 12 weeks of beginning active treatment and 2) Achievement of a sustained stable platelet response; defined as no 2 visits, at least 4 weeks apart, with a platelet count < 50,000/μL, without an intervening visit with a platelet count of $\geq$ 50,000/μL unrelated to rescue therapy, within a period of 12 months following initial achievement of the target platelet count. The second version of the primary efficacy endpoint was for the purpose of a within-subject, between study comparison of fostamatinib and placebo among subjects randomized to placebo in either of the prior studies. This version of the primary efficacy endpoint was the achievement and maintenance of a stable platelet count defined as follows: 1) Achievement of a platelet count of at least 50,000/μL within 12 weeks of beginning treatment (placebo treatment in the prior study and fostamatinib treatment in the present study) and 2)

Achievement of a sustained stable platelet response: defined as no two visits, at least 4 weeks apart, with a platelet count < 50,000/μL, without an intervening visit with a platelet count of $\geq$ 50,000/μL, unrelated to rescue therapy, within a period of 12 weeks following initial achievement of the target platelet count. Version 2 of the primary endpoint considers intra-individual changes in treatment response for subjects randomized to placebo treatment in the prior randomized study. Comparable data on subjects who were randomized to fostamatinib are missing. Four of 17 responders in the placebo-controlled studies did not have a long term response in extension study 49 (> 12 months after week 12; primary efficacy endpoint, version 1).

Efficacy data and additional analyses

In study 047 the proportion of subjects achieving the primary efficacy endpoint of a stable platelet response by week 24 (defined as a platelet count of at least 50,000/μL on at least 4 of the last 6 scheduled visits between weeks 14 and 24 inclusive) was 17.6% (9/51) in the fostamatinib group and 0% (0/25) in the placebo group (p = 0.0261). When removing patient 047-470-001 from the analysis (only 3/6 visits with platelet counts of at least 50,000/μL when counting from the randomization day) the efficacy endpoint is 15.7% (95% CI 5.7%, 25.7%); the study still shows significance although with very wide CIs (p=0.0471).

In study 048 the proportion of subjects in the intent-to-treat (ITT) population achieving the primary efficacy endpoint of a stable platelet response was 18.0% (9/50) in the fostamatinib group and 4.2% (1/24) in the placebo group (p = 0.1519: NS).

The data from the two placebo-controlled studies was pooled: The estimated proportion of subjects achieving a stable platelet response was 17.8% (18/101) in the fostamatinib group and 2.1% (1/49) in the placebo group (p = 0.0072).When removing patient 047-470-001 the response was 16.8% (17/101) in the fostamatinib group and 2.1% (1/49) in the placebo group (p=0.0071). The studies had identical study design, but the mean age of the patients differed by 7.5 years, and thus the populations are not entirely comparable.

In the open-label extention study 049 the version 2 efficacy endpoint (Stable Platelet Response in Placebo Crossover Subjects) is *supportive* of the primary efficacy endpoint from the placebo-controlled studies: 10/44 subjects (22.7%) achieved a stable platelet response including one subject who had achieved this endpoint during treatment with placebo in the prior study. The difference (fostamatinib – placebo) in the proportion responding was 20.5% (95% CI, normal approximation: 8.5%, 32.4%).

The secondary efficacy endpoints of platelet count at week 12 and 24 for the entire population and for patients with at low baseline platelet count are considered *supportive* of the primary efficacy endpoint. The Applicant proposed a hierarchal testing to control for the type I error in the SAPs. However, this was not implemented and therefore it is concluded that the confidence intervals and p-values from the secondary endpoints are only nominal and cannot lead to strong conclusions.

To better understand the effect of fostamatinib on platelet counts the Applicant was requested to provide an analysis of the absolute and relative change in platelet counts over time. To this end, results were presented from a mixed effects model for the ratio of post baseline to baseline platelet counts, which was fit based on pooled data from both studies. Corresponding results indicate an improvement in platelet counts starting from Week 2, which somehow remains stable until Week 12. The mean relative change (%) in platelet count at Week 12 was 81.6% for subjects in the fostamatinib group, compared with 7.6% for subjects in the placebo group. Given the large amount of discontinuation after Week 12, it is not possible to present firm conclusions regarding the effect at Week 24.

The median number of unique prior therapies was 3 in both studies in the fostamatinib arms and 5 and 4 for all ITP therapies in study 047 and 048, respectively, excluding splenectomy, which had been performed in 39% and 28% of the patients, respectively (adding another ITP treatment for these patients). 6% had persistent ITP (3-12 months). Given the low efficacy compared to recommended treatments in second line such as splenectomy, rituximab, and TPO-receptor agonists (Provan et al., 2010, Neunert et al., 2011, Lambert and Gernsheimer, 2017, George and Arnold, 2018, Matzdorff et al, 2018) and the non-negligible adverse events in a non-malignant disease, the use of fostamatinib can be considered in adult patients who are refractory to other treatments.

2.5.4. Conclusions on the clinical efficacy

The efficacy is considered established in the indicated patient population.

2.6. Clinical safety

Table 1 Summary of Clinical Development Program for Fostamatinib

Population	Number of Studies	Number of Subjects Exposed to Fostamatinib
Completed Studies	**50**	**4585**
Healthy Subjects	26	724[1]
Other Clinical Pharmacology Studies	4	101[2]
ITP	3	119 (Phase 3 studies: N=102 Phase 2 study: N=17)[3]
Rheumatoid Arthritis	13	3,437[4]
Oncology	4	204 (Sponsor studies: N =167 NCI study: N=37)[5]
Ongoing Studies	**3**	**193**
ITP (Study C-935788-049)	1	123[6]
Ongoing Studies (Other Indications)	2	70
IgAN (Study C-935788-050)	1	51
AIHA (Study C-935788-053)	1	19[7]
Total number of subjects exposed to fostamatinib		**4699**

Source: m5, ISS-HS, Table 1 and Table 2; m5, ISS-ITP, Appendix 2: Table 1.1.2; and D4300-022, Table 14.1.1; m5, ISS-RA, Appendix 2: Table 1.1.2; m5, ISS-ONC, Appendix 2: Table 1.1.1

Abbreviations: AIHA = autoimmune hemolytic anemia; IgAN = immunoglobulin A nephropathy; ITP = immune thrombocytopenia

1 Includes 26 Studies: N = 439 (single dose); N= 183 (Multiple dose), N = 183 (drug-drug interaction)

2 Includes clinical pharmacology studies in subjects with renal impairment (N=16), and with hepatic impairment (N = 24), a drug-drug interaction study with methotrexate in RA subjects (N = 16), and a Phase 1 study with R406 the active metabolite of fostamatinib (N =45).

3 Includes one Phase 2 study (N = 17 unique subjects) and 2 Phase 3 Studies (N=102)

4 Includes 9 placebo-controlled studies (N = 2414) and 4 extension studies in rheumatoid arthritis.

Patient exposure

ITP:

Placebo-Controlled Period: data from the double-blind studies (047 and 048).

Fostamatinib Exposure Period: data from 146 subjects receiving fostamatinib at any time in the double-blind and extension studies (047, 048, and 049).

In the ITP extension study 98 patients received fostamatinib ≥24 weeks (168 days) with a median of 204 days (Table 2). Long-term safety is thus not evaluable in this indication. In the RA placebo-controlled studies 627 patients received fostamatinib 200-300 mg/day for ≥24 weeks but <36 weeks with a median of 168 days for the entire cohort (Table 4), whereas in the entire fostamatinib dataset in RA (Table 5) 217 patients received fostamatinib (200-300 mg/day) for ≥3 years with a median of 483 days for the entire cohort (Table 6). These patients usually have many co-morbidities making it difficult to evaluate long-term safety without a comparator/placebo, and the placebo-controlled period is less than 36 weeks. The Applicant has not suggested any new ways to evaluate long-term safety other than following the patients in study 049. Given the low number of patients, this is not satisfactory [19/123 subjects (15.4%) achieved platelet response within 12 weeks and maintained stable platelet response for at least 12 months (95% CI: 9.6%, 23.1%)]. The Applicant has agreed to the request to submit the protocol for a PASS within 3 months after the CHMP opinion and before commencing the study.

The safety information from the ITP and RA studies is accepted as the main source of safety data.

Table 2 Extent of Exposure in ITP Studies – Placebo-Controlled and Fostamatinib Exposure Periods

Variable	Placebo-Controlled Period[a] (N=150)		Fostamatinib Exposure[b] Period
	Fostamatinib (N=102)	Placebo (N=48)	(N=146)
Total Subject-Years Exposure	29.34	12.12	163.1
Duration of Exposure (days)			
Median	86.0	85.0	204.0
Min - Max	8 - 183	16 - 173	8 - 1257
Duration of Exposure Category, n (%)[c]			
< 4 weeks (< 28 days)	4 (3.9)	3 (6.3)	4 (2.7)
≥ 4 weeks (≥ 28 days)	98 (96.1)	45 (93.8)	142 (97.3)
≥ 8 weeks (≥ 56 days)	93 (91.2)	45 (93.8)	134 (91.8)
≥ 12 weeks (≥ 84 days)	78 (76.5)	38 (79.2)	125 (85.6)
≥ 24 weeks (≥ 168 days)	20 (19.6)	2 (4.2)	98 (67.1)
Total Daily Dose (mg)	n = 102	n = 48	n = 146
Median	258.84	258.97	255.6
Min - Max	40.0 - 389.7	131.3 - 270.2	40.0 - 389.7

Source: m5, ISS-ITP, Appendix 2: Table 2.2.1.1 and Table 2.2.2.1
Abbreviations: ITP = immune thrombocytopenia; Min = minimum; Max = maximum; SD = standard deviation.
[a] Duration of exposure was defined as study drug stop date minus study drug start date plus 1.
[b] Duration of exposure was defined as the sum of all available fostamatinib treatment durations within each study (Studies C788-047, C788-048, C788-049) for a given subject.
[c] Subjects can appear in more than one category.

RA:

Placebo-Controlled Safety Set:

Table 3: Blinded Study Drug Exposure in RA by Dose (Placebo-Controlled Safety Set)

		No. treated subjects by total daily dose			
	Duration of blinded period	Fostamatinib 100–150 mg/day	Fostamatinib 200–300 mg/day	All Fostamatinib	Placebo
Phase 2					
C788-006	12 weeks	46	96	142	47
C788-010	26 weeks	152	152	304	153
C788-011	13 weeks	0	146	146	73
D4300-004	6 weeks	104	87	191	81
D4300-008	12 weeks	99	31	130	33
D4300-033	4 weeks	0	68	68	67
Phase 3					
D4300-001	24 weeks	304	310	614	304
D4300-002	24 weeks	298	308	606	302
D4300-003	24 weeks	108	105	213	109
Total		**1111**	**1303**	**2414**	**1169**

Source: m5, ISS-RA, Appendix 2: Table 1.1.1
Abbreviations: RA = rheumatoid arthritis

Table 4: Duration of Blinded Study Drug Exposure in RA (Placebo-Controlled Safety Set)

	Fostamatinib 100–150 mg/day	Fostamatinib 200–300 mg/day	All Fostamatinib	Placebo
N	1111	1303	2414	1169
Days of exposure				
Mean (SD)	127.8 (52.4)	121.8 (53.8)	124.6 (53.2)	114.6 (55.1)
Median	169.0	163.0	168.0	92.0
Range	3, 183	2, 183	2, 183	2, 190
Categorical weeks of exposure				
< 4 weeks	19 (1.7)	20 (1.5)	39 (1.6)	64 (5.5)
≥ 4 weeks	1092 (98.3)	1283 (98.5)	2375 (98.4)	1105 (94.5)
≥ 8 weeks	952 (85.7)	1091 (83.7)	2043 (84.6)	952 (81.4)
≥ 12 weeks	866 (77.9)	1004 (77.1)	1870 (77.5)	852 (72.9)
≥ 24 weeks	603 (54.3)	627 (48.1)	1230 (51.0)	505 (43.2)
≥ 36 weeks	0	0	0	0
Total subject exposure years	389	435	823	367

Source: m5, ISS-RA, Appendix 2: Table 3.1.1
Abbreviations: RA = rheumatoid arthritis; SD = standard deviation

The **Fostamatinib Safety Set** (*Table* 5-6) encompasses all treatment with fostamatinib, including the double-blinded period in the primary studies, any open-label or crossover treatment in the primary studies, and all fostamatinib treatment in the extension studies.

Table 5: Fostamatinib Exposure by Dose in RA (Fostamatinib Safety Set)

	No. treated subjects by dose		
	Fostamatinib 100–150 mg/day	**Fostamatinib 200–300 mg/day**	**All Fostamatinib**
Phase 2			
C788-006	46	96	142
C788-010	152	152	304
C788-011	0	146	146
D4300-004	124	119	243
D4300-008	99	31	130
D4300-033	0	68	68
Phase 3			
D4300-001	304	498	802
D4300-002	298	459	757
D4300-003	108	105	213
Subtotal	1131	1674	2805
Extension treatment (placebo crossover)	101	531	632
Total exposed	1232	2205	3437

Source: m5, ISS-RA, Appendix 2: Table 1.1.2
Abbreviations: RA = rheumatoid arthritis

Table 6: Extent of Fostamatinib Exposure in RA (Fostamatinib Safety Set)

	Fostamatinib Dose		
	100–150 mg/day	**200–300 mg/day**	**All**
N	1232	2205	3437
Days of exposure			
Mean (SD)	547.0 (444.7)	544.8 (461.9)	545.6 (455.8)
Median	511.5	483.0	490.0
Range	3, 2481	1, 2338	1, 2481
Categorical weeks of exposure			
< 4 weeks	47 (3.8)	60 (2.7)	107 (3.1)
≥ 4 weeks	1185 (96.2)	2145 (97.3)	3330 (96.9)
≥ 12 weeks	1106 (89.8)	2005 (90.9)	3111 (90.5)
≥ 36 weeks	849 (68.9)	1521 (69.0)	2370 (69.0)
≥ 1 year	728 (59.1)	1321 (59.9)	2049 (59.6)
≥ 2 year	294 (23.9)	457 (20.7)	751 (21.9)
≥ 3 year	117 (9.5)	217 (9.8)	334 (9.7)
Total subject exposure years	1845	3289	5134

Source: m5, ISS-RA, Appendix 2: Table 3.1.2
Abbreviations: RA = rheumatoid arthritis

Licensure in RA is not being pursued as fostamatinib did not affect bone erosion and joint destruction in 2/3 phase 3 studies. Development and licensure in oncology is not being pursued.

Adverse events

ITP: Placebo controlled period (study 047):

Table 12-2: Overview of Adverse Events – Safety Population

	Fostamatinib (N=51)	**Placebo (N=25)**
Number of Subjects (%) with:		
Any AE	49 (96.1)	19 (76.0)
Any Serious AE	8 (15.7)	5 (20.0)
Any Treatment Related AE[a]	39 (76.5)	7 (28.0)
Any AE Leading to Dose Reduction	5 (9.8)	1 (4.0)
Any AE Leading to Dose Interruption	16 (31.4)	4 (16.0)
Any AE Leading to Study Drug Withdrawal	8 (15.7)	2 (8.0)
Any AE Leading to Dose Reduction, Dose Interruption, or Study Drug Withdrawal	23 (45.1)	6 (24.0)
Any AE Leading to Death	0	1 (4.0)

Source: Table 14.3.1.1
AE = adverse event
[a] Treatment related AEs are events with a possible, probable, or missing causal relationship to study drug.

Placebo controlled period (study 048):

Table 12-2: Overview of Adverse Events – Safety Population

	Fostamatinib (N=51)	Placebo (N=23)
Number of Subjects (%) with:		
Any AE	36 (70.6)	18 (78.3)
Mean Number of AEs per Subject[a]	3.9	2.9
Any Serious AE	5 (9.8)	6 (26.1)
Any Treatment Related AE[b]	20 (39.2)	6 (26.1)
Any AE Leading to Dose Reduction[c]	5 (9.8)	0
Any AE Leading to Dose Interruption[c]	3 (5.9)	1 (4.3)
Any AE Leading to Study Drug Withdrawal[c]	2 (3.9)	2 (8.7)
Any AE Leading to Dose Reduction, Dose Interruption, or Study Drug Withdrawal[c]	9 (17.6)	2 (8.7)
Any AE Leading to Death	1 (2.0)	0

Source: Table 14.3.1.1

[a] Among subjects with at least one AE

[b] Treatment related AEs are events with a possible, probable, or missing causal relationship to study drug.

[c] Only one action taken, the most severe one, was reported for each AE, with the following ordering in increasing severity of actions taken: dose interruption, dose reduction, and study drug withdrawal.

In the Placebo-Controlled Period, 85 subjects (83.3%) receiving fostamatinib and 36 subjects (75%) receiving placebo experienced at least 1 TEAE (Table 16).

Table 16 Overall Summary of Safety in ITP: Placebo-Controlled Period and Fostamatinib Exposure Period

Parameter	Placebo-Controlled Period		Fostamatinib Exposure Period
	Fostamatinib (N = 102) n (%)	Placebo (N = 48) n (%)	Fostamatinib (N = 146) n (%)
Number of Subjects with at least 1 AE (n)	85	36	127
Average Number of AEs per Subject among Patiens with at Least 1 AE (n)	5.4	4.1	8.5
All AEs[a]	85 (83.3)	36 (75.0)	127 (87.0)
Mild	33 (32.4)	20 (41.7)	32 (21.9)
Moderate	36 (35.3)	9 (18.8)	60 (41.1)
Severe	16 (15.7)	7 (14.6)	35 (24.0)
Treatment-Related AEs[b]	60 (58.8)	13 (27.1)	96 (65.8)
Serious AE	13 (12.7)	10 (20.8)	39 (26.7)
AEs Leading to Dose Reduction[c]	9 (8.8)	1 (2.1)	15 (10.3)
Any AEs Leading to Dose Interruption[c]	18 (17.6)	5 (10.4)	35 (24.0)
Any AEs Leading to Study Drug Withdrawal[c]	10 (9.8)	4 (8.3)	27 (18.5)
Any AEs Leading to Dose Reduction, Dose Interruption, or Study Drug Withdrawal	32 (31.4)	8 (16.7)	60 (41.1)
Any AEs Leading to Death	1 (1.0)	1 (2.1)	3 (2.1)

Source: m5, ISS-ITP, Appendix 2: Table 3.1.1.1.1 and Table 3.1.1.2.1
Abbreviations: AE = adverse event; ITP = immune thrombocytopenia

[a] Subjects are counted only once based upon their most severe AE. One AE with missing severity was classified as severe.

[b] Treatment-Related AEs are events with a possible, probable, or missing causal relationship to study drug.

[c] The most severe action taken was reported for each subject (dose interruption < dose reduction < study drug withdrawal)

Fostamatinib Exposure Period:

The following table provides an overview over the incidence of AE in the fostamatinib exposure period:

Table 41: Overview of Incidence of Adverse Events – Fostamatinib Exposure Period

Parameter	Fostamatinib Exposure Period (C788-047, C788-048, and C788-049) N = 146 n (%)
Number of Subjects with at least 1 AE	127
Average No. of AEs per Subject among Subjects with ≥ 1 AE	8.5
All AEs[a]	127 (87.0)
Mild	32 (21.9)
Moderate	60 (41.1)
Severe	35 (24.0)
Treatment-Related AEs[b]	96 (65.8)
Serious AE	39 (26.7)
AEs Leading to Dose Reduction[c]	15 (10.3)
Any AEs Leading to Dose Interruption[c]	35 (24.0)
Any AEs Leading to Study Drug Withdrawal[c]	27 (18.5)
Any AEs Leading to Dose Reduction, Dose Interruption, or Study Drug Withdrawal	60 (41.1)
Any AEs Leading to Death	3 (2.1)

Source: Appendix 2: Table 3.1.1.2.1
Abbreviations: AE = adverse event

[a] Subjects are counted only once based upon their most severe AE. One AE with missing severity was classified as severe.
[b] Treatment-related AEs are events with a possible, probable, or missing causal relationship to study drug.
[c] The most severe action taken reported for each subject (dose interruption < dose reduction < study drug withdrawal).

Organ Classes with the highest subject incidences were Gastrointestinal disorders, Infections and infestations, Respiratory, thoracic and mediastinal disorders, General disorders and administration site conditions, Skin and subcutaneous tissue disorders, Nervous system disorders, Investigations, and Vascular disorders. The Organ classes of occurrence can be deemed comparable to the placebo-controlled period with no major discrepancies.

The most commonly reported adverse event was diarrhoea, which is in accordance to the findings observed in the placebo-controlled period.

Overall, no major discrepancies in the observed AE profile could be observed in the fostamatinib exposure period.

RA:

Table 17: Overall Summary of Safety in RA (Placebo-Controlled Safety Set)

	Fostamatinib, n (%)			
	100–150 mg/day	200–300 mg/day	All Fostamatinib	Placebo, n (%)
N	1111	1303	2414	1169
Any AE	751 (67.6)	893 (68.5)	1644 (68.1)	634 (54.2)
AE related to study drug	441 (39.7)	535 (41.1)	976 (40.4)	273 (23.4)
Grade 3 AE	49 (4.4)	78 (6.0)	127 (5.3)	39 (3.3)
AE leading to treatment modification	170 (15.3)	205 (15.7)	375 (15.5)	89 (7.6)
AE leading to treatment discontinuation	87 (7.8)	93 (7.1)	180 (7.5)	45 (3.8)
Serious AE	47 (4.2)	71 (5.4)	118 (4.9)	31 (2.7)
Fatal AE	1 (0.1)	1 (0.1)	2 (0.1)	3 (0.3)

Source: m5, ISS-RA, Appendix 2: Table 4.1.1.1 and Table 4.1.8.1
Abbreviations: AE = adverse event; RA = rheumatoid arthritis

Table 4.1.1.2
Summary of Adverse Events
(Fostamatinib Safety Analysis Set)

Variable	Fostamatinib 100-150mg/day (N=1232) Frequency n (%)	Fostamatinib 100-150mg/day (N=1232) Incidence Rate (Person Years) [a]	Fostamatinib 200-300mg/day (N=2205) Frequency n (%)	Fostamatinib 200-300mg/day (N=2205) Incidence Rate (Person Years) [a]	Fostamatinib Overall (N=3437) Frequency n (%)	Fostamatinib Overall (N=3437) Incidence Rate (Person Years) [a]
Adverse Event (AE) [b]	1061 (86.1)	224.3 (473)	1881 (85.3)	236.7 (795)	2942 (85.6)	232.1 (1267)
Serious	158 (12.8)	9.1 (1744)	324 (14.7)	10.5 (3086)	482 (14.0)	10.0 (4831)
AE Leading to Study Drug Dose Modification [c]	377 (30.6)	26.0 (1449)	692 (31.4)	27.6 (2508)	1069 (31.1)	27.0 (3956)
Serious	63 (5.1)	3.5 (1807)	141 (6.4)	4.4 (3183)	204 (5.9)	4.1 (4990)
AE Leading to Study Drug Discontinuation [d]	220 (17.9)	11.9 (1846)	358 (16.2)	10.9 (3296)	578 (16.8)	11.2 (5142)
Serious	59 (4.8)	3.2 (1867)	97 (4.4)	2.9 (3335)	156 (4.5)	3.0 (5201)
AE Related to Study Drug [e]	727 (59.0)	73.7 (986)	1249 (56.6)	73.0 (1710)	1976 (57.5)	73.3 (2697)
Serious	38 (3.1)	2.0 (1855)	82 (3.7)	2.5 (3295)	120 (3.5)	2.3 (5150)
Severe AE [f]	138 (11.2)	7.8 (1765)	292 (13.2)	9.4 (3113)	430 (12.5)	8.8 (4878)
Serious	79 (6.4)	4.3 (1820)	162 (7.3)	5.0 (3243)	241 (7.0)	4.8 (5063)

Note: Percentages are based on the number of patients in the Fostamatinib Safety Analysis Set within each treatment group. Patients may be counted in more than one treatment group if they received that fostamatinib dose during the course of their treatment. Patients reporting more than one adverse event meeting each criterion are counted only once per treatment group.
[a] Refer SAP Section 5.4.
[b] AEs are assigned to treatment based on the start date of the AE. AEs with onset prior to the first dose of study drug are considered to have occurred pre-treatment and are listed separately in Listing 7.1.4. AEs with onset more than 28 days after the last dose of study drug are considered to have occurred post-treatment and are listed separately in Listing 7.1.5.
[c] Refer SAP Section 4.7.1.
[d] Refer SAP Section 4.7.1.
[e] Refer SAP Section 4.7.1 and Section 4.6.
[f] Refer SAP Section 4.7.1 and Section 4.6.
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Looking at the data, the AEs were generally higher in the 200-300 mg/day arm compared to the 100-150 mg/day arm. 200-300 mg is the intended dose for ITP.

There were generally more AEs in study 047 than 048 also compared to placebo; (patients in 047 were on average 7.5 years younger than in 048). No certain cause for the difference in AEs between the two placebo-controlled studies can be found.

With longer treatment there were more adverse events especially SAEs, moderate and severe AEs, and dose interruptions and withdrawals (Table 16). This is also the case for the RA-studies. The incidence of infections in the ITP studies also increased with long term treatment as seen when comparing the placebo-controlled period to the fostamatinib exposure period; 30.4% and 42.5%, respectively. There does not seem to be a period after which the AEs decrease/stabilise, which is a concern since the treatment is continuous.

Treatment emergent adverse events (TEAE)

ITP:

The types (SOC and PT) of AEs in the ITP and RA pooled placebo-controlled studies were overall consistent (Tables 18 and 21 for SOC and tables 19 and 22 for PT for ITP and RA, respectively):

Table 18 Common Adverse Events in ITP by System Organ Class (≥ 10% Subject Incidence): Placebo-Controlled Period

	Placebo-Controlled Period	
System Organ Class/ Preferred Term	Fostamatinib (N = 102) n (%)	Placebo (N = 48) n (%)
Gastrointestinal disorders	49 (48.0)	15 (31.3)
Investigations	28 (27.5)	5 (10.4)
Infections and infestations	27 (26.5)	10 (20.8)
Nervous system disorders	26 (25.5)	13 (27.1)
Vascular disorders	24 (23.5)	9 (18.8)
Respiratory, thoracic and mediastinal disorders	23 (22.5)	10 (20.8)
Skin and subcutaneous tissue disorders	18 (17.6)	5 (10.4)
General disorders and administration site conditions	17 (16.7)	5 (10.4)
Blood and lymphatic system disorders	14 (13.7)	4 (8.3)

Source: m5, ISS-ITP, Appendix 2: Table 3.1.2.1.1
Abbreviations: AE = adverse event; ITP = Immune thrombocytopenia

Table 19 Adverse Events Reported in ≥ 5% of ITP Subjects in Any Treatment Group by Preferred Term: Placebo-Controlled Period

Preferred Term	Placebo-Controlled Period (C788-047 and C788-048)	
	Fostamatinib (N = 102) n (%)	Placebo (N = 48) n (%)
Any Adverse Event	85 (83.3)	36 (75.0)
Diarrhoea	30 (29.4)	7 (14.6)
Hypertension	20 (19.6)	4 (8.3)
Nausea	19 (18.6)	4 (8.3)
Epistaxis	16 (15.7)	5 (10.4)
Alanine aminotransferase increased	11 (10.8)	0
Dizziness	11 (10.8)	4 (8.3)
Headache	11 (10.8)	9 (18.8)
Aspartate aminotransferase increased	9 (8.8)	0
Rash	9 (8.8)	1 (2.1)
Upper respiratory tract infection	6 (5.9)	2 (4.2)
Chest pain	6 (5.9)	1 (2.1)
Fatigue	6 (5.9)	1 (2.1)
Contusion	6 (5.9)	0
Petechiae	4 (3.9)	3 (6.3)
Vomiting	3 (2.9)	3 (6.3)

Source: m5, ISS-ITP, Appendix 2: Table 3.1.2.4.1
Abbreviations: ITP = immune thrombocytopenia

Severe AEs (grade 3-4) were reported in 16 subjects (15.7%) receiving fostamatinib and 7 subjects (14.6%) receiving placebo. Dyspnea (2% fostamatinib, 0% placebo) and thrombocytopenia (1% fostamatinib, 4.2% placebo) were the only severe AEs reported for > 1 subject in either treatment group.

Table 12: Common Adverse Events (Reported in ≥ 5% of Subjects) with Incidence 2-fold Greater for Fostamatinib than Placebo – Placebo-Controlled Period

Preferred Term	Placebo-Controlled Period (C788-047 and C788-048)	
	Fostamatinib (N = 102) n (%)	Placebo (N = 48) n (%)
Diarrhoea	30 (29.4)	7 (14.6)
Hypertension	20 (19.6)	4 (8.3)
Nausea	19 (18.6)	4 (8.3)
Alanine Aminotransferase Increased	11 (10.8)	0
Aspartate Aminotransferase Increased	9 (8.8)	0
Rash	8 (7.8)	1 (2.1)
Chest Pain	6 (5.9)	1 (2.1)
Fatigue	6 (5.9)	1 (2.1)
Contusion	6 (5.9)	0

Source: Appendix 2: Table 3.1.2.5.1

RA:

The greatest differences between treatment groups were seen in Gastrointestinal (26.8% vs. 16.0%), Vascular (15.2% vs. 5.5%), and Investigations (15.1% vs. 7.2%) for fostamatinib vs. placebo, respectively (Table 21).

Regarding fostamatinib dose effects, the 200–300 mg/day group tended to have higher incidences within several SOCs relative to the 100–150 mg/day group, but these differences were typically only 2% or less. With regard to dose-related differences within fostamatinib, there were 3 AEs with a difference in incidence greater than 1%: hypertension, dizziness, and vomiting. The greatest difference was in hypertension (12.8% vs. 14.2% for the lower vs. higher doses; Table 22).

Table 21: Common TEAEs (> 10%) in RA by System Organ Class (Placebo-Controlled Safety Set)

SOC	Fostamatinib, n (%)			Placebo, n (%)
	100–150 mg/day	200–300 mg/day	All Fostamatinib	
N	1111	1303	2414	1169
Gastrointestinal	293 (26.4)	355 (27.2)	648 (26.8)	187 (16.0)
Infections	272 (24.5)	345 (26.5)	617 (25.6)	235 (20.1)
Vascular	158 (14.2)	209 (16.0)	367 (15.2)	64 (5.5)
Investigations	157 (14.1)	208 (16.0)	365 (15.1)	84 (7.2)
Musculoskeletal	119 (10.7)	145 (11.1)	264 (10.9)	136 (11.6)
Nervous	98 (8.8)	135 (10.4)	233 (9.7)	85 (7.3)

Source: m5, ISS-RA, Appendix 2: Table 4.1.2.1
Abbreviations: RA = rheumatoid arthritis; SOC = system organ class

Table 22: Common Adverse Events Occurring in > 2% of RA Subjects (Placebo-Controlled Safety Set)

Preferred term	Fostamatinib, n (%)			Placebo, n (%)
	100–150 mg/day	200–300 mg/day	All Fostamatinib	
N	1111	1303	2414	1169
Any	751 (67.6)	893 (68.5)	1644 (68.1)	634 (54.2)
Diarrhoea	147 (13.2)	181 (13.9)	328 (13.6)	52 (4.4)
Hypertension	142 (12.8)	185 (14.2)	327 (13.5)	53 (4.5)
Nausea	54 (4.9)	76 (5.8)	130 (5.4)	42 (3.6)
Headache	58 (5.2)	59 (4.5)	117 (4.8)	50 (4.3)
Nasopharyngitis	42 (3.8)	50 (3.8)	92 (3.8)	24 (2.1)
Neutropenia	34 (3.1)	53 (4.1)	87 (3.6)	6 (0.5)
Blood pressure increased	40 (3.6)	39 (3.0)	79 (3.3)	23 (2.0)
ALT increased	31 (2.8)	45 (3.5)	76 (3.1)	18 (1.5)
Dizziness	20 (1.8)	41 (3.1)	61 (2.5)	11 (0.9)
Vomiting	20 (1.8)	38 (2.9)	58 (2.4)	22 (1.9)
Upper respiratory tract infection	21 (1.9)	36 (2.8)	57 (2.4)	22 (1.9)
RA	26 (2.3)	28 (2.1)	54 (2.2)	44 (3.8)
Abdominal pain	23 (2.1)	30 (2.3)	53 (2.2)	10 (0.9)
Abdominal pain upper	26 (2.3)	24 (1.8)	50 (2.1)	23 (2.0)
AST increased	20 (1.8)	29 (2.2)	49 (2.0)	14 (1.2)
Dyspepsia	17 (1.5)	32 (2.5)	49 (2.0)	12 (1.0)

Source: m5, ISS-RA, Appendix 2: Table 4.1.1.1 and Table 4.1.2.1
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; RA = rheumatoid arthritis

Table 12: Severe Adverse Events Occurring in > 0.2% of Patients (Placebo-Controlled Safety Set)

Preferred Term	Fostamatinib, n (%)			Placebo, n (%)
	100–150 mg/day	200–300 mg/day	All Fostamatinib	
N	1111	1303	2414	1169
Any	49 (4.4)	78 (6.0)	127 (5.3)	39 (3.3)
Rheumatoid arthritis	2 (0.2)	7 (0.5)	9 (0.4)	5 (0.4)
Diarrhea	3 (0.3)	6 (0.5)	9 (0.4)	2 (0.2)
ALT increased	2 (0.2)	5 (0.4)	7 (0.3)	0
Gastritis	1 (0.1)	4 (0.3)	5 (0.2)	0
Vomiting	1 (0.1)	4 (0.3)	5 (0.2)	1 (0.1)

Source: Appendix 2: Table 4.1.5.1

Treatment related adverse events (TRAE)

ITP:

Table 23 Treatment-Related Adverse Events Reported in ≥ 5% of ITP Subjects in Either Treatment Group: Placebo-Controlled Period

Preferred Term	Placebo-Controlled Period (C788-047 and C788-048)					
	Fostamatinib (N = 102)			Placebo (N = 48)		
	Possibly Related n (%)	Probably Related n (%)	Total Related n (%)	Possibly Related n (%)	Probably Related n (%)	Total Related n (%)
Any TRAE	27 (26.5)	33 (32.4)	60 (58.8)	7 (14.6)	6 (12.5)	13 (27.1)
Diarrhoea	14 (13.7)	13 (12.7)	27 (26.5)	3 (6.3)	3 (6.3)	6 (12.5)
Nausea	10 (9.8)	5 (4.9)	15 (14.7)	0	3 (6.3)	3 (6.3)
Hypertension	10 (9.8)	6 (5.9)	16 (15.7)	1 (2.1)	1 (2.1)	2 (4.2)
Dizziness	9 (8.8)	0	9 (8.8)	2 (4.2)	0	2 (4.2)
ALT increased	4 (3.9)	6 (5.9)	10 (9.8)	0	0	0
AST increased	2 (2.0)	5 (4.9)	7 (6.7)	0	0	0

Source: m5, ISS-ITP, Appendix 2: Table 3.1.16.1.1
Subjects are counted only once in each preferred term category. Adverse events with missing relationship were classified as probable relationship.
Abbreviations: ITP = immune thrombocytopenia; TRAE = treatment-related adverse event

Fostamatinib exposure period:

96 subjects (65.8%) had adverse events that were considered by the investigator to be possibly or probably related to the study drug with diarrhoea being the most frequently reported treatment-related adverse event. This is in accordance to the findings observed in the placebo-controlled period. Overall, no major discrepancies in the observed AE profile could be observed in the fostamatinib exposure period. A higher than expected rebound (decrease) in the platelet count after stopping treatment with fostamatinib either in patients defined as responders or non-responders has not been detected.

Adverse Events by Severity

Fostamatinib Placebo controlled period (PCP):

Dyspnea (2% fostamatinib, 0% placebo) and thrombocytopenia (1% fostamatinib, 4.2% placebo) were the only severe AEs reported for > 1 subject in either treatment group.

Fostamatinib exposure period (FEP):

Most AE observed in the fostamatinib exposure period were mild to moderate. 35 subjects (24.0%) compared to 16 subjects (15.7%) receiving fostamatinib in the PCP and 7 subjects (14.6%) receiving placebo in the PCP had severe AE. In the FEP severe AE reported were thrombocytopenia and diarrhoea, pneumonia, sepsis, dyspnea, petechiae, platelet count decreased, transaminases increased, nephrolithiasis. These Events can be considered to be related to the mechanism of action and are comparable to the findings in the PCP or

to those observed in the RA program, where more subjects compared to the ITP program have been included.

RA:

Table 24: Treatment-Related Adverse Events Occurring in > 2% of RA Subjects (Placebo-Controlled Safety Set)

Preferred term	Fostamatinib, n (%)			Placebo, n (%)
	100–150 mg/day	200–300 mg/day	All Fostamatinib	
N	1111	1303	2414	1169
Any TRAE	441 (39.7)	535 (41.1)	976 (40.4)	273 (23.4)
Hypertension	111 (10.0)	135 (10.4)	246 (10.2)	32 (2.7)
Diarrhoea	90 (8.1)	121 (9.3)	211 (8.7)	32 (2.7)
Nausea	36 (3.2)	57 (4.4)	93 (3.9)	29 (2.5)
Neutropenia	31 (2.8)	48 (3.7)	79 (3.3)	4 (0.3)
Headache	27 (2.4)	28 (2.1)	55 (2.3)	23 (2.0)
ALT increased	20 (1.8)	32 (2.5)	52 (2.2)	13 (1.1)
Blood pressure increased	23 (2.1)	26 (2.0)	49 (2.0)	13 (1.1)

Source: m5, ISS-RA, Appendix 2: Table 4.1.4.1
Abbreviations: ALT = alanine aminotransferase; RA = rheumatoid arthritis; TRAE = treatment-related adverse event

Adverse events of special interest (AESI)

ITP:

Placebo controlled period:

Table 21: Adverse Event of Interest Types and Subtypes – Placebo-Controlled Period

Type Subtype	Placebo-Controlled Period (C788-047 and C788-048)	
	Fostamatinib (N = 102) n (%)	Placebo (N = 48) n (%)
Any GI complaints (nausea, vomiting, Non-infectious diarrhoea [SMQ], abdominal pain)	42 (41.2)	10 (20.8)
Nausea	19 (18.6)	4 (8.3)
Non-infectious diarrhoea (SMQ)[a]	32 (31.4)	7 (14.6)
Abdominal pain[b]	7 (6.9)	2 (4.2)
Vomiting[b]	4 (3.9)	3 (6.3)
Infection[b]	31 (30.4)	10 (20.8)
Hypertension (SMQ)[a]	28 (27.5)	6 (12.5)
Neutropenia[b]	7 (6.9)	0
Drug-related hepatic disorders (SMQ)[a]	16 (15.7)	1 (2.1)
ALT increased	11 (10.8)	0
AST increased	9 (8.8)	0
Blood bilirubin increased	2 (2.0)	0
GGT increased	1 (1.0)	0
Hepatic cyst	1 (1.0)	0
Hepatic enzyme increased	1 (1.0)	0
Liver function test abnormal	1 (1.0)	0
Ocular icterus	0	1 (2.1)

Source: Appendix 2: Table 3.1.8.1.1
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyltransferase; GI = gastrointestinal; SMQ = Standardised MedDRA Query
[a] The adverse event was evaluated using preferred terms from the associated SMQ.
[b] Includes multiple adverse event preferred terms

GI complaints are commonly seen in tyrosine kinase inhibitor treatment. As such nausea/vomiting, non-infectious diarrhea SMQ events, and abdominal pain were among the most common AEs reported in fostamatinib treated subjects. Non-infectious diarrhea events and nausea are considered definitely related and abdominal pain possibly related to fostamatinib treatment.

Hypertension: Fostamatinib treatment clearly increases the risk for hypertension with the possibility of the very high increase of BP leading to hypertensive crisis. Therefore, regular monitoring of blood pressure is

deemed necessary in the already polypathic patient population in order to insure prompt counter measures such as dose adjustments or antihypertensive medication. Overall, around 80% of fostamatinib subjects and 83% of placebo subjects with Hypertension required no intervention for a hypertension event during the Placebo-controlled Period.

Drug-related hepatic disorders: Hy's Law criteria for drug-induced liver injury was not met in any subject. However, a clear pattern towards transaminase increase could be observed in fostamatinib treated subjects. This is consistent with the observations in tyrosine kinase inhibitors.

Increased ALT/AST is an important identified risk associated with the use of fostamatinib as well as with other tyrosine kinase inhibitors.

Neutropenia: In the clinical development program of fostamatinib reduction in neutrophils could already be observed, which were reversible with discontinuation of the study drug. In most cases dose reduction mitigated the neutropenia allowing subjects to remain on the study drug. Neutropenia may potentially bear the risk of an infection, thus the complete blood count with differential to evaluate the absolute neutrophil count is deemed necessary during therapy as already reflected in the SmPC.

Infection: A clear association between neutropenia and infection is difficult to obtain from the available date. However, this remains a non-negligible uncertainty. A small tendency towards upper respiratory tract infections could be observed in fostamatinib treated subjects. Fostamatinib's inhibition of the Syk pathway in macrophages suggests a theoretical risk of infection.

RA:

Table 16: Adverse Events of Special Interest by Broad Category (Placebo-Controlled Safety Set)

Category	Fostamatinib (N = 2414)		Placebo (N = 1169)	
	All AEs	SAEs	All AEs	SAEs
Gastrointestinal	619 (25.6)	18 (0.7)	166 (14.2)	1 (0.1)
Hypertension	424 (17.6)	3 (0.1)	78 (6.7)	0
Hepatic	163 (6.8)	1 (0.0)	40 (3.4)	1 (0.1)
Allergic	101 (4.2)	0	34 (2.9)	0
Cardiovascular	43 (1.8)	13 (0.5)	11 (0.9)	3 (0.3)
Renal function	3 (0.1)	3 (0.1)	1 (0.1)	0
Drug abuse, dependence, withdrawal	0	0	0	0

Source: Appendix 2: Table 4.1.9.1

Placebo-controlled period

In general, the occurrences of significant **hypertension** were handled by means of antihypertension medications (discussed in the individual clinical study reports), dose modifications, and treatment discontinuation. Hypertension led to treatment discontinuation in 0.7% of fostamatinib subjects vs. 0.1% of placebo subjects.

Neutropenia: The percentage of subjects who maintained their baseline toxicity grade during treatment were 80.6% vs. 95.8% for fostamatinib vs. placebo, respectively downward shifts were generally of only 1 or

2 grades. The overall incidence of treatment-emergent Grade 3/4 toxicity for fostamatinib vs. placebo was 1.1% vs. 0.2%, respectively. Treatment discontinuation due to neutropenia occurred in 0.2% of subjects receiving fostamatinib and 0.1% of subjects receiving placebo.

Infection: 25.6% of fostamatinib subjects and 20.1% of placebo subjects experienced at least 1 AE in the Infections and Infestations SOC. Nasopharyngitis and upper respiratory infections were the only AEs reported in more than 2% of subjects (3.8% and 2.4% in the fostamatinib group respectively; slightly lower that than the placebo group [2.1% and 1.9%, respectively]). No SAE by preferred term was reported at a frequency exceeding 0.3%.

Drug-related hepatic disorders (Preferred Term) in the RA placebo-controlled studies are presented in Table 4.1.10.1:

Table 4.1.10.1
Adverse Events of Special Interest during the Placebo-Controlled Period by SMQ Narrow Search and Preferred Term
(Placebo-Controlled Safety Analysis Set)

Event Category Standardised MedDRA Query (SMQ) Preferred Term [a]	Statistic	Fostamatinib 100-150 mg/day (N=1111)		Fostamatinib 200-300 mg/day (N=1303)		Fostamatinib Overall (N=2414)		Placebo (N=1169)		Total (N=3583)	
Patients Reporting At Least 1 hepatic Event	n (%)	67	(6.0)	96	(7.4)	163	(6.8)	40	(3.4)	203	(5.7)
Drug Related Hepatic Disorders - Comprehensive Search	n (%)	67	(6.0)	96	(7.4)	163	(6.8)	40	(3.4)	203	(5.7)
Alanine Aminotransferase Increased	n (%)	31	(2.8)	45	(3.5)	76	(3.1)	18	(1.5)	94	(2.6)
Aspartate Aminotransferase Increased	n (%)	20	(1.8)	29	(2.2)	49	(2.0)	14	(1.2)	63	(1.8)
Transaminases Increased	n (%)	10	(0.9)	13	(1.0)	23	(1.0)	3	(0.3)	26	(0.7)
Hepatic Enzyme Increased	n (%)	7	(0.6)	12	(0.9)	19	(0.8)	4	(0.3)	23	(0.6)
Gamma-Glutamyltransferase Increased	n (%)	4	(0.4)	8	(0.6)	12	(0.5)	6	(0.5)	18	(0.5)
Blood Bilirubin Increased	n (%)	1	(0.1)	7	(0.5)	8	(0.3)	1	(0.1)	9	(0.3)
Hepatic Function Abnormal	n (%)	3	(0.3)	5	(0.4)	8	(0.3)	0		8	(0.2)
Liver Function Test Abnormal	n (%)	3	(0.3)	5	(0.4)	8	(0.3)	0		8	(0.2)

Note: Percentages are based on the number of patients in the Placebo-Controlled Safety Analysis Set within each treatment group. AEs are assigned to treatment based on the onset date of the AE. AEs with onset prior to the first dose of study drug are considered to have occurred pre-treatment and are listed separately in Listing 7.1.4. AEs with onset more than 28 days after the last dose of study drug are considered to have occurred post-treatment and are listed separately in Listing 7.1.5.
[a] Adverse events are coded to system organ class and preferred term using MedDRA, version 18.1. At each level of summarization (event category, SMQ and preferred term) patients reporting more than one adverse event are counted only once. Preferred terms within each SMQ are sorted in descending order of overall fostamatinib frequency.

Healthy subjects:

A summary of the most commonly occurring TEAEs from the 4 multiple-dose placebo studies with 10 or more subjects each (C788-003, C788-013, D4300-007, and D4300-012) is provided in Table 10 showing the placebo and fostamatinib incidences for each study separately and the cumulative incidences across studies.

Table 10: Common Adverse Events – Multiple-Dose Studies with Placebo Control (> 1% Across Studies)

	Subject Incidence by Study, n (%)									
	C788-003		C788-013		D4300-007		D4300-012		Total Placebo[1] n (%)	Total Fostamatinib[1] n (%)
Preferred Term	Placebo	Fostamatinib	Placebo	Fostamatinib	Placebo	Fostamatinib	Placebo	Fostamatinib		
N	2	8	52	103	14	42	33	30	101	183
≥ 1 TEAE	2 (100.0)	8 (100.0)	17 (32.7)	30 (29.1)	5 (35.7)	7 (16.7)	16 (48.5)	8 (26.7)	40 (39.6)	53 (30.0)
Headache		2 (25.0)	4 (7.7)	11 (10.7)		3 (7.1)	8 (24.2)		12 (11.9)	16 (8.7)
Nausea		3 (37.5)	1 (1.9)	5 (4.9)			1 (3.0)	1 (3.3)	2 (2.0)	9 (4.9)
Diarrhea		5 (62.5)	1 (1.9)	2 (1.9)	1 (7.1)	1 (2.4)			2 (2.0)	8 (4.4)
Dizziness		2 (25.0)	4 (7.7)	3 (2.9)			1 (3.0)		5 (5.0)	5 (2.7)
Dermatitis contact					3 (21.4)	3 (7.1)			3 (3.0)	3 (1.6)
Puncture site pain			3 (5.8)	3 (2.9)					3 (3.0)	3 (1.6)
Rash		2 (25.0)		2 (1.9)				1 (3.3)	0	5 (2.7)
Rash papular		4 (50.0)							0	4 (2.2)
Vomiting		1 (12.5)		3 (2.9)					0	4 (2.2)
Dysmenorrhea				3 (2.9)			1 (3.0)		1 (1.0)	3 (1.6)
Pharyngolaryngeal pain		2 (25.0)	1 (1.9)	1 (0.9)					1 (1.0)	3 (1.6)
Syncope			1 (1.9)	1 (0.9)				1 (3.3)	1 (1.0)	2 (1.1)

TEAE = treatment-emergent adverse event
[1] Totals manually calculated across studies. Cutoff for display of AEs based on > 1% of the sum of placebo plus fostamatinib (N = 284).

Taken together, the following incidences were generally higher in the fostamatinib compared to the placebo cohorts for the following TEAEs: nausea, diarrhoea, rash, and vomiting. This is consistent with the TEAEs reported across all healthy volunteers' studies. Overall, the incidence of treatment-related adverse events was low in healthy subjects, regardless of dose.

Conclusion on comparison between ITP studies versus RA studies

The adverse events of special interest in study 047 and 048 are in line with the previously described AESIs from the RA studies: No new AESI was identified. The incidence of the various AESIs were generally higher in the ITP population (see data for hypertension, hepatic disorders and neutropenia in the following). An acceptable explanation for the blood pressure effects and the neutropenia is that the dose level generally studied in the ITP population, 150mg BID, was higher than that studied in the RA patient population, 150mg QD -100mg BID.

The higher incidence of hepatic disorders in the ITP population compared to the RA population is by a panel of hepatologist considered to be coincidental caused by the low number of ITP patients and events (overlapping CI). Furthermore, one would not expect a worse safety profile in ITP patients compared to RA patients, which supports the finding as coincidental.

Hypertension SMQ (narrow) AEs during the placebo-controlled period was reported for 27.5% of subjects receiving fostamatinib and 12.5% of subjects receiving placebo in the ITP population whereas in the RA population (200-300 mg/day) the corresponding numbers were 17.8% vs. 6.7%.

For **drug related hepatic disorders** (SMQ, narrow search) the results in the RA population receiving 200-300 mg/day fostamatinib was 7.4% (96/1303) compared to 3.4% (40/1169) in the placebo arm. The relatively high incidence observed in the placebo arm is most likely linked to the current or previous use of other hepatotoxic drugs for the treatment of RA, for instance methotrexate. The corresponding incidences in ITP were 15.4% (16/102) vs 2.1% (1/48) confirming the hepatotoxic effect of fostamatinib especially in the ITP population.

Neutropenia was 4.1% in the fostamatinib 200-300 mg/day cohort compared to 0.5% in the placebo arm in RA studies. This is lower than seen in ITP, where the corresponding percentages were 6.9% vs 0%.
Infections were observed in 30.4% (31/102) of ITP subjects receiving fostamatinib and 20.8% (10/48) in

the placebo arm. The corresponding numbers for the 200-300 mg/day cohort in the placebo-controlled RA studies were 26.5% (345/1303) and 20.1% (235/1169) in the placebo arm.

Serious adverse events and deaths

Deaths

ITP: In the ITP studies 3 deaths have been recorded. 1 patient died of sepsis, 1 of lobar pneumonia and 1 of multiple myeloma. In the former first 2 cases the death is considered unlikely related to fostamatinib which therefore is not regarded as contributing to the fatal outcome. In the latter case, neoplasms have not been reported more frequently in the fostamatinib arm compared to placebo, but this may also be due to the short treatment period. In RA there were 19 neoplasms (n=2205) in the fostamatinib 200-300 mg/day arm and 12 (n=1232) in the 100-150 mg/day arm in the Fostamatinib safety analysis set, both with and incidence rate of 0.6 person years

RA:

Table 13: Fatal Adverse Events (Placebo-Controlled Safety Set)

	Patient Incidence, n (%)	
	All Fostamatinib	**Placebo**
N	2414	1169
Fatal AE	2 (0.1)	3 (0.3)
Acute kidney injury	1 (0.0)	
Cardiorespiratory arrest	1 (0.0)	
Diabetes mellitus		1 (0.1)
Pulmonary embolism		1 (0.1)
Septic shock		1 (0.1)

Source: Appendix 2: Table 4.1.8.1

In the RA studies (all) deaths from infections were higher than expected when comparing to registry rates, which is of concern.

Deaths across all RA studies and study periods

Within 28 days of the last dose of study drug 31 of 3427 subjects (0.9%) exposed to fostamatinib died. 7 deaths were deemed potentially drug related and occurred after 37–184 weeks of fostamatinib exposure. These included interstitial lung disease, circulatory collapse, cardiogenic shock, viral pneumonia, toxic epidermal necrolysis, sepsis, and cardiopulmonary failure.

AstraZeneca conducted an independent epidemiology study ("Fostamatinib Epidemiology Program") in 2013. Goal was to compare outcomes in the RA clinical development program with 5 established Registries. 3240 fostamatinib treated subjects contributed to 4486 person-years of follow up. In 2013 27/3240 subjects died throughout the clinical program. The incidence rate of all-cause mortality was calculated to be 0.6 per 100 person-years (95% CI: 0.40, 0.88), which lies within the incidence rate from the 5 registries (0.19 to 0.80 deaths per 100 person-years).

The rate of cardiovascular mortality in the fostamatinib program was calculated at 0.22 per 100 person-years (95% CI: 0.11, 0.41), compared with the rates from the registries which ranged from 0.07 to 0.23 per 100 person-years.

However, the rate of infection mortality was higher in the fostamatinib program: 0.20 per 100 person-years (95: CI: 0.09, 0.38) compared with the registry rates that ranged from 0.03 to 0.13 per 100 person-years. Considering that trends towards infections could be observed in the RA clinical development program as well as in the ITP development program, a non-negligible amount of uncertainties remains which may have impact on the overall Benefit Risk, especially since the ITP program cannot be set into context due to the limited subject number available. commmitments has been taken in order that the incidence of serious or opportunistic infections will be monitored in a PASS. Furthermore, the RMP and the SmPC have been reflecting this concern including guidance on risk minimisation measure.

Healthy subjects

No deaths were reported in the clinical pharmacology studies conducted in a total of 622 healthy subjects.

SAEs

SAEs reported in subjects exposed to fostamatinib included infectious complications, diarrhoea, and, in subjects with ITP, bleeding complications.

ITP:

Placebo controlled period

Table 16: Serious Adverse Events Reported in > 1 Subject in Any Treatment Group by Preferred Term – Placebo-Controlled Period

Preferred Term	Placebo-Controlled Period (C788-047 and C788-048)	
	Fostamatinib (N = 102) n (%)	Placebo (N = 48) n (%)
Any SAE	13 (12.7)	10 (20.8)
Epistaxis	2 (2.0)	1 (2.1)
Thrombocytopenia	1 (1.0)	2 (4.2)
Menorrhagia	0	2 (4.2)

Source: Appendix 2: Tables 3.1.3.1.1 and 3.1.1.1.1
Abbreviations: SAE = serious adverse event

Table 17: Serious Bleeding Adverse Events in Any Treatment Group by Preferred Term – Placebo-Controlled Period

Preferred Term	Placebo-Controlled Period (C788-047 and C788-048)	
	Fostamatinib (N = 102) n (%)	Placebo (N = 48) n (%)
Any Bleeding SAE	5 (4.9)	5 (10.4)
Epistaxis	2 (2.0)	1 (2.1)
Menorrhagia	0	2 (4.2)
Immune thrombocytopenic purpura	1 (1.0)	0
Vaginal hemorrhage	1 (1.0)	0
Contusion	1 (1.0)	0
Petechiae	0	1 (2.1)
Gastrointestinal hemorrhage	0	1 (2.1)

Source: Appendix 2: Table 3.1.3.1.1; m5, C788-047 CSR, Table 12-5; m5, C788-048 CSR, Table 12-5.
Abbreviations: SAE = serious adverse event

Fostamatinib Exposure Period

In the Fostamatinib Exposure period, 39 subjects (26.7%) (13 included in Fos-PCP) had SAE. The most frequently reported SAEs were Thrombocytopenia (7 subjects, 4.8%) and epistaxis (5 subjects, 3.4%). Other SAEs reported in more than 1 subject were pneumonia, sepsis, diarrhea, GI hemorrhage, and transaminases increased (2 subjects, 1.4% each) (1 diarrhea event in Fos-PCP).

Nine subjects had serious AE deemed related to the study drug of whom 4 reported these SAE while on fostamatinib treatment during the PCP. Therefore overall 4 subjects had treatment related SAE in the FEP with diarrhea (1 subject), sepsis (1 subject), atrial fibrillation (subject), transaminases increased (1 subject), upper respiratory tract infection and pyrexia (both events reported in 1 subject) being the most common ones. Overall, the type of SAE can be deemed comparable to the PCP.

3 treatment-related serious adverse events (febrile neutropenia, hypertensive crisis, atrial fibrillation) led to study drug interruptions and 4 to withdrawal (pneumonia, diarrhea, sepsis, and transaminase increased).

Overall, the SAE occurred in the FEP are in accordance with the known safety profile with no new emerging SAE in comparison to the PCP.

RA:

Table 14: Serious Adverse Events Occurring in > 0.1% of Patients (Placebo-Controlled Safety Set)

Preferred Term	Fostamatinib, n (%)			Placebo, n (%)
	100–150 mg/day	200–300 mg/day	All Fostamatinib	
N	1111	1303	2414	1169
Any	47 (4.2)	71 (5.4)	118 (4.9)	31 (2.7)
Gastroenteritis	4 (0.4)	3 (0.2)	7 (0.3)	0
Atrial fibrillation	2 (0.2)	2 (0.2)	4 (0.2)	0
Rheumatoid arthritis	2 (0.2)	2 (0.2)	4 (0.2)	3 (0.3)
Acute kidney injury	1 (0.1)	2 (0.2)	3 (0.1)	0
Cholelithiasis	2 (0.2)	1 (0.1)	3 (0.1)	0
Gastritis	0	3 (0.2)	3 (0.1)	0
Gastroenteritis bacterial	1 (0.1)	2 (0.2)	3 (0.1)	0
Pneumonia	0	3 (0.2)	3 (0.1)	1 (0.1)
Noncardiac chest pain	1 (0.1)	2 (0.2)	3 (0.1)	3 (0.1)
Chest pain	0	2 (0.2)	2 (0.1)	2 (0.1)
Osteoarthritis	0	2 (0.2)	2 (0.1)	0
Osteomyelitis	0	2 (0.2)	2 (0.1)	0
Syncope	2 (0.2)	0	2 (0.1)	1 (0.1)

Source: Appendix 2: Table 4.2.2.1

All SAEs reported in the 6 RA studies that were categorized by the investigator as cardiovascular were adjudicated by a blinded independent committee. Results of this adjudication process are summarized in Appendix 2: Tables 4.3.1.1 (*below*) and 4.3.2.1.

Table 4.3.1.1
Summary of Cardiovascular Serious Adverse Event Adjudication Results for the Placebo-Controlled Period
(Placebo-Controlled Safety Analysis Set, AstraZeneca-sponsored Studies)

SAE Adjudication Results [a]	Statistic [b]	Fostamatinib 100-150 mg/day (N=1111)	Fostamatinib 200-300 mg/day (N=1303)	Fostamatinib Overall (N=2414)	Placebo (N=1169)	Total (N=3583)
Placebo-Controlled Safety Analysis Set, AstraZeneca Studies [c]	n	913	909	1822	896	2718
All SAEs Sent for CV Adjudication	n (%)	13 (100.0)	12 (100.0)	25 (100.0)	8 (100.0)	33 (100.0)
Adjudicated to be CV event	n (%)	10 (76.9)	7 (58.3)	17 (68.0)	3 (37.5)	20 (60.6)
Adjudicated to be non-CV event	n (%)	3 (23.1)	5 (41.7)	8 (32.0)	3 (37.5)	11 (33.3)
Undetermined SAE	n (%)	0	0	0	2 (25.0)	2 (6.1)
Fatal SAEs Sent for CV Adjudication	n (%)	1 (100.0)	2 (100.0)	3 (100.0)	2 (100.0)	5 (100.0)
Adjudicated to be Fatal CV event	n (%)	1 (100.0)	0	1 (33.3)	0	1 (20.0)
Adjudicated to be Fatal non-CV event	n (%)	0	2 (100.0)	2 (66.7)	0	2 (40.0)
Undetermined Fatal SAE	n (%)	0	0	0	2 (100.0)	2 (40.0)
Non-fatal SAEs Sent for CV Adjudication	n (%)	12 (100.0)	10 (100.0)	22 (100.0)	6 (100.0)	28 (100.0)
Adjudicated to be non-fatal CV event	n (%)	9 (75.0)	7 (70.0)	16 (72.7)	3 (50.0)	19 (67.9)
Adjudicated to be non-fatal non-CV event	n (%)	3 (25.0)	3 (30.0)	6 (27.3)	3 (50.0)	9 (32.1)
Undetermined non-fatal SAE	n (%)	0	0	0	0	0

CV = Cardiovascular; SAE = Serious Adverse Event
[a] Independent Caridovascular Adjudication Committee adjudication results for events with onset <=28 Days post study drug discontinuation.
[b] Percentages are based on the number of events with onset <=28 Days post study drug discontinuation that were sent for CV adjudication in the category (i.e., SAEs, fatal SAEs non-fatal SAEs). Listing 7.1.9 gives the outcome of adjudication for events that occurred more than 28 days post study drug discontinuation.
[c] Number of patients in the Fostamatinib Safety Analysis Set, excluding patients from Rigel-sponsored Studies C788-006, C788-010,and C788-011. Adjudication results from extension Study D4300-021 are not included, as deaths and potential CV non-fatal SAEs were not adjudicated in the source studies (Rigel-sponsored Studies C788-006, C788-006X, C788-010, and C788-011).Adjudication results for Study D4300-021 are available in the clinical study report.
Program Name: sissaead.sas; Creation: 01MAR17, 05:02

In ITP SAEs observed in the fostamatinib arm only (>1 subject, Table 17) included the most commonly observed adverse events of diarrhoea and hypertension (hypertensive crisis) and 5 subjects with bleeding-related SAEs. There were twice as many bleeding complications in the placebo arm compared to the fostamatinib arm.

There were 18 SAEs in 13 patients in the fostamatinib arm in the placebo-controlled studies (ISS-ITP, Appendix 2, Table 3.1.1.1.1). Looking at the individual patient narratives only 17 SAEs were identified. Patient 047-500-003 had 2 serious adverse events of thrombocytopenia.

Laboratory findings

Only data from the placebo-controlled studies in ITP and RA have been evaluated.

Haematology

ITP:

Table 3.1.2.1.1

ADVERSE EVENTS (AEs): INCIDENCE BY SYSTEM ORGAN CLASS AND PREFERRED TERM (SUBJECT LEVEL)
PLACEBO-CONTROLLED SAFETY POPULATION: PLACEBO-CONTROLLED PERIOD

System Organ Class/Preferred Term	Fostamatinib (N=102) n (%)	Placebo (N=48) n (%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	14 (13.7)	4 (8.3)
Anaemia	3 (2.9)	2 (4.2)
Neutropenia	5 (4.9)	0 (0.0)
Thrombocytopenia	1 (1.0)	2 (4.2)
Leukopenia	2 (2.0)	0 (0.0)
Febrile Neutropenia	1 (1.0)	0 (0.0)
Immune Thrombocytopenic Purpura	1 (1.0)	0 (0.0)
Leukocytosis	1 (1.0)	0 (0.0)
Lymphadenopathy	1 (1.0)	0 (0.0)
Thrombocytosis	1 (1.0)	0 (0.0)

RA:

No treatment effects on platelet counts were seen in the summary statistics, with median values in both treatment groups fluctuating modestly in the upper 200 x 10^9/L range.

Table 4.1.2.1
Adverse Events during the Placebo-Controlled Period by System Organ Class and Preferred Term
(Placebo-Controlled Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT) [a]	Statistic	Fostamatinib 100-150 mg/day (N=1111)		Fostamatinib 200-300 mg/day (N=1303)		Fostamatinib Overall (N=2414)		Placebo (N=1169)		Total (N=3583)	
Blood And Lymphatic System Disorders	n(%)	76	(6.8)	102	(7.8)	178	(7.4)	42	(3.6)	220	(6.1)
Neutropenia	n(%)	34	(3.1)	53	(4.1)	87	(3.6)	6	(0.5)	93	(2.6)
Leukopenia	n(%)	14	(1.3)	26	(2.0)	40	(1.7)	4	(0.3)	44	(1.2)
Anaemia	n(%)	16	(1.4)	22	(1.7)	38	(1.6)	22	(1.9)	60	(1.7)
Lymphopenia	n(%)	4	(0.4)	4	(0.3)	8	(0.3)	3	(0.3)	11	(0.3)
Monocytopenia	n(%)	2	(0.2)	4	(0.3)	6	(0.2)	1	(0.1)	7	(0.2)

PT neutropenia was 4.1% in the fostamatinib 200-300 mg/day cohort compared to 0.5% in the placebo arm (ISS-RA, Table 4.1.2.1). This is lower than seen in ITP, where the corresponding percentages were 6.9% vs 0% (see also AESIs).

Clinical chemistry

No pattern of **renal** AEs was observed in ITP or RA placebo-controlled studies.

During the Placebo-Controlled Period in the ITP studies, 16 subjects (15.7%) treated with fostamatinib and 1 placebo subject (2.1%) had a **Drug Related Hepatic Disorder** SMQ AE. This was mainly related to increased ALT and AST and bilirubin (see Table 3.1.8.1.1 in section 4.3). Safety in patients with hepatic insufficency has not been investigated: Patients with AST, ALT or bilirubin >1.5 ULN were excluded. See also the AESI section above.

Safety in special populations

Given the small number of patients in the two placebo controlled studies no meaningful differences can be discerned.

Table 1 Adverse Events in Special Populations – Placebo Controlled Period (Studies C788-047 and C788-048)

AE Category[a]	Age <65		Age 65-74		Age 75-84		Age 85+	
	Placebo (N = 37) n (%)	Fostamatinib (N = 74) n (%)	Placebo (N = 7) n (%)	Fostamatinib (N = 17) n (%)	Placebo (N = 4) n (%)	Fostamatinib (N = 7) n (%)	Placebo (N = 0) n (%)	Fostamatinib (N = 4) n (%)
Total AEs	30 (81)	59 (80)	3 (43)	16 (94)	3 (75)	6 (86)	0	4 (100)
Serious AEs – Total	9 (24)	7 (9)	0	4 (24)	1 (25)	1 (14)	0	1 (25)
Fatal	0	0	0	1 (6)	1 (25)	0	0	0
Hospitalization/prolong existing hospitalization	9 (24)	6 (8)	0	4 (24)	1 (25)	1 (14)	0	1 (25)
Life-threatening	0	0	0	0	0	0	0	0
Disability/incapacity	0	0	0	0	0	0	0	0
Other (medically significant)	0	1 (1)	0	1 (6)	0	0	0	0
AE leading to drop-out	2 (5)	5 (7)	0	2 (12)	2 (50)	3 (43)	0	1 (25)
Psychiatric disorders	0	3 (4)	0	1 (6)	0	1 (14)	0	0
Nervous system disorders	13 (35)	20 (27)	0	2 (12)	0	3 (43)	0	1 (25)
Accidents and injuries	30 (81)	59 (80)	3 (43)	16 (94)	3 (75)	6 (86)	0	4 (100)
Cardiac disorders	1 (3)	3 (4)	0	0	0	0	0	0
Vascular disorders	7 (19)	16 (22)	2 (29)	3 (18)	0	3 (43)	0	2 (50)
Cerebrovascular disorders	0	0	0	0	0	0	0	0
Infections and infestations	9 (24)	20 (27)	0	3 (18)	1 (25)	1 (14)	0	3 (75)
Anticholinergic syndrome	0	0	0	0	0	0	0	0
Quality of life decreased	0	0	0	0	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	4 (11)	6 (8)	0	1 (6)	0	3 (43)	0	1 (25)
<other AE appearing more frequently in older patients>	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Source: q204_t_safety
AE = adverse event; N/A = Not Applicable
a. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

ITP:

Analysis by Gender

Exposure:

With regards to exposure the median total daily dose of study drug were similar between females and males during the Placebo-Controlled Period. The median duration of exposure was longer for females than for males in the fostamatinib exposure period.

Adverse Events:

When looking at AE reported in either treatment group in relation to gender it could be observed, that the AE reported in the fostamatinib exposure period were generally comparable with those observed for fostamatinib treated subjects in the PCP. Nausea and headache were more frequently reported for females in the PCP. AE reported with ≥ 10% higher treatment difference were hypertension and dizziness occurring more commonly in female subjects and epistaxis occurring more commonly in males in the PCP.

In the fostamatinib exposure period, nausea and hypertension occurred more frequently in female subjects.

Adverse Events of Interest:

When looking at AE of interest gastrointestinal complaints were reported for both treatment groups in the PCP more commonly in female subjects and also more commonly in female subjects in the fostamatinib exposure period.

Hypertension

Hypertension SMQ AEs occurred with a higher incidence in female subjects in the PCP, while in the fostamatinib exposure period male subjects were more effected. Increased BP (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg) was comparable for males and females during the Fostamatinib Exposure Period, although maximum SBP ≥ 140 and < 160 mmHg was more common among females than males. A greater difference between the fostamatinib and placebo treatment group could be observed for females (32.8% fostamatinib, 10.0% placebo) compared to males (36.6% fostamatinib, 22.2% placebo). This also applies for the SBP ≥ 140 and < 160 mmHg and DBP DBP ≥ 90 and < 100 mmHg.

Transaminase and Bilirubin Elevations

When looking at transaminase and bilirubin elevations Drug-Related Hepatic Disorders SMQ were comparable for both genders in the PCP. Drug-Related Hepatic Disorders SMQ were more frequently observed in fostamatinib treated subjects. This trend also applies for the fostamatinib exposure period.

Neutropenia

With regards to neutropenia AEs and neutrophil count no major discrepancies in incidence between both genders could be observed. With regards to infections, no major discrepancies between gender could be observed in either the PCP or the fostamatinib exposure period.

Overall, AE seem to occur more frequently in female subjects. Although it can be argued that bodyweight may play a role, preclinical findings seem to indicate, that females may have a greater exposure, which may result in different AE profile. Preclinical findings and exposure-response analysis seem to indicate only negligible differences in exposure to fostamatinib concerning gender.

Overall, nevertheless, it could be observed, that the incidence of GI complaints was higher for females in the PCP (44.3% vs. 36.6%), mainly triggered due to the differences in the preferred term nausea (26.2% vs. 7.3%). Same applies for the FEP with differences in incidences of (49.4% vs. 40.7%), again, mainly driven by the differences observed with regards to the preferred term nausea (26.4% vs. 8.5%).

As for Hypertension in the PCP, the differences for the incidences between female and male fostamatinib treated subjects were 34.4% versus 19.5%. In the FEP differences were 33.3% vs. 20.3%.

Therefore, it cannot be fully concluded that these observations result in no clinically relevant difference between gender, especially with regards to the AE´s Nausea and Hypertension. Therefore, the Applicant has committed that the incidence of this adverse event will be monitored in a PASS.

RA:

Gender

Women tended to have higher incidences of the common AEs: those differing by more than 3% between sexes were diarrhea (25.4% vs. 16.7%), urinary tract infection (7.2% vs. 1.2%), neutropenia (6.4% vs. 1.5%), headache (7.9% vs. 4.3%), ALT increase (6.3% vs. 3.1%), and nausea (8.3% vs. 5.3%).

However, it has to be kept in mind that the overall RA population included more women (82.8%) than men which may confound the observations made. Explanation for the higher portion of female subjects may be that generally RA affects more females between the ages of 40 to 70 years than men do. Nonetheless, the observation that women may be more prone for AE would comply with the observations made in the ITP program.

Race

The incidences for neutropenia and pyrexia were higher in the Asian population while the white population showed higher incidences of diarrhoea, nausea and ALT increase. The incidence of hypertension by race demonstrated inconsistent results depending upon the analysis. Based on AE reports of hypertension by the investigator as reflected, Asians and blacks had more hypertension than the white population. Based on actual BP measurement from the Placebo-Controlled Period, blacks had the highest incidence and Asians the lowest.

The applicant states as possible explanation the difference in evaluating hypertension, capturing pre-existing hypertension versus evaluation of treatment-emergent hypertension. However, taking the fixed mg dosing into account, lower bodyweight may bear the possibility for a higher exposure and in consequence higher susceptibility to develop hypertension, as for the Asian population. Unfortunately, only 5 subjects with bodyweight <50 kg were included in the ITP program. Therefore, no profound conclusions can be drawn from the comparison between bodyweight. However, considering the RA population the average number of adverse events per subject treated with fostamatinib was similar across the weight categories, including the lowest weight category of <50 kg. The average number of events per subject was 3.4 in the <50 kg group, 3.1 in the ≥50 to <75 kg group, 3.0 in the ≥75 to <100 kg group, and 3.0 in the ≥100 kg group indicating no major impact of bodyweight. This is consistent with non-clinical findings and exposure response analysis.

Pregnancy

Nonclinical studies have established that fostamatinib given early in pregnancy can increase the risk of embryonic loss, retard growth, and promote specific malformations of the kidney (including agenesis) and associated urogenital (eg, ureter) tissues, as well as variations/ malformations in major vessel and skeletal development. These effects are consistent with known targets of fostamatinib including Syk (target) and Ret-kinase (off-target).

To date, 15 pregnancies have been reported during the course of the clinical development program for fostamatinib (Phase 2 and 3 trials) with outcomes of 3 healthy babies, 1 premature baby, 1 stillbirth, 4 spontaneous abortions or miscarriages, and 6 elective abortions. Fourteen of these pregnancies occurred in the RA program, and 1 in the ITP program. Most of these subjects were taking potentially teratogenic drugs such as methotrexate.

Safety related to drug-drug interactions and other interactions

The TEAEs in healthy subjects reflect the AESIs. For more details see the pharmacology section.

Discontinuation due to AEs

The TEAEs leading to dose reduction and dose interruption in ITP patients were generally in line with the known AESIs.

ITP:

TEAEs leading to dose interruption:

Table 3.1.11.1.1

ADVERSE EVENTS (AEs) LEADING TO DOSE INTERRUPTION: INCIDENCE BY SYSTEM ORGAN CLASS AND PREFERRED TERM (SUBJECT LEVEL)
PLACEBO-CONTROLLED SAFETY POPULATION: PLACEBO-CONTROLLED PERIOD

System Organ Class/Preferred Term	Fostamatinib (N=102) n (%)	Placebo (N=48) n (%)
INVESTIGATIONS	7 (6.9)	1 (2.1)
Alanine Aminotransferase Increased	5 (4.9)	0 (0.0)
Aspartate Aminotransferase Increased	1 (1.0)	0 (0.0)
Blood Bilirubin Increased	1 (1.0)	0 (0.0)
Neutrophil Count Decreased	1 (1.0)	0 (0.0)
Platelet Count Increased	0 (0.0)	1 (2.1)
GASTROINTESTINAL DISORDERS	3 (2.9)	2 (4.2)
Diarrhoea	3 (2.9)	0 (0.0)
Dyspepsia	0 (0.0)	1 (2.1)
Gastrointestinal Haemorrhage	0 (0.0)	1 (2.1)
VASCULAR DISORDERS	3 (2.9)	0 (0.0)
Hypertension	1 (1.0)	0 (0.0)
Hypertensive Crisis	1 (1.0)	0 (0.0)
Peripheral Venous Disease	1 (1.0)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (2.0)	0 (0.0)
Influenza Like Illness	2 (2.0)	0 (0.0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	1 (1.0)	1 (2.1)
Arthralgia	1 (1.0)	0 (0.0)
Musculoskeletal Pain	0 (0.0)	1 (2.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	2 (2.0)	0 (0.0)
Dyspnoea	1 (1.0)	0 (0.0)
Epistaxis	1 (1.0)	0 (0.0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (1.0)	0 (0.0)
Febrile Neutropenia	1 (1.0)	0 (0.0)
CARDIAC DISORDERS	0 (0.0)	1 (2.1)
Cardiac Failure Congestive	0 (0.0)	1 (2.1)

Program Name: F:\RIGEL\ITP\ISS_ITP\PROGRAMS\TABLES\T_AE_SOC_SUBJ.SAS Creation Date, Time: 27MAR17 18:31
Note: Adverse events were coded using MedDRA version 18.1. The denominator for the calculation of the percentage is N, the number of subjects in the treatment group, and the numerator is the number of such subjects with at least one AE in that system organ class or with that preferred term.

TEAEs leading to dose reduction:

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Table 3.1.10.1.1

ADVERSE EVENTS (AEs) LEADING TO DOSE REDUCTION: INCIDENCE BY SYSTEM ORGAN CLASS AND PREFERRED TERM (SUBJECT LEVEL)
PLACEBO-CONTROLLED SAFETY POPULATION: PLACEBO-CONTROLLED PERIOD

System Organ Class/Preferred Term	Fostamatinib (N=102) n (%)	Placebo (N=48) n (%)
INVESTIGATIONS	3 (2.9)	1 (2.1)
Alanine Aminotransferase Increased	1 (1.0)	0 (0.0)
Aspartate Aminotransferase Increased	1 (1.0)	0 (0.0)
Neutrophil Count Decreased	1 (1.0)	0 (0.0)
Platelet Count Increased	0 (0.0)	1 (2.1)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (2.0)	0 (0.0)
Febrile Neutropenia	1 (1.0)	0 (0.0)
Thrombocytosis	1 (1.0)	0 (0.0)
GASTROINTESTINAL DISORDERS	2 (2.0)	0 (0.0)
Diarrhoea	2 (2.0)	0 (0.0)
VASCULAR DISORDERS	2 (2.0)	0 (0.0)
Hypertension	2 (2.0)	0 (0.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	1 (1.0)	0 (0.0)
Chest Pain	1 (1.0)	0 (0.0)

TEAEs leading to withdrawal of fostamatinib:

Placebo-controlled Period:

122 of the 150 subjects discontinued from the study before Week 24 (75.5% fostamatinib, 93.8% placebo). The most common reason was lack of response at week 12 or later (59.8% fostamatinib, 85.4% placebo). It has to be noted in this context, that subjects were allowed per protocol to discontinue their participation at week 12 in the PCP to roll over to the open-label study C788-049. Study drug was withdrawn due to AEs in 10 (9.8%) fostamatinib treated subjects and 4 (8.3%) placebo treated subjects. AEs leading to study drug discontinuation is presented in Table 20 below.

Table 20: Subjects Withdrawing Study Drug Due to Adverse Events – Placebo-Controlled Period

Subject Number	Treatment	Adverse Event Leading to Study Drug Withdrawal
047-063-007	Fostamatinib	Syncope
047-420-002	Fostamatinib	Pneumonia
047-443-005	Fostamatinib	Alanine aminotransferase increased
047-452-001	Fostamatinib	Diarrhoea
047-490-002	Fostamatinib	Chest pain
047-500-003	Fostamatinib	Thrombocytopenia
047-553-002	Fostamatinib	Abdominal pain
047-556-002	Fostamatinib	Neutropenia
048-433-005	Fostamatinib	Plasma cell myeloma
048-570-001	Fostamatinib	Headache
047-467-002	Placebo	Epistaxis
047-488-002	Placebo	Abdominal discomfort
048-433-002	Placebo	Hypertension
048-433-007	Placebo	Diarrhoea

Source: m5, C788-047 CSR, Narratives; m5, C788-048 CSR, Narratives

Fostamatinib Exposure Period:

34.1% of the 123 subjects receiving fostamatinib in study C788-049 were still continuing medication at the data cut off March, the 8th 2018 and 65.9% had discontinued prematurely. The most common reason was lack of response in 35.8% of the cases. AE leading to discontinuation in more than 1 subject were diarrhea (6 subjects, 4.1%), neutropenia (3 subjects, 2.1%), thrombocytopenia, hepatic enzyme increased, and pneumonia (2 subjects, 1.4% for all).

In the fostamatinib exposure period 15 subjects had a dose reduction with hepatic enzyme increased and diarrhoea being the most common reason. Withdrawal from the study drug occurred in 27 subjects with diarrhoea and neutropenia being the most common reason.

In the fostamatinib exposure period 35 subjects had a dose interruption with alanine aminotransferase increased and diarrhoea being the most common reason.

Overall, no major discrepancies could be observed in comparison to the PCP.

RA:

In the Placebo-Controlled RA studies, 7.5% of fostamatinib subjects and 3.8% of placebo subjects experienced AEs that resulted in discontinuation of study drug. Of those randomized to fostamatinib, 69.1% completed the blinded treatment period. Reasons for premature discontinuation in this group included lack of efficacy (10.9%), AE (9.9%), and withdrawal of consent by the patient (7.9%). The only AE that led to discontinuation of study drug reported at a > 1% higher incidence in the fostamatinib group compared with the placebo group was diarrhea (1.5% vs 0%, respectively).

Post marketing experience

Based on the information in the 3 US Periodic Adverse Drug Experience Report (PADER) and all currently available data, no significant new safety data was identified that would change the safety profile of fostamatinib, when used for its approved indication, at the recommended dose, and in the approved population. No change in the current approved product label was warranted.

2.6.1. Discussion on clinical safety

In the ITP extension study 98 patients received fostamatinib ≥24 weeks (168 days) with a median of 204 days. Long-term safety is thus not evaluable in this indication. In the RA placebo-controlled studies 627 patients received fostamatinib 200-300 mg/day for ≥24 weeks but <36 weeks with a median of 168 days for the entire cohort, whereas in the entire fostamatinib dataset in RA 217 patients received fostamatinib (200-300 mg/day) for ≥3 years with a median of 483 days for the entire cohort.

The types (SOC and PT) of **AEs** in the ITP and RA pooled placebo-controlled studies were overall consistent. The **adverse events of special interest** [(AESI; gastrointestinal, hypertension, neutropenia, infection, drug-related hepatic disorders (transaminase and bilirubin elevation)] in study 047 and 048 are in line with the previously described AESIs from the RA studies: No new AESI was identified. The incidence of the various AESIs were generally higher in the ITP population especially with regards to hypertension, hepatic disorders, and neutropenia.

When considering **treatment related AE** 60 (58.8%) fostamatinib treated subjects and 13 (27.1%) placebo treated subjects had AE possibly or probably related to study drug in the placebo controlled period. The most common reported treatment related AE was diarrhoea (26.5% fostamatinib, 12.5% placebo) followed by nausea, hypertension, dizziness and ALT or AST increase.

The TEAEs leading to **dose reduction and dose interruption** in ITP patients were generally in line with the known AESIs.

SAEs reported in subjects exposed to fostamatinib included infectious complications, diarrhoea, and, in subjects with ITP, bleeding complications. In ITP SAEs observed in the fostamatinib arm only included the most commonly observed adverse events of diarrhoea and hypertension (hypertensive crisis) and 5 subjects with bleeding-related SAEs. There were twice as many bleeding complications in the placebo arm compared to the fostamatinib arm (12.7% versus 20.8%), but this appears to be mainly driven by the fact, that the placebo group had more bleeding events classified as SAE (fostamatinib: 4,9% versus Placebo 10,4%).

With regards to **deaths**, 1 fostamatinib treated subject and one placebo treated subject died in the *placebo controlled period (PCP)*. Both events were considered to be unrelated to the study medication, which can be endorsed (Plasma Cell Myeloma in the fostamatinib group and Sepsis in the placebo group). In the *fostamatinib exposure period* 3 fatal events occurred. One was included in Fos-PCP. One subject died of lobar pneumonia after approximately 9.5 months of open-label treatment and 4 days after the end of study visit in Study C788-049. This event was considered to by unlikely related to the study medication, which can be endorsed.

A second patient died of sepsis. This 55 year old fostamatinib-treated (non-responder) woman had a fever and vomiting and diarrhoea two days before being admitted. As part of her previous ITP treatments she had been splenctomised. Blood cultures revealed streptococcus pneumoniae. She deteriorated rapidly. Fatal infection due to this type of bacteria is a well-known risk in splenectomised subjects. The investigator

deemed this event to be unlikely related, whereas the Sponsor could not rule out an aggravating effect entirely.

The possible detrimental effect on bone formation in patients > 18 years of age that have not reached full skeletal maturity, and patients healing after fractures has been included as important potential risks in the RMP and a warning has been included in the SmPC.

Moreover, to better investigate on long term safety which is missing in the specific studies for fostamtinib in ITP population, it has been imposed a post authorisation safety study (PASS) with the objective to to collect information on the long-term safety/tolerability of fostamitanib in clinical practice, for the treatment of chronic ITP in adult patients who have received or are not candidates for three or more other treatments. The main safety concerns addressed will be: Serious and opportunistic infections; Bone fractures and fracture healing; Osteoporosis; ADRs leading to dose reduction or discontinuation of fostamatinib treatment; SAEs; Pregnancies; Deaths of any cause Long term safety data; Selected adverse events including Diaorrhea, Hypertension, Hepatoxicity, Neutropenia and Infections in line with the described Adverse event of special interest.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

Fostamatinib displays a non-negligible risk profile as outlined throughout the assessment. However, the AE of interest were detectable with clinical monitoring measures and were overall manageable with dose reduction/modification. The SmPC reflects appropriate precaution measures in this context.

The Applicant has agreed to the request to submit the protocol for a PASS within 3 months after the CHMP opinion and before commencing the study.

In summary, the risk profile for fostamatinib is generally manageable.

2.7. Risk Management Plan

Safety concerns

Important identified risks	• Diarrhoea • Hypertension • Hepatotoxicity • Neutropenia • Infections
Important potential risk	• Off label use in paediatrics (effect of fostamatinib during bone formation and regrowth during development) • Use in patients with osteoporosis, patients with fractures, or young adults where epiphyseal fusion has not yet occurred (effect of fostamatinib during bone formation and regrowth during development)
Missing information	• Long term safety information

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required in the RMP to investigate a safety concern or to evaluate the effectiveness of risk minimisation activities				
Post authorization safety surveillance study of fostamatinib in adult patients with chronic immune thrombocytopenia (ITP) who are refractory to other treatments Planned	To collect information on the long-term safety/tolerability of fostamatinib in clinical practice, for the treatment of chronic ITP in adult patients who are refractory to other treatments.	Serious and opportunistic infections; Bone fractures and fracture healing Osteoporosis ADRs leading to dose reduction or discontinuation of fostamatinib treatment; SAEs; Pregnancies; Deaths of any cause Long term safety data Selected adverse events: • Diarrhoea, • Hypertension • Hepatoxicity • Neutropenia	Protocol submission to EMA for agreement:	Within 3 months of CHMP opinion
			Interim analysis:	In every PSUR
			Study Report submission to EMA:	March 2025

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
		• Infections		

Risk minimisation measures

Safety concern	Routine risk minimisation activities
Important identified risks	
Diarrhoea	Routine risk communication: *SmPC section 4.8.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for monitoring for diarrhoea and interruption of fostamatinib treatment in case of a severe event are included in SmPC Section 4.2 and Section 4.4.* Other routine risk minimisation measures beyond the Product Information: *Legal status: fostamatinib will be available as a prescription only medicine.*
Hypertension	Routine risk communication: *SmPC Section 4.8.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for monitoring changes in blood pressure, administration of anti-hypertensive treatment and interruption of fostamatinib treatment in case blood pressure remains 160/100 mmHg or higher for more than 4 weeks are included in SmPC Section 4.2 and 4.4.* Other routine risk minimisation measures beyond the Product Information: *Legal status: fostamatinib will be available as a prescription-only medicine*.

Safety concern	Routine risk minimisation activities
Hepatotoxicity	Routine risk communication: *SmPC Section 4.8.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for monitoring liver function tests monthly and considering interruption, dose reduction or discontinuation if ALT/ AST increase more than 3 x ULN are included in SmPC Section 4.2 and 4.4. A concomitant total bilirubin increase greater than 2 x ULN should lead to treatment discontinuation.* Other routine risk minimisation measures beyond the Product Information: *Legal status: fostamatinib will be available as a prescription only medicine*.
Neutropenia	Routine risk communication: *SmPC Section 4.8.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendation for monitoring the ANC monthly and interrupt, reduce or discontinue fostamatinib if ANC decreases to less than 1.0 x 109/L are included in SmPC Section 4.2 and 4.4.* Other routine risk minimisation measures beyond the Product Information: *Legal status: fostamatinib will be available as a prescription only medicine.*
Infections	Routine risk communication: *SmPC Section 4.4 and Section 4.8.* *Patient Information Leaflet Section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Recommendations in Section 2 of Patient Information Leaflet on* *initial signs of infections and advice to contact the treating health* *care provider. Regular monitoring to identify adverse outcomes* *related to infections..* Other routine risk minimisation measures beyond the Product Information: *Legal status: fostamatinib will be available as a prescription only medicine.*

Safety concern	Routine risk minimisation activities
Important potential risk	
Off label use in paediatrics (effect of fostamatinib during bone formation and regrowth during development)	Routine risk communication: *SmPC Section 4.2.* Routine risk minimisation activities recommending specific clinical measures to address the risk: *Section 4.2 of the SmPC includes warning not to use fostamatinib in children.* Other routine risk minimisation measures beyond the Product Information: *Legal status: fostamatinib will be available as a prescription only medicine.*
Missing information	
None	NA

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.2 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 17 April 2018. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant compared the structure of fostamatinib with active substances contained in authorised medicinal products in the European Union and declared that it is not a salt, ester, ether, isomer, mixture of isomers, complex or derivative of any of them.

The CHMP, based on the available data, considers fostamatinib to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet does not yet meet the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.* The applicant will submit the results of a user consultation with target patient groups on the package leaflet that meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use* prior to placing the product on the market.

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Tavlesse (fostamatinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it has a PASS imposed at the time of authorisation.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Primary immune thrombocytopenia (ITP) is an acquired immune mediated disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count less than 100 x 10^9/L, and the absence of any underlying cause. Until recently, the abbreviation ITP stood for idiopathic thrombocytopenic purpura, but due to the current knowledge of the immune mediated mechanism of the disease, and the absence or minimal signs of bleeding in most cases have led to a revision of the terminology.

ITP is classified by duration into newly diagnosed, persistent (3-12 months' duration) and chronic (≥ 12 months' duration). Whereas ITP in adults typically has an insidious onset with no preceding viral or other illness and it normally follows a chronic course, ITP in children is usually short-lived with at least two-thirds recovering spontaneously within 6 months.

Common clinical symptoms of ITP include bruising, menorrhagia, and bleeding from the gastrointestinal and/or urinary mucosal tracts, as well as epistaxis. To some extent, overt bleeding is related to the platelet count, with nearly all major bleeding occurring when platelet levels are below 30,000/μL (Arnold 2015). The rate of fatal hemorrhage has been estimated to be between approximately 0.02 and 0.04 cases per adult patient-year and the predicted 5-year mortality was 2.2% for patients younger than 40 years with an increase to 47.8% for patients older than 60 years (Cohen 2000). Non-intracerebral severe bleeding was estimated to occur at a rate of 9.6% (95% CI: 4.1-17.1%) based on a systematic review of all prospective

ITP studies (10,908 patients) (Neunert 2015). A recent analysis of nearly 300,000 U.S. patient discharges recorded for adult ITP from 2006 to 2012 revealed that the prevalence of mortality was highest in association with septicemia and intracranial hemorrhage (An 2017). The number of hospital discharges for ITP was also found to increase by 30% during this 7 year span despite the introduction of new treatment options, including rituximab and TPO-RAs (An 2017), indicating challenges in achieving or maintaining sufficient platelet control in adult patients living with ITP.

The estimated adult prevalence was 23.6 [95% CI 23.4 – 23.8] per 100,000 persons, translating to approximately 52,700 (95% CI 52,200 – 53,100) adult chronic ITP cases in the US (Feudjo-Tepie et al, 2007).

The Applicant was seeking the following indication:

"Tavlesse is indicated for the treatment of thrombocytopenia in adult patients with chronic or persistent immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment."

Considering the assessment and the discussion on the dossier the Applicant has agreed to the following final indication:

"Tavlesse is indicated for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (see section 5.1)".

3.1.2. Available therapies and unmet medical need

First-line treatment options for ITP include corticosteroids, intravenous immunoglobulin (IVIG), and intravenous anti-D immunoglobulin (IV anti-D Ig). Many patients fail to achieve a durable remission, or will find the long-term side effects of corticosteroids unacceptable (George 2012).

Available second-line treatment options for adult ITP patients can be broadly categorized into those that are given only once (or for only 1 course) and are intended to induce long-term remission (splenectomy, rituximab), and those that need continued or chronic administration (corticosteroids, immunosuppressive agents [azathioprine, cyclosporine A, cyclophosphamide, mycophenolate mofetil], and thrombopoietin (TPO)-receptor agonists [romiplostim and eltrombopag]).

Splenectomy provides long-term efficacy in approximately 60% of cases. Nonetheless, splenectomy is invasive, irreversible, associated with postoperative complications, and its effectiveness is currently unpredictable, leading many physicians and patients toward postponement and use of alternative approaches.

There is an unmet medical need for primary ITP patients relapsing after steroids, splenectomy (if viable), rituximab, TPO-RAs, IVIG, and potentially dapsone and immunosuppresants (cyclosporine and mycophenolate mofetil).

3.1.3. Main clinical studies

The main clinical studies provided in the dossier are C788-047 and C788-048 (*identical in design*): Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Fostamatinib Disodium in the Treatment of Persistent/Chronic ITP:

Phase 3 studies C788-047 and C788 048 evaluated the efficacy of fostamatinib compared with placebo in the treatment of thrombocytopenia in subjects with persistent/chronic ITP over a period of 24 weeks. Starting at Week 12 in these studies, subjects with a platelet count < 50,000/μL (or, if the baseline platelet count was < 15,000/μL, subjects whose platelet count had not increased from baseline by ≥ 20,000/μL), were allowed to transition to Study C788 049, in which all subjects received fostamatinib. Subjects who completed the 24-week evaluation in Study C788 047 or C788 048 also had the option of subsequently receiving open-label fostamatinib in Study C788 049. Most of the subjects participating in the trials had chronic ITP (93%).

3.2. Favourable effects

In study 047 the proportion of subjects achieving the primary efficacy endpoint of a stable platelet response by week 24 (defined as a platelet count of at least 50,000/μL on at least 4 of the last 6 scheduled visits between weeks 14 and 24 inclusive) was 15.7% (8/51) in the fostamatinib group and 0% (0/25) in the placebo group (p = 0.0471).

In study 048 the proportion of subjects in the intent-to-treat (ITT) population achieving the primary efficacy endpoint of a stable platelet response was 18.0% (9/50) in the fostamatinib group and 4.2% (1/24) in the placebo group (p = 0.1519).

The data from the two placebo-controlled studies was *pooled*: The estimated proportion of subjects achieving a stable platelet response was 16.8% (17/101) in the fostamatinib group and 2.1% in the placebo group (p = 0.0071). The studies had identical study design, but the mean age of the patients differed by 7.5 years, and thus the populations are not completely comparable.

In the open-label extenstion study 049 the version 2 efficacy endpoint (Stable Platelet Response in Placebo Crossover Subjects) is supportive of the primary efficacy endpoint from the placebo-controlled studies: 10/44 subjects (22.7%) achieved a stable platelet response including one subject who had achieved this endpoint during treatment with placebo in the prior study. The *difference* (fostamatinib – placebo) in the proportion responding was 20.5% (95% CI, normal approximation: 8.5%, 32.4%).

The secondary efficacy endpoints of platelet count at week 12 and 24 for the entire population and for patients with at low baseline platelet count are considered supportive of the primary efficacy endpoint. The Applicant proposed a hierarchical testing to control for the type I error in the SAPs. However, this was not implemented and therefore it is concluded that the confidence intervals and p-values from the secondary endpoints are not meaningful.

The number of responding patients is too low to conclude anything with regards to various subgroups.

The applicant has also been requested to further indicate the population in which the B/R would be considered more appropriate and they have provided data in refractory patients who have received three or more prior ITP therapies. For all platelet count parameters, the results for the total pooled population are comparable to the refractory patient population. On this ground the final indication agreed is:

"TAVLESSE is indicated for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (see section 5.1)"

3.3. Uncertainties and limitations about favourable effects

The percentage of responders in the double-blinded placebo-controlled studies 047 and 048 were 15.7% and 18.0%, respectively. The 95 % CI in both studies are very wide and approach zero, meaning that the possibility of observing very few responders in clinical practice cannot be neglected.

There is no support from clinically relevant endpoints such as prevention of bleeding or reduction of concomitant ITP treatment. The EMA GL proposes to include bleeding signs/symptoms, time to response, duration of response, concomitant treatment reduction and need for rescue treatment as secondary endpoints. This is only sparsely covered by the submitted phase III trials. In case of bleeding other scores/scales were used than those recommended by the GL. Overall, the provided data do not allow clear conclusions regarding bleeding risk of included patients and of the effect of fostamatinib on the bleeding risk. Assessment of efficacy of fostamatinib is then based on the surrogate parameter platelet counts.

3.4. Unfavourable effects

Adverse event analysis for Fostamatinib has been considered in the frame of the submitted ITP studies. Unfortunately, even though a follow up of patients has been performed in study C788-049, the long-term safety is not fully evaluable in this indication. For this reason pull of safety data from study conducted in rheumatoid arthritis (RA) have been considered. In general the safety profile evidenced in ITP population can be considered consistent to the one reported for the RA population. In specific, the adverse events of special interest in study 047 and 048 are in line with the previously described AESIs from the RA studies: gastrointestinal disorders (including gastrointestinal complaints, non-infectious diarrhoea, nausea and abdominal pain), hypertension, hepatic disorders, neutropenia, and infection. No new AESI was identified. The incidence of the various AESIs were generally higher in the ITP population. Dose reduction and dose interruption in ITP patients were generally in line with the known AESIs. The reported AESI are considered manageable and guidance has been given in the SmPC for the approach to their occurrence.

The most common reported treatment related AE was diarrhoea (26.5% fostamatinib, 12.5% placebo) followed by nausea, hypertension, dizziness and ALT or AST increase.

The very few occurred deaths in the safety profile have been considered unlikely related to the treatment.

3.5. Uncertainties and limitations about unfavourable effects

In the ITP extension study 98 patients received fostamatinib ≥24 weeks (168 days) with a median of 204 days (Table 2). Long-term safety is thus not evaluable in this indication. In the rheumatoid arthritis studies 217 patients received fostamatinib 200-300 mg/day for ≥3 years with a median of 483 days for the entire cohort, but these patients usually have many co-morbidities making it difficult to evaluate long-term safety without a comparator/placebo, and the placebo-controlled period is less than 36 weeks. On this ground the Applicant will perform a Post Authorsiation Safety Sstudy (PASS) to evaluate the long-term safety.

The outcome of preclinical studies raises significant concerns regarding changes of the skeletal system including modification of the growth plates, chondrodystrophy and/or hypocellularity of the bone marrow. Especially juvenile animals appear to be more sensitive to these changes. Data suggests that VEGF/VEGFR is involved in bone remodelling as well as bone formation (Wan et al., 2010; Clarkin and Gerstenfeld, 2012; Hu and Olsen, 2016) possibly inferring an adverse effect in fostamatinib-treated patients with fractures in relation to regrowth, considering fractures being a relatively common event especially in the elderly

population. There may also be an issue in relation to osteoporosis (Liu et al, 2012; Senel et al, 2013) and in young adults where epiphyseal fusion has not yet completely occurred. The SmPC reports with a warning as to the possible detrimental effect on bone metabolism. Overall, these findings may be regarded as off-target effects of VEGF inhibiting medicinal products. By targeting as well a range of other TKIs including SYK, all of which are involved to some extent in the bone metabolism with either potentially deleterious or favourable effects, it is difficult to accurately estimate the risk that is related to bone metabolism, especially for long term administration in patients at risk (e.g. elderly, patients with concomitant steroid treatment, patients with osteoporosis/osteopenia, patients with fractures or young adults where epiphyseal fusion may not have entirely occurred), which were not specifically investigated in clinical studies. To address the above reported concerns and other long-term safety aspects of Tavlesse, a post authorisation safety study (PASS) has been agreed as described in the risk management plan (RMP).

The antiangiogenic VEGFR inhibiting character of fostamatinib seems to be also responsible for several noteworthy findings in fertility, developmental and perinatal/postnatal reproduction studies in rats and rabbits. The preclinical toxicities comprise significantly reduced pregnancy rates, increased maternal toxicities, an increased number of nonviable embryos at higher doses, decreased uterine weights, growth retardation of the foetus as well as variations and malformations of the offspring. Juvenile rabbits displayed degenerate and necrotic ovarian follicles at all dose levels. In light of the embryo-fetal effects of fostamatinib, fostamtinib is contraindicated in pregnancy and effective contraception during treatment and at least one month after the last dose must be used. Fostamatinib has to be discontinued in case the patient becomes pregnant.

3.6. Effects Table

Table 1. Effects Table for fostamatinib in relapsed ITP (data cut-off: 08 March 2018).

Effect	Short description	Unit	fostamatinib	Placebo	Uncertainties / Strength of evidence	References
Favourable Effects						
Stable platelet response by week 24 Study 047:	A platelet count of at least 50,000/μl on at least four of the last six scheduled visits over weeks 14 to 24	% (n) 95 % CI:	15.7 (8/51) 5.7%, 25.7%	0 (0/25)	Wide CI (5.7, 25.7) reflecting the small sample size which was calculated based on an expected efficacy of 40% in the fostamatinib arm and 5% in the placebo arm	
Stable platelet response by week 24 Study 048:	A platelet count of at least 50,000/ml on at least four of the last six scheduled visits over weeks 14 to 24	% (n) 95 % CI:	18.0 (9/50) 7.4%, 28.7%	4.2 (1/24) 0%, 12.2%	Difference (Fostamatinib-placebo) 13.8%. Wide CI (-6.1, 27.9) One responder was a LOCF adding to the uncertainty of the efficacy results	
Pooled placebo-controlled studies,	A platelet count of at least 50,000/ml on	% (n) 95	16.8 (17/101) 9.5%, 24.1%	2.0 (1/49) 0%, 6.0%	Difference (Fostamatinib-placebo) 14.8%. Wide CI (6.5, 23.1)	

Effect	Short description	Unit	fostamatinib	Placebo	Uncertainties / Strength of evidence	References
047+048:	at least four of the last six scheduled visits over weeks 14 to 24	% CI:				
Unfavourable Effects (data from pooled placebo-controlled studies 047+048). None of the AEs listed below were reported in >1 patient as grade 3/4 or SAE.						
Gastrointestinal complaints		%	41.2	10.0		
Hypertension (SMQ)		%	27.5	12.5		
Drug related hepatic disorder (SMQ)		% (n)	15.7 (16/102)	2.5 (1/48)	Small numbers; in the RA placebo-controlled studies the corresponding numbers for the same dose interval were 7.4% (96/1303) vs 3.4% (40/1169)	
Neutropenia (PT)		%	6.9	0		
Infections (multiple PTs)		%	30.4	20.8		

Abbreviations: CI: Confidence Interval. LOCF: Last Observation Carried Forward. SMQ; Standardized MedDRA Query. PT: Preferred Term. RA: Rheumatoid arthritis

Notes: CI based on normal approximation, not Clopper-Pearson, as set out in the SAP

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

There is an unmet medical need for efficacious treatments in relapsed primary ITP. Fostamatinib could therefore be an interesting treatment, although the results are not as encouraging as the Applicant had anticipated expecting an efficacy of 40% for the primary endpoint of a platelet count of at least 50,000/µL on at least 4 of the last 6 scheduled visits between Weeks 14 and 24: The percentage of responders in the double-blinded placebo-controlled studies 047 and 048 were 15.7 % and 18.0%, respectively. The 95 % CI in both studies are very wide and approach zero, meaning that the possibility of observing very few responders in clinical practice cannot be neglected.

The comparator is placebo, making it difficult to evaluate fostamatinib's position in the line of possible treatments also given the high efficacy of TPO-RAs and other suggested treatments (GL). The median number of unique prior therapies was 3 in both studies in the fostamatinib arms and 5 and 4 for all ITP therapies in study 047 and 048, respectively, excluding splenectomy, which had been performed in 39% and

28% of the patients, respectively (adding another ITP treatment for these patients) thus precluding the use of fostamatinib as second-line treatment when also taking into account the low efficacy.

The short-term adverse events are generally manageable and generally not severe/serious. The long-term effect in ITP patients is poorly investigated given the fact that this is a continuous treatment. In this regards a PASS study evaluating long term safety has been agreed by the applicant. Given the effect on bone growth in laboratory animal considered to be caused by the off-target effect on VEGF/VEGFR there is a concern that there could be a detrimental effect on the regrowth on fractures, which are fairly frequent in the elderly, as well as a possible adverse effect on osteoporosis, which is already a risk in this population given the frequent use of corticosteroids. Contraindication for the use during pregnancy and lactation and in children < 18 years of age has been clearly stated in the SmPC as well as bone related issues such as the risk in growing adults > 18 years, who have not yet reached skeletal maturity, and precautions in relation to fractures and the potential risk of osteoporosis.

3.7.2. Balance of benefits and risks

Efficacy of Fostamatinib has been shown in a refractory patient population, where there is a high unmet medical need. In these patients who have exhausted several treatment options, even a relatively modest effect size is considered clinically relevant. The non-negligible safety profile is manageable with dose reduction and appropriate precaution measures are reflected in the SmPC. Furthermore, treatment discontinuation is recommended for patients who do not respond to treatment in terms of platelet counts within 12 weeks.

The benefit-risk balance is therefore considered positive in the target population of adult patients refractory to other treatments as represented by the above mentioned indication.

3.7.3. Additional considerations on the benefit-risk balance

In conclusion, taking into consideration the refractory population benefiting from the treatment as per the submitted data and the manageable safety profile, the final agreed indication is the following:

"Fostamatinib is indicated for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (see section 5.1)",

Reference to section 5.1 is included in section 4.1 to guide prescriber to a deeper understanding of the clinical setting in which the product has been studied in particular in reference to previous treatments used on the patient population.

3.8. Conclusions

The overall B/R of Tavlesse is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Tavlesse is favourable in the following indication:

"Fostamatinib is indicated for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments (see section 5.1)"

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that fostamatinib is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.