EU RISK MANAGEMENT PLAN

for

Fostamatinib (fostamatinib disodium)

Data lock point for this RMP: 16 October 2021

RMP version to be assessed as part of this application	2.0
Date of final sign off	See left margin
Rationale for submitting an updated RMP	Change in Marketing authorization holder. Updated DLP and safety data with no impact on safety concerns removal or change.
Summary of significant changes in this RMP	No changes in safety concerns
Other RMP versions under evaluation	Not applicable
Details of the currently approved RMP	Version number: 1.2 Approved with procedure: Not applicable Date of approval (opinion date): 25 October 2019

EU QPPV: Juan Oliveras

Email address: [redacted]

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation holder´s QPPV. The electronic signature is available on the cover page**.**

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
DIC	Disseminated intravascular coagulation
DLP	Data Lock Point
CNS	Central nervous system
EEA	European Economic Area
EMA	European Medicines Agency
EU	European Union
Fos-PCP	Fostamatinib-treated subjects during the placebo-controlled period.
GLP	Good Laboratory Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
ICD	International Statistical Classification of Diseases and Related Health Problems
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IL	Interleukin
INN	International Non-proprietary Name
ITP	Immune thrombocytopenia
IVIG	Intravenous immunoglobulin
MedDRA	Medical Dictionary for Regulatory Activities
Max	Maximum
Min	Minimum
NDA	New Drug Application
PK	Pharmacokinetic
PIL	Patient Information Leaflet
PPND	Post-natal developmental study
PT	Preferred Term
PY	Patient-years
QPPV	Qualified Person for Pharmacovigilance
RA	Rheumatoid arthritis
RET	Receptor tyrosine kinase

RMP	Risk Management Plan
RWE	Real World Evidence
SAE	Serious adverse event
SD	Standard deviation
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
SYK	Spleen tyrosine kinase
TTP	Thrombotic thrombocytopenic purpura
TPO	thrombopoietin
UK	United Kingdom
ULN	Upper limit of normal
US	United States (of America)
VEGFR	Vascular endothelial growth factor receptor

1 PART I: PRODUCT OVERVIEW

An overview of the product is provided in Table 1.

Table 1: Product Overview

Active substance (INN or common name)	Fostamatinib disodium (fostamatinib)
Pharmacotherapeutic group (ATC Code)	B02BX09
Marketing Authorisation Applicant	Instituto Grifols, S.A. Can Guasch, 2 08150 Parets del Vallès Barcelona SPAIN
Medical products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	Tavlesse
Marketing authorisation procedure	Centralised
Brief description of the product	*Chemical class*: Phosphoric acid *Chemical name:* [6-({5-fluoro-2-[(3,4,5-trimethoxyphenyl)amino]pyrimidin-4-yl}amino)-2,2-dimethyl-3-oxo-2,3-dihydro-4H-pyrido[3,2-b]-1,4-oxazin-4-yl]methyl disodium phosphate hexahydrate
	Summary of mode of action: Fostamatinib is a potent and relatively selective spleen tyrosine kinase (SYK) inhibitor. It prevents platelet destruction by interrupting Fc receptor-mediated platelet engulfment on macrophages through inhibition of SYK signalling
	Important information about its composition: Not applicable
Hyperlink to the Product Information	See product information

Indication in the EEA	*Current*: Fostamatinib is indicated for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who are refractory to other treatments
	Proposed: Not applicable
Dosage in the EEA	*Current*: The recommended starting dose of Tavlesse is 100 mg twice daily. After initiating Tavlesse, the dose can be increased to 150 mg twice daily after 4 weeks based on platelet count and tolerability. A daily dose of 300 mg must not be exceeded. Fostamatinib dosing requirements must be individualised based on the patient's platelet counts. The lowest dose of fostamatinib to achieve and maintain a platelet count of at least 50,000/µL should be used. Dose adjustments are based upon the platelet count response and tolerability.
	Proposed: Not applicable
Pharmaceutical forms and strengths	*Current*: • Fostamatinib 100 mg film-coated tablet • Fostamatinib 150 mg film-coated tablet
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	This medicinal product is subject to additional monitoring in EU. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

2 PART II: SAFETY SPECIFICATION

2.1 Module SI – Epidemiology of the Indication and Target Population

2.1.1 Chronic immune thrombocytopenia (ITP) in adult patients who are refractory to previous treatments

2.1.1.1 Incidence

Immune thrombocytopenia (ITP), also referred to as idiopathic thrombocytopenic purpura or immune thrombocytopenic purpura, is a disorder manifested by immune mediated platelet destruction, impairment of platelet production and a variable bleeding tendency. The MAH conducted an exhaustive PubMed literature search to retrieve published articles relative to the epidemiology of ITP in the European Community. Literature references over the past ten years (i.e. since 01 January 2007) were considered, with no geographical restriction as data are not available for the whole Community. Therefore, national incidence data are gathered in Table 2.

Table 2: Estimates of incidence of ITP among adults in the EU

Country (Reference)	Population Study design	Study period	ITP definition & selection criteria	Number of ITP incidents in adults	Reported incidence of ITP in adults (per year)
France (Moulis, 2014)	French population data edited by the Institut National de la Statistique et des Etudes Economiques*	1st July 2009 to 31st December 2011	- Long-term disabling disease (LTD) encoded as ITP (ICD-10 code D69.3 ITP and/or ≥1 hospital stay with a main or related diagnosis encoded as D69.3) - Further exclusions: cases that have been miscoded, diagnosis code starting with D69 but different from D69.3 (eg, D69.6 thrombocytopenia, unspecified)	2,885	2.9 / 100,000
United-Kingdom (Schoonen, 2009)	Not available	1990-2005	ITP patients retrieved from the ITP patients first diagnosed in 1990-2005 were identified in the UK General Practice Research Database (GPRD).	1,145	Men: 3.4 / 100,000 Women: 4.4/ 100,000
Northern England (Neylon, 2003)	Former Northern Health Region in the UK (population 3.08 million)	1st January 1993 to 31st December 1999	- Platelet count <50,000/µL - Further exclusions: relapsed cases; thrombocytopenia due to drugs or gestation; cases without bone marrow exam to rule out haematological malignancy - Presumed autoimmune	245	1.6 / 100,000

Country (Reference)	Population Study design	Study period	ITP definition & selection criteria	Number of ITP incidents in adults	Reported incidence of ITP in adults (per year)
Denmark (Frederiksen, 1999)	Residents of Funen County, Denmark (9% of the total Danish adult population)	1st April 1973 to 31st December 1995	-Platelet count: <100,000/µL Medical record diagnosis of ICD-8 (287.10, 287.11, 287.18, 287.19, 675.09) or ICD-10 (D69.3, D69.4, D69.5, D69.6 O72.3) - Further exclusions: solid tumours, other haematologic disorders, hepatic disease or alcoholism, lupus, TTP, drug or gestation induced TCP, DIC, HIV	221	2.68 / 100,000

Abbreviations: DIC=disseminated intravascular coagulation; HIV=human immunodeficiency virus; ICD=International Statistical Classification of Diseases and Related Health Problems; ITP=immune thrombocytopenia; TTP=thrombotic thrombocytopenic purpura; TCP=thrombocytopenic purpura.

The reported incidence data of ITP varies somewhat from country to country in the EU and ranges from 1.6 to 4.4 per 100,000. The same range of incidence is reported in the United States: the National Organization of Rare Disorders reports an incidence of 3.3 ITP cases per 100,000 adults per year.

2.1.1.2 Prevalence

The reported incidence data for ITP varies somewhat from country to country in the European Union (EU) and ranges from 1.6 to 4.4 per 100,000 (Moulis 2014; Schoonen 2009; Neylon 2003; Frederiksen 1999). The same range of incidence is reported in the United States: the National Organization of Rare Disorders reports an incidence of 3.3 ITP cases per 100,000 adults per year. There are an estimated 50,000 adult patients with chronic ITP in the EU (Gernsheimer 2008).

The duration of ITP varies between children and adults. Among children, ITP is typically acute in duration (<6 months), while in adults it is usually a chronic condition lasting for some years (Bennett 2011). The average disease duration (including children and adults) is reported as D = 0.5-1 year. The highest reported figure is used for calculation purposes.

2.1.1.3 Demographics of the population in the proposed indication and risk factors for the disease

ITP affects people of both sexes and all ages. ITP prevalence (among adults in Europe) was shown to be higher in women and increased with age and over time (Bennet, 2011). However, in a Danish survey, this sex difference was only apparent in patients younger than 65 years (Frederiksen 1999; Michel 2009). As life expectancy in Europe increases, the number of elderly patients with ITP and subsequent comorbidities is also set to increase. In the Danish study, the incidence rate more than doubled in those individuals aged over 60 years compared with younger patients. This observation was confirmed by the results from a UK cohort study, where patients aged over 60 years had the highest incidence of ITP (Neylon, 2003).

There are several genetic risk factors that predispose to ITP, including polymorphisms in immunity-related genes. Many studies have reported associations between ITP and single nucleotide polymorphisms in immunity-related genes. Polymorphisms in genes encoding specific cyto- or chemokines, such as interleukin (Garnett et al.)-1, IL-2, IL-4, IL-6, IL-10, IL-17, tumour necrosis factor-α, tumour growth factor-β, and interferon-γ, have been associated with ITP (Wu, 2005; Emmerich, 2007; Rocha, 2010; Pehlivan, 2011; Saitoh, 2011). Polymorphisms in Fcγ receptors (FcγRs) have also been associated with the onset and pathogenesis of ITP (Foster, 2001; Carcao, 2003; Bruin, 2004; Breunis, 2008; Amorim, 2012; Eyada, 2012; Papagianni, 2013; Wang, 2014).

It has been suggested that infections may comprise an important trigger for the development of auto-immunity against platelets in ITP [Swinkels, 2018]. Some of the most occurring and most studied infectious agents are *Helicobacter pylori* [Takahashi, 2004; Stasi, 2009], Hepatitis C virus (Rajan, 2005; Zhang, 2009) and human immunodeficiency virus (HIV) (Hohmann, 1993; Bettaieb, 1996; Dominguez, 1998; Nardi, 2004; Li, 2005; Nardi, 2007). Evidence also exists for *Cytomegalovirus* (DiMaggio, 2009; Wu, 2013), Epstein Barr virus (Wu, 2013), and some other viruses (Wright, 1996; Musaji, 2004).

2.1.1.4 The main existing treatment options

First-line treatment options for ITP include corticosteroids, intravenous immunoglobulin (IVIG) and intravenous anti-D immunoglobulin (Ig). IVIG and anti-D Ig are usually used as rescue treatments for acute rather than chronic management of ITP. 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 immune thrombocytopenia (Provan, 2010). The main goal of second-line therapy is to attain a sustained increase of the platelet count that is considered haemostatic for the individual patient:

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

Long-term risks/ effects from use of TPO-receptor agonists are still being determined. Potential risks with eltrombopag are bone marrow fibrosis and thrombosis, hepatic and ocular toxicities. Romiplostim requires a weekly injection. TPO-receptor agonists as a class are associated with overshoot and potential thrombosis.

It appears there is also off-label use of rituximab, 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 one 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 post-operative complications, and its effectiveness is currently unpredictable, leading many physicians and patients toward postponement and use of alternative approaches.
- *Hematopoietic stem cell transplantation*

  Remissions have been induced in some patients with chronic refractory ITP using autologous or allogeneic hematopoietic stem cell transplantation (HSCT). However, potentially fatal toxicities such as neutropenic fever, cerebral haemorrhage, and septicaemia may occur (Provan, 2010). HSCT is warranted only in patients with severe, chronic refractory ITP with bleeding complications unresponsive to other modalities. However, very few long-term responses have been recorded.

2.1.1.5 Natural history of the indicated condition in the untreated population, including mortality and morbidity

Immune thrombocytopenia (ITP) arises in 2 clinical contexts. The first is in a paediatric setting and is usually short lived with recovery within weeks to months. However, this is beyond the scope of this application.

Immune thrombocytopenia (ITP) in adults is typically a chronic disease, with a low spontaneous remission rate. Although responses to glucocorticoids, IVIG, splenectomy, and thrombopoietic agents may be encouraging, a significant number of patients remain severely thrombocytopenic for long durations and subject to risk of spontaneous or trauma-induced haemorrhage. Even in asymptomatic patients, platelet counts below 20,000–30,000/μL often prompt the need for treatment.

There is evidence for anti-platelet antibodies in most, though not all, patients. The targets of the antibodies are often various glycoproteins found on the surface of platelets and occasionally megakaryocytes, the bone marrow platelet precursor. The circulating antibody-platelet complexes are cleared by the reticuloendothelial system, principally in the spleen, with the liver participating. A normal platelet count is between 150,000 and 400,000/μL of blood. A platelet count <100,000/μL, with no other reason for low platelets count, is considered to be suggestive of ITP (Rodeghiero, 2009).

The clinical severity of ITP is inversely proportional to the platelet count and may depend on the underlying illnesses as well. Platelet counts above 50,000/μL are rarely associated with spontaneous bleeding and would only be clinically threatening in the event of interruption of vascular integrity (surgery, trauma). Platelet counts below 30,000/μL are more worrisome. Many patients are asymptomatic or may have minimal bruising. Others experience serious bleeding, which may include gastrointestinal haemorrhage, extensive skin and mucosal haemorrhage, or intracranial haemorrhage. The severity of thrombocytopenia correlates with the risk of bleeding to some extent, but not completely. The latter is a life-threatening event. For those patients with severely depressed platelet counts, their daily life is one of repeated minor haemorrhage linked to the fear of a life-altering one, filled with the anxiety attached to the latter (Rodeghiero, 2009; Lakshmanan, 2012).

Patients with ITP typically have severe thrombocytopenia, putting them at risk for serious bleeding. While ITP is generally a benign disease, the risk of mortality in affected patients is roughly twice that of the general population, particularly in patients who are older or who have more advanced disease with a history of bleeding. Causes of death in ITP include severe gastrointestinal bleeding and intracranial haemorrhage, post-splenectomy complications, and infections secondary to long-term immunosuppression from therapy. In a follow-up study looking at morbidity and mortality in adults with ITP, 12 (9%) of 134 patients, all with severe thrombocytopenia, had refractory disease and suffered a mortality risk of 4.2 (95% confidence interval, 1.7–10.0). Bleeding and infection equally contributed to the death of these patients and are the most frequently reported causes of death in ITP (Rodeghiero, 2009; Lakshmanan, 2012; Portielje, 2001).

2.1.1.6 Important co-morbidities

ITP may be primary or secondary to a variety of conditions, including generalised autoimmune disease (as in systemic lupus erythematosus), lymphomatous disease, or chronic viral diseases (as in hepatitis and HIV infection).

In a study by Feudjo-Tepie et al. (2009), ITP was shown to be associated with haematological diseases, dermatological conditions, bleeding disorders and constitutional conditions such as chills, rigors, malaise, and lethargy.

2.2 Module SII – Non-clinical Part of the Safety Specification

A summary of key non-clinical findings and their relevance to humans is outlined in Table 3.

Table 3: Key non-clinical safety findings and relevance to human use

Findings	Relevance to human usage
Toxicity	
Key issues identified from acute and repeat-dose toxicity studies	
Acute-dose toxicity: No formal acute studies were done. At a dose of 400 mg/kg/day (split dose over 3 hours) R406 (a circulating active metabolite of fostamatinib) resulted in adverse clinical signs and mortality (1/6 mice), while single high doses of 200 mg/kg/day were tolerated in the mouse micronucleus study. In particular, following the first dose administration of the vehicle and the high dose level of R406 (200 mg/kg of the total 400 mg/kg/day), animals appeared lethargic and ataxic. After the second administration of 200 mg/kg, animals had piloerection and partially closed eyes. One high dose male exhibited prostration and irregular breathing following the second administration and was found dead on Day 2 (24 hours post-dose). Remaining high dose mice were normal by Day 3. Following dose administration of 200 mg/kg, animals were ataxic and lethargic but were normal by the end of Day 1 and during the course of the study. Repeat-dose toxicity: In a 13-week repeat-dose toxicity study in mice, mild liver and lymphoid depletion effects were noted in the highest dose range, but a maximum tolerated dose was not exceeded. Repeat-dose studies in rats with R406 and fostamatinib (calcium salt for up to 28 days) and fostamatinib (sodium salt for up to 6 months) were completed. Effects observed in these studies included reversible lymphohematopoietic changes (decreased white blood cells and lymphocytes, bone marrow hypocellularity, decreased spleen and thymus weights) and reversible increases in transaminases associated with decreased liver weights. Other changes included femoral head chondrodystrophy in 1 and 6-month studies with fostamatinib (sodium salt) and increased adrenal vacuolation in the 6-month study with fostamatinib (sodium salt). Consistent with the bone growth plate effects in rats in the general toxicity studies, a related finding of odontodysplasia was also observed in the rat 2 year carcinogenicity study. Repeat-dose studies in the cynomolgus monkey were done with R406 for up to 28 days and with fostamatinib for up to 9 months. Findings included transient or sporadic gastrointestinal disturbances, reversible decreased haematological indices and increased transaminases, and bone marrow hypocellularity similar to rats.	The toxicology programme has identified lymphohematopoietic and liver function test abnormalities (mild and fully reversible) in rats and primates that may be seen at anticipated doses/exposure levels to be used in humans.

The effects on bone with thickening of the growth plates in long bones and effects on teeth in rats may translate to a risk of development issues for these tissues in a paediatric setting.	
Reproductive/developmental toxicity	
Developmental toxicity studies with fostamatinib clearly demonstrated skeletal and/or soft tissue (organ) variations and malformations in both rats and rabbits. Reductions in female fertility were consistent with the findings in the development studies. However, there were no effects observed on male fertility.	Based upon the reproductive and/or developmental effects seen in rats and rabbits, administration of fostamatinib early in human pregnancy or during lactation could pose a risk to the foetus/child.
Genotoxicity	
Fostamatinib and R406 were not mutagenic or clastogenic in a battery of *in vi*tro and *in vivo* genotoxicity studies. Five impurities were not mutagenic in an Ames test; one impurity was found to be mutagenic and is controlled in accordance with M7.	There was no evidence for mutagenic or clastogenic effects for R406 or fostamatinib.
Carcinogenicity	
Two-year carcinogenicity studies in mice and rats did not show any evidence for carcinogenic effects in either species.	Fostamatinib is not considered to have carcinogenic potential as assessed in carcinogenicity studies. The ratio of R406 exposure in the mouse carcinogenicity study to human ITP patient exposure was approximately 5 to 20-fold. In the rat, the ratio was lower, at 0.7 to 1.4-fold.
Safety Pharmacology	
In a pharmacology study in a transgenic mouse prone to extensive arteriosclerotic plaque formation (Apo-E mouse model), an increase of ALT and liver weight, and unexpected early death in 7/15 mice in the group exposed to fostamatinib and rosuvastatin concurrently was observed. Data from follow-up safety studies indicate that the effects seen are likely to be due to hepatic effects possibly as a result of PK interaction with fostamatinib resulting in raised rosuvastatin levels in an animal model sensitive to rosuvastatin.	In order to understand the significance of a potential interaction between statins and fostamatinib seen in nonclinical studies with Apo*E mice, a clinical study assessed the pharmacokinetics (PK) of rosuvastatin and simvastatin in healthy subjects, when administered alone or in combination with fostamatinib. Mean ratios of AUC and Cmax were increased for rosuvastatin, simvastatin, and simvastatin acid up to approximately 2-fold; there were no safety or tolerability concerns identified in the healthy subjects. There were no trends or clinically relevant changes in clinical laboratory,

	vital signs, or electrocardiogram findings following dosing.
Cardiovascular system and nervous system	
In the core battery of safety pharmacology studies (respiratory, central nervous system [CNS], and cardiovascular including human ether-à-go-go-related gene), R406 was well tolerated. There was a slight reduction in heart rate, and a trend for increased blood pressure at 50 mg/kg R406 in the monkey cardiovascular study, and mild behavioural abnormalities (e.g., hypoactivity) at the same dose in the rat CNS study. Otherwise, these safety pharmacology studies found no serious effects at expected pharmacodynamic dose ranges.	The effect of fostamatinib on blood pressure is moderate in nature, reversible on removal of treatment, and is responsive to clinical management with standard drug therapies for control. It is also not associated with any histopathologic changes or other adverse pathology.
Other Toxicity-Related Information	
Phototoxicity potential	
R406 lacked any evidence for phototoxic potential in the phototoxicity assay.	There was no evidence for a phototoxic potential of fostamatinib.
Immunotoxicity	
Fostamatinib did not show any immunotoxic effect in mouse streptococcal, Influenza, and Listeria host resistance models. Throughout the non-clinical evaluation there was no evidence for increases in opportunistic infections in any of the species in the toxicology programme (rodents, rabbits, and monkeys).	Taken together this indicates that fostamatinib has a very low likelihood of adversely affecting broadly immune functionality.

Abbreviations: ALT=alanine aminotransferase; AUC=area under the curve; CNS=central nervous system; ITP=immune thrombocytopenia; PK=pharmacokinetic.

2.3 Module SIII – Clinical Trial Exposure

The fostamatinib clinical development programme consists of 57 studies (Table 4), including 26 clinical pharmacology studies in healthy subjects, 5 studies in ITP, 13 studies in RA, 4 studies in oncology (B- and T cell non Hodgkin lymphomas and solid tumours), 3 studies in autoimmune haemolytic anemia (AIHA), 1 study in COVID-19, and 1 study in IgA nephropathy. An additional 4 "Other Clinical Pharmacology" studies were performed. Cumulatively, 4,680 subjects have been exposed to fostamatinib in 52 completed clinical trials and 411 subjects have been exposed to fostamatinib in 5 ongoing clinical trials.

In addition to studies in ITP, the majority of the safety data for fostamatinib is derived from studies in rheumatoid arthritis (RA), studies in oncological indications (lymphomas and solid tumours), and studies in healthy subjects. In February 2010, AstraZeneca signed a global license agreement with Rigel to develop and commercialise fostamatinib. AstraZeneca conducted a comprehensive programme for the treatment of RA (through Phase 3). Although fostamatinib showed a significant, consistent, favourable effect with regard to RA signs, symptoms, and functional improvement (primary endpoint in all 3 Phase 3 studies), fostamatinib did not affect bone erosion and joint destruction in 2 of the studies, which led AstraZeneca to return the development rights to Rigel. Licensure in RA is not being pursued. Data from the RA programme support the clinical safety of fostamatinib and contributed to the selection of the dose and regimen of fostamatinib evaluated in the Phase 3 studies in ITP.

The oncology subjects (n=204 total) provide safety data for higher doses (200-500 mg/day) of fostamatinib than were used in the RA or ITP subjects and hence are less relevant. Development and licensure in oncology also has not been pursued. Four studies of fostamatinib were conducted in adult patients with malignancies, 3 studies in B cell or T cell lymphomas (total n=167) and 1 in advanced solid tumors (n=37). The similarities of the 3 lymphoma studies allowed pooling of data across studies. Each study was open-label and employed similar methods of safety data collection. Safety data from the 3 company-sponsored lymphoma studies are thus presented in an integrated fashion in the tables below.

Safety data from studies in Healthy subjects and in Other studies were based primarily on single dosing or short duration multiple dosing. Since the safety data from these studies and the one conducted in patients with IgA nephropathy (n=51)did not add clinically important information to the safety profile of fostamatinib, details are not included in the tables below.The fostamatinib clinical development programme also includes five ongoing studies, three in AIHA (C-935788-053, C935788-057 and C935788-058), one in ITP (R788-1301), and one in COVID-19 (C-935788-061). Since these studies are ongoing, they are not included in the analyses of safety that follow.

Table 4: Summary of clinical development programme for fostamatinib

Population	Number of studies	Number of subjects exposed to fostamatinib
Healthy subjects	26	724
ITP	5[a]	(163+34*) = 197
RA	13[b]	3,437
Oncology	4[c]	204
Other	4[d]	101
IgAN	1	51
AIHA	3	169
COVID-19	1	208
Total number of subjects exposed to fostamatinib		5,091

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

[a] *Includes Phase 2 Study D4300-022, not part of the integrated safety analysis (N=17 unique subjects)*

[b] *Includes 9 placebo-controlled studies (N=2414) and 4 extension studies in RA*

[c] *Includes a study from the literature comprising 37 subjects with solid tumours*

[d] *Includes clinical pharmacology Study D4300-009 (N=16 with renal impairment), Study D4300-010 (N=24 with hepatic impairment), drug-drug interaction study with methotrexate in RA, Study C788-004 (N=16), and Study C406-001 with a R406, the primary fostamatinib metabolite (N=45).*

**Subject exposed to Fostamatinib in going study (R788-1301)*

Abbreviations: ITP=immune thrombocytopenia; RA=rheumatoid arthritis.

2.3.1 Immune Thrombocytopenia in completed studies

A total 163 of subjects exposed in completed studies with ITP received at least 1 dose of fostamatinib: 17 subjects in the Phase 2 study, and 146 subjects from the Phase 3 studies, including 102 randomised to fostamatinib in the placebo-controlled studies and 44 additional subjects initially randomised to placebo and then rolled over to fostamatinib in the extension study.

An overview of exposure data is provided in Table 5.

The Fostamatinib Exposure Period includes data from 146 subjects receiving fostamatinib at any time in the placebo-controlled and the extension study.

Overall, including the open-label extension study, oral doses of fostamatinib were administered to 146 subjects in the Phase 3 studies, including 91 subjects for at least 24 weeks and 31 subjects for at least 48 weeks; the maximum fostamatinib treatment duration was approximately 2 years.

The upper end of the range of exposure to fostamatinib among subjects with ITP increased to over 3.5 years (1257 days) with 98/146 subjects (67.1%) exposed to fostamatinib for ≥24 weeks. Total patient-years (PY) of exposure was 29.34 in the fostamatinib group and 12.12 in the placebo group.

Table 5: Duration of exposure in ITP studies – placebo-controlled and fostamatinib exposure periods

Variable	Placebo-Controlled Period[a] (N=150)		Fostamatinib Exposure Period[b]	As of 08 March 2018
	Fostamatinib (N=102)	Placebo (N=48)	(N=146)	(N=146)
Total Patient-Years Exposure	29.34	12.12	91.20	163.1
Duration of Exposure (days)				
Mean	105.1	92.2	228.2	408.0
SD	43.9	31.7	158.6	364.4
Median	86.0	85.0	179.0	204.0
Min - Max	8 - 183	16 - 173	8 - 712	8 - 1257
Duration of Exposure Category, n (%)[c]				
< 4 weeks (< 28 days)	4 (3.9)	3 (6.3)	4 (2.7)	4 (2.7)
≥ 4 weeks (≥ 28 days)	98 (96.1)	45 (93.8)	142 (97.3)	142 (97.3)
≥ 8 weeks (≥ 56 days)	93 (91.2)	45 (93.8)	134 (91.8)	134 (91.8)
≥ 12 weeks (≥ 84 days)	78 (76.5)	38 (79.2)	124 (84.9)	125 (85.6)
≥ 24 weeks (≥ 168 days)	20 (19.6)	2 (4.2)	91 (62.3)	98 (67.1)
Mean Total Daily Dose (mg)	n = 102	n = 48	n = 145	n = 146
Mean	241.16	246.16	232.62	242.13
SD	45.20	28.97	47.89	51.90
Median	258.84	258.97	247.50	255.59
Min - Max	40.0 - 389.7	131.3 - 270.2	40.0 - 389.7	40.0 - 389.7

Source: m2.7.4 Table 2 and 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 patient.*
[c] *Patients can appear in more than one category.*
[d] *Mean daily dose was calculated as total dose administered (mg) / duration of exposure (days).*

Demographical data in ITP are presented in Table 6. Demographical characteristics were generally balanced between treatment groups in the ITP placebo-controlled period. Median age (range) was 53.5 years (20–88) in the fostamatinib group and 54.0 years (20–78) in the placebo group. Most of the subjects were female (59.8% fostamatinib, 62.5% placebo). Most subjects were white (93.1% fostamatinib, 91.7% placebo) and not Hispanic or Latino (97.1% fostamatinib, 97.9% placebo).

Table 6: Subject demographics in ITP – placebo-controlled period and fostamatinib exposure period

Variable	Placebo-Controlled Period (C788-047 and C788-048)		Fostamatinib Exposure Period
	Fostamatinib[a] (N = 102)	Placebo (N = 48)	Fostamatinib (N = 146)
Age (years), n (%)			
Mean	53.1	51.6	52.4
SD	16.9	16.3	16.6
Median	53.5	54.0	53.0
Min - Max	20 - 88	20 - 78	20 - 88
Age Category (years)			
<50	42 (41.2)	21 (43.8)	62 (42.5)
50 - <65	32 (31.4)	16 (33.3)	47 (32.2)
≥65	28 (27.5)	11 (22.9)	37 (25.3)
65 - <75	17 (16.7)	7 (14.6)	24 (16.4)
≥75	11 (10.8)	4 (8.3)	13 (8.9)
Gender, n (%)			
Female	61 (59.8)	30 (62.5)	87 (59.6)
Male	41 (40.2)	18 (37.5)	59 (40.4)
Race, n (%)			
Asian	[redacted]	[redacted]	[redacted]
Black or African American			
White	95 (93.1)	44 (91.7)	135 (92.5)
Other	[redacted]	[redacted]	[redacted]
Ethnicity, n (%)			
Hispanic or Latino	[redacted]	[redacted]	[redacted]
Not Hispanic or Latina	99 (97.1)	47 (97.9)	142 (97.3)
Unique Prior Therapies			
Mean	3.8	4.3	N/A
SD	2.37	2.69	N/A
Median (Min - Max)	3.0 (1, 13)	3.0 (1, 10)	N/A
Unique prior ITP medications and/or splenectomy, n(%)			
1	14 (13.7)	6 (12.5)	N/A
2	16 (15.7)	9 (18.8)	N/A
3	23 (22.5)	6 (12.5)	N/A
4+	49 (48.0)	27 (56.3)	N/A

Source: m5, ISS-ITP, Appendix 2: Table 1.4.1 and Table 1.4.2, post hoc table q126a_t_prioritp_unique_saf and post hoc table q126a_t_prioritp_unique_nonsple_saf.

Abbreviations: max=maximum value; min=minimum value; SD=standard deviation.

[a] *Subjects receiving fostamatinib in the Placebo-Controlled Period are the same patients receiving fostamatinib at outset in the fostamatinib exposure period.*

2.3.2 Rheumatoid arthritis

An overall summary of fostamatinib exposure across all 9 RA studies is provided in Table 7. A total of 2,414 subjects received fostamatinib during the treatment period. Doses ranged from 100–300 mg per day all given on a bid basis. A total of 1,303 subjects with RA received a fostamatinib dose of 100–150 mg bid (i.e., 200–300 mg/day), which is the clinical dose for the intended indication in ITP. The combined placebo groups consisted of 1,169 subjects. Mean duration of fostamatinib exposure across dose groups was 545.6 days, ranging from 1 to 2,481 days; hence, dosing in some subjects extended beyond 6 years. Almost 60% of subjects were treated for 1 or more years, and 334 patients (9.7%) were treated for 3 or more years. Exposure in this population was 5,134 PY.

Table 7: Extent of fostamatinib exposure in RA

Placebo-controlled safety set				
	Fostamatinib 100–150 mg/day	**Fostamatinib 200–300 mg/day**	**All Fostamatinib**	**Placebo**
N	1,111	1,303	2,414	1,169
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	1,092 (98.3)	1,283 (98.5)	2,375 (98.4)	1,105 (94.5)
≥ 8 weeks	952 (85.7)	1,091 (83.7)	2,043 (84.6)	952 (81.4)
≥ 12 weeks	866 (77.9)	1,004 (77.1)	1,870 (77.5)	852 (72.9)
≥ 24 weeks	603 (54.3)	627 (48.1)	1,230 (51.0)	505 (43.2)
≥ 36 weeks	0	0	0	0
Total patient exposure years	389	435	823	367
Fostamatinib safety set				
	Fostamatinib 100–150 mg/day	**Fostamatinib 200–300 mg/day**	**All Fostamatinib**	**Placebo**
N	1,232	2,205	3,437	-
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	1,185 (96.2)	2,145 (97.3)	3,330 (96.9)	-
≥ 12 weeks	1,106 (89.8)	2,005 (90.9)	3,111 (90.5)	-
≥ 36 weeks	849 (68.9)	1,521 (69.0)	2,370 (69.0)	-
≥ 1 year	728 (59.1)	1,321 (59.9)	2,049 (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 patient exposure	1,845	3,289	5,134	-

Source: m5, ISS-RA, Appendix 2: Table 3.1.1 & Table 3.1.2.
Abbreviations: RA=rheumatoid arthritis; SD=standard deviation.

Demographical data in RA are presented in Table 8. The majority of subjects in the RA studies were female (82.8%). Median age of the subjects was 54 years across all treatment groups. Most subjects were white, with Asian being the most highly represented minority. Overall the treatment groups were well balanced in demographic variables and were representative of the RA population as a whole.

Table 8: Demographics in RA (placebo-controlled safety set)

	Fostamatinib			
	100–150 mg/day	200–300 mg/day	All Fostamatinib	Placebo
N	1111	1303	2414	1169
Gender, n (%)				
Female	920 (82.8)	1080 (82.9)	2000 (82.9)	968 (82.8)
Male	191 (17.2)	223 (17.1)	414 (17.1)	201 (17.2)
Age (years)				
Mean (SD)	52.7 (11.8)	52.7 (12.3)	52.7 (12.1)	52.8 (12.3)
Median	54.0	54.0	54.0	54.0
Range	18, 81	18, 87	18, 87	19, 86
<65	932 (83.9)	1099 (84.3)	2031 (84.1)	965 (82.5)
≥65	179 (16.1)	204 (15.7)	383 (15.9)	204 (17.5)
≥75	18 (1.6)	36 (2.8)	54 (2.2)	31 (2.7)
Race, n (%)				
White	744 (72.2)	853 (78.5)	1597 (75.4)	817 (77.1)
Asian	124 (12.0)	53 (4.9)	177 (8.4)	59 (5.6)
Black	37 (3.6)	47 (4.3)	84 (4.0)	56 (5.3)
Other	125 (12.1)	134 (12.3)	259 (12.2)	127 (12.0)

Source: m5, ISS-RA, Appendix 2: Table 2.1.1.
Abbreviations: RA=rheumatoid arthritis; SD=standard deviation

Demographical data in oncological indications is presented in Table 10. Across all dose groups, the median age of the population was 64 years, ranging from 29 to 91 years. Approximately two-thirds were male and most were white (88.6%).

2.3.3 Lymphoma patients

An overall summary of fostamatinib exposure across all 3 lymphoma studies is provided in Table 9. A total of 167 subjects with lymphomas received fostamatinib in these open label trials. Doses ranged from 200 to 500 mg per day, all given on a bid basis. The majority of subjects in the lymphoma studies received fostamatinib doses higher than the intended dose for ITP, which is 100–150 mg bid.

Table 9: Duration of fostamatinib exposure in lymphoma studies

	Fostamatinib 200 mg	Fostamatinib 400 mg	Fostamatinib 500 mg	All Fostamatinib
N	21	139	7	167
Days of Exposure				
Mean (SD)	70.6 (96.4)	89.5 (102.6)	172.9 (220.8)	90.6 (109.4)
Median	54.0	54.0	56.0	54.0
Range	4 - 406	4 - 640	15 - 501	4 - 640
Categorical Weeks of Exposure, n (%)				
<4 weeks	5 (23.8)	27 (19.4)	1 (14.3)	33 (19.8)
≥4 to <8 weeks	7 (33.3)	47 (33.8)	2 (28.6)	56 (33.5)
≥8 to <12 weeks	6 (28.6)	23 (16.5)	2 (28.6)	31 (18.6)
≥12 to <24 weeks	1 (4.8)	22 (15.8)	0	23 (13.8)
≥24 to <36 weeks	0	11 (7.9)	0	11 (6.6)
≥36 to <1 year	1 (4.8)	4 (2.9)	0	5 (3.0)
≥1 year	1 (4.8)	5 (3.6)	2 (28.6)	8 (4.8)
Total patient exposure	4.1	34.1	3.3	41.5

Source: Appendix 2: Table 3.1.1.
Abbreviations: SD=standard deviation.

Table 10: Demographics in lymphoma studies

	Fostamatinib Dose			
	200 mg	400 mg	500 mg	All
N	21	139	7	167
Age (years)				
Mean (SD)	62.9 (12.4)	63.8 (11.3)	62.9 (10.2)	63.6 (11.4)
Median	64.0	64.0	61.0	64.0
Range	31 - 84	29 – 91	52 – 80	29 - 91
Gender, n (%)				
Male	12 (57.1)	95 (68.3)	[redacted]	109 (65.3)
Female	9 (42.9)	44 (31.7)		58 (34.7)
Race, n (%)				
White	19 (90.5)	124 (89.2)	5 (71.4)	148 (88.6)
Black/ African American	[redacted]	[redacted]	[redacted]	[redacted]
Asian				
Other	0	4 (2.9)	0	4 (2.4)

Source: m5, ISS-ONC Appendix 2: Table 2.1.1.
Abbreviations: SD=standard deviation.

2.4 Module SIV – Populations Not Studied in Clinical Trials

2.4.1 Exclusion criteria in pivotal clinical studies within the development programme

Important exclusion criteria in the pivotal ITP clinical studies across the development programme are presented in Table 11.

Table 11: Important exclusion criteria in pivotal ITP clinical studies

Exclusion Criteria	Criteria Reason for exclusion	Is it considered to be included as missing information?	Rationale, if not
Pregnant or lactating women.	Standard exclusion criterion for clinical trials.	No	Fostamatinib is contraindicated during pregnancy. Women of childbearing potential must use effective contraception during treatment and at least one month after the last dose. Breast-feeding should be discontinued during treatment and for at least one month after the last dose of fostamatinib.
Patients younger than 18 years of age.	The proposed indication is pertinent to the adult population.	No	Off label use in paediatric population is considered an important potential risk for fostamatinib.
Subjects with ITP associated with lymphoma, chronic lymphocytic leukaemia, viral infection, autoimmune disorders, thyroid disease, human immunodeficiency virus (HIV), or hepatitis or induced or allo-immune thrombocytopenia or thrombocytopenia associated with myeloid dysplasia.	Individual influence on the trial results.	No	General risk consideration in experimental treatment. There is no scientific evidence that would suggest that the efficacy or safety profile of fostamatinib in patients with secondary ITP would differ from that in the remaining target population. Therefore, this exclusion criterion is not considered missing information.
Subjects with autoimmune haemolytic anaemia.	Individual influence on the trial results.	No	General risk consideration in experimental treatment. There is no scientific evidence that would suggest that the safety profile of fostamatinib in patients with autoimmune haemolytic anaemia would differ from that in the remaining target population. Therefore, this exclusion criterion is not considered missing information.

Exclusion Criteria	Criteria Reason for exclusion	Is it considered to be included as missing information?	Rationale, if not
Subjects who had a history of or active, clinically significant respiratory, gastrointestinal, 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.	Concomitant disease may interfere with valid results of the trial.	No	General risk consideration in experimental treatment. Benefit may still be derived for the target indication despite patients having a history of or concomitant disease. Therefore, this exclusion criterion is not considered missing information.
Subjects who had uncontrolled or poorly controlled hypertension, defined as systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg, whether or not the subject was receiving anti-hypertensive treatment. Subjects could have been rescreened if their blood pressure was successfully and promptly controlled (within 30 days) using conventional anti-hypertensive therapy to achieve optimal blood pressure control (<140/90 mmHg).	Unstable disease could interfere with valid results of the trial.	No	Hypertension is considered an important identified risk for fostamatinib.
Subjects who 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 deep vein thrombosis within 6 months before randomisation.	Individual influence on the trial results.	No	General risk consideration in experimental treatment. Benefit may still be derived for the target indication despite patients having a history of coagulopathy. Therefore, this exclusion criterion is not considered missing information.
Subjects who had a bleeding assessment score of Grade 2 at any site by ITP Bleeding Scale.	Individual influence on the trial results.	No	General risk consideration in experimental treatment. Benefit may still be derived for the target indication despite patients having a bleeding assessment score of Grade 2. Therefore, this exclusion criterion is not considered missing information.

Exclusion Criteria	Criteria Reason for exclusion	Is it considered to be included as missing information?	Rationale, if not
Subjects who had 1 or more of the following laboratory abnormalities: leukocyte count <2500/µL, neutrophil count <1500/µL, lymphocyte count <750/µL, haemoglobin <10 g/dL without ongoing transfusion support, or transaminase levels (ALT, AST) >1.5 times upper limit of normal, total bilirubin >2.0 mg/dL, or estimated glomerular filtration rate <30 mL/minute at the time of screening.	Individual influence on the trial results.	No	Only relevant in a trial setting; therefore, this exclusion criterion is not considered missing information. Increased levels of ALT/AST are considered an important identified risk for fostamatinib.
Subjects who had a significant infection, or an acute infection such as influenza, or were known to have an active inflammatory process at the time of screening and/or baseline (Day 1).	Unstable disease could interfere with valid results of the trial.	No	Infections are considered an important identified risk for fostamatinib.
Subjects who had acute gastrointestinal symptoms at the time of screening and/or baseline (e.g., nausea, vomiting, diarrhoea, or abdominal pain).	Individual influence on the trial results.	No	Diarrhoea is considered an important identified risk for fostamatinib.
Subjects who had increased the dose of, or added, prescription drugs within the 2 weeks before Day 1, unless agent was agreed to be not clinically relevant by both the investigator and sponsor.	Concomitant treatments may interfere with trial results.	No	General risk consideration in experimental treatment. Benefit may still be derived for the target indication despite patients having concomitant prescription drugs. Therefore, this exclusion criterion is not considered missing information.
Subjects who had positive results for HIV, hepatitis B virus (HBV), or hepatitis C virus (HCV) by standard serologic tests.	Individual influence on the trial results.	No	General risk consideration in experimental treatment. Benefit may still be derived for the target indication despite patients having positive results for HIV, HBV, or HCV. Therefore, this exclusion criterion is not considered missing information.

Exclusion Criteria	Criteria Reason for exclusion	Is it considered to be included as missing information?	Rationale, if not
Subjects who had received any blood or blood products within the 2 weeks before randomisation. (intravenous immunoglobulin or anti-D immunoglobulin G was allowed if used for rescue therapy, unless platelet count was >30 000/μL at the time of randomizsation.	Blood products may interfere with trial results.	No	General risk consi-deration in experimental treatment. Benefit may still be derived for the target indication despite patients having received blood or blood products. Therefore, this exclusion criterion is not considered missing information.
Subjects who were currently enrolled in an investigational drug or device study or had used an investigational drug or device within 30 days or 5 half-lives (whichever was longer) of Day 1.	Standard exclusion criterion to avoid confounding and increased risk.	No	Only relevant in a trial setting; therefore, this exclusion criterion is not considered missing information.
Subjects who had a history of alcohol or substance abuse that, in the judgment of the investigator, impaired or risked the subject's full participation in the study.	Individual influence on the trial results. Concerns regarding the patient's ability to participate in the trial.	No	General risk consideration in experimental treatment. Benefit may still be derived for the target indication despite patients having a history of alcohol or substance abuse. Therefore, this exclusion criterion is not considered missing information.
Subjects who had a known allergy and/or sensitivity to the study drug or its components.	Concomitant disease may interfere with trial results.	No	General risk consideration in experimental treatment.
Subjects who had major surgery within 28 days before randomisation or had a surgical wound that was not fully healed.	Individual influence on the trial results. Concerns regarding the patient's ability to participate in the trial.	No	General risk consideration in experimental treatment. Benefit may still be derived for the target indication despite patients having had a major surgery. Therefore, this exclusion criterion is not considered missing information.

Abbreviations: ALT=alanine aminotransferase; AST=aspartate aminotransferase; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; ITP=immune thrombocytopenia.

2.4.2 Exposure of special populations not included in clinical trial development programmes

Pregnant women, breastfeeding women, subpopulations carrying relevant genetic polymorphisms and patients with relevant comorbidities such as those with cardiovascular impairment, immunocompromised patients and patients with a disease severity different from inclusion criteria in clinical trials) were not included in clinical trial development programmes. However fourteen pregnancies occurred in the RA program and one in the ITP clinical program. In study D4300-022 (an open-label study in subjects with ITP) a [redacted] for more than 3 years to fostamatinib. The subject has a history of ITP refractory to splenectomy, hypertension, and irregular periods. [redacted] is reported to have initiated treatment with fostamatinib in Jan-2007. Doses of fostamatinib were increased regularly up to 175 mg bid as of Nov 2009. [redacted] In April 2010, [redacted] had [redacted] and abdominal cramps, presented to the emergency room (ER) where [redacted] She was discharged the next day. [redacted] and elected to continue treatment with fostamatinib.

2.4.3 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

2.4.4 Limitations in respect to populations typically under-represented in clinical trial development programmes

Limitations in special populations are summarised in Table 12.

Table 12: Exposure of special populations included in clinical trial development programmes

Type of special population	Exposure
Population with relevant different ethnic origin	See SIII Table 6, Table 8, and Table 10, providing demographic data.
Patients with relevant comorbidities	
Patients with hepatic impairment	Eight subjects with mild, 8 subjects with moderate and 8 subjects with severe hepatic impairment received a single dose of 150 mg fostamatinib. Study D4300-010 assessed the PK of R406 (an active metabolite of fostamatinib) in subjects with hepatic impairment compared to healthy subjects. Data from this study suggested that hepatic impairment does not affect the PK of R406 to an extent that would be considered clinically relevant. Phase 2 and 3 studies excluded patients with significant hepatic disease; therefore, clinical experience in this population is limited.
Patients with renal impairment	Eight subjects with mild, 8 subjects with moderate and 8 subjects with end stage renal impairment received a single dose of 150 mg fostamatinib. Study D4300-009 assessed the PK of R406 in subjects with renal impairment compared with healthy subjects. Data from this study suggested that renal impairment does not affect the PK of R406 to an extent that would be considered clinically relevant. Creatinine clearance was not identified as a significant covariate in population PK analyses, consistent with the results from the renal impairment study. Therefore, no dose adjustment is warranted in subjects with mildly impaired renal function.

Source: CTD Module 2.7.2.
Abbreviations: PK=pharmacokinetics.

2.5 Module SV – Post-authorisation Experience

The International Birth Date for fostamatinib is 17 April 2018, based on the first approval date in the United States. As of the data lock point, fostamatinib is approved in the United Stated of America (USA), Canada, Israel, United Kingdom and in all the EEA (European Economic Area) countries (the 27 Member States of the European Union plus Iceland, Norway, and Liechtenstein) by the centralized procedure.

Fostamatinib is indicated for the treatment of chronic ITP in adult patients who are refractory to other treatments.

Method used to calculate exposure

The total number of doses has been estimated assuming an average dosage of 200 mg daily. The usual mean starting dose is 100 mg twice daily and dose modification is recommended based on tolerability and platelet counts; a daily dose of 300 mg daily must not be exceeded and if further dose reduction below 100 mg daily is required, fostamatinib must be discontinued. Thus, the total number of doses has been estimated using the following equation:

Number of daily doses = Commercialised fostamatinib (mg) / (200mg/day)

The total number of patients treated during a year has been estimated using the following equation:

Patient*year = Number of daily doses / 365 days

Exposure

The total amount of fostamatinib distributed by the manufacturer from [redacted]

[redacted]

The reported AEs and overall safety information is consistent with the safety profile of the medicinal product in ITP patients.

2.6 Module SVI - Additional EU Requirements for the Safety Specification

2.6.1 Potential for misuse for illegal purposes

There is no potential for misuse of fostamatinib for illegal purposes.

2.7 Module SVII – Identified and Potential Risks

2.7.1 Identification of safety concerns in the initial RMP submission

2.7.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

1. **Risks with minimal clinical impact on patients (in relation to the severity of the indication treated)**

   The indication for treatment with fostamatinib is ITP. Untreated ITP is associated with a risk of spontaneous or trauma-induced haemorrhage. The following ADRs are expected to have a minimal impact when viewed from the perspective of the seriousness and severity of the indication and the low numbers/low percentage of patients experiencing these events:

   - Dizziness
   - Dysgeusia
   - Rash
   - Rash erythematous
   - Rash macular

2. **Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and considered to be acceptable in relation to the severity of the indication treated**

   - Chest pain
   - Dizziness

3. **Known risks that require no further characterisation and are followed up via routine pharmacovigilance, namely through signal detection and adverse reaction reporting, and for which the risk minimisation messages in the product information are adhered to by prescribers (e.g., actions being part of standard clinical practice in each EU Member state where the product is authorised)**

    - Pregnancy and lactation

      Based on findings from animal studies and its mechanism of action, fostamatinib can cause foetal harm when administered to a pregnant woman. In animal reproduction studies, administration of fostamatinib to pregnant rats and rabbits during organogenesis caused adverse developmental outcomes including embryo-fetal mortality (post-implantation loss), alterations to growth (lower fetal weights), and structural abnormalities (variations and malformations) at maternal exposures (AUCs) approximately 0.3 and 10 times the human exposure at the maximum recommended human dose (MRHD) respectively. Pregnant women should be advised about the potential risk to a foetus.

      Some pregnancies occurring during clinical trials resulted in healthy newborns as well as stillbirths/spontaneous abortions and miscarriages.

      If a patient becomes pregnant while taking fostamatinib, therapy should be discontinued. Fostamatinib is contraindicated during pregnancy.

      It is unknown whether fostamatinib/metabolites are excreted in human milk.

4. **Available pharmacodynamic/toxicological data in animals have shown excretion of fostamatinib /metabolites in milk**. A risk to the suckling child cannot be excluded. Breast-feeding should be discontinued during treatment with fostamatinib and for at least one month after the last dose.

5. **Known risks that do not impact the risk-benefit profile**

    - Fatigue
    - Influenza like illness

6. **Other reasons for considering the risks not important**

    None.

For information on the frequency of each ADR please see Section 4.8 or the SmPC for fostamatinib.

2.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

The rationale for considering the important identified and potential risks and missing information to impact the risk-benefit balance of fostamatinib in the ITP indication is presented in Table 13 and Table 14, respectively.

The following categories of important identified risks have been observed throughout the fostamatinib clinical development program. These risks are easily ascertained by routine clinical monitoring; they are mostly mild to moderate in severity; they are rapidly reversible upon reduction or interruption of dose; and they are manageable by readily available therapeutics, such as loperamide (for diarrhoea), or antihypertensive agents.

Formal guidelines for the management of these important identified risks is included in Section 4.4 of the SmPC. Details of justification of the risk-benefit impact are provided in Table 13.

Table 13: Justification for risk-benefit impact of important identified risks

Important identified risk	Justification for risk-benefit impact
Diarrhoea	Diarrhoea has been the most commonly noted adverse drug reaction in all clinical development programmes (including ITP, RA and oncology studies) [m2.5]. Diarrhoea is listed in Section 4.8 of the SmPC.
Hypertension	During the clinical development programme, hypertension events led to 2 study drug interruptions, 2 dose reductions and 1 study drug withdrawal in ITP subjects receiving fostamatinib [m2.5]. The risk can be adequately minimised with advice provided in Section 4.4 of the SmPC stating that during fostamatinib treatment blood pressure should be monitored every 2 weeks until stable, then monthly and anti-hypertensive therapy should be adjusted or initiated.
Hepatotoxicity	Fostamatinib administration can result in blood transaminase (ALT and/or AST) elevations that may necessitate drug dose reduction or discontinuation [m2.5]. However no cases met the Hy's Law criteria during the clinical development of fostamatinib. The risk can be adequately minimised with advice provided in Section 4.4 of the SmPC stating that liver function tests should be monitored monthly during fostamatinib treatment.
Neutropenia	Early in clinical development, fostamatinib was recognised to produce reductions in neutrophils that were rapidly reversible upon discontinuation of therapy. Transient neutropenia (ANC $<1 \times 10^9$/L) was observed in approximately 1% of subjects receiving fostamatinib across all populations (ITP, RA and oncology) [m2.5]. This is consistent with findings from nonclinical toxicity studies which identified bone marrow hypocellularity. The risk can adequately be minimised with advice provided in Section 4.4 of the SmPC to monitor ANC monthly and in Section 4.2 of the SmPC to interrupt, reduce, or discontinue fostamatinib treatment upon an ANC decrease to less than 1.0×10^9/L, over at least 72 hours.

Important identified risk	Justification for risk-benefit impact
Infections	In the placebo-controlled ITP clinical studies, adverse reactions recorded as "infection" were numerically higher in the fostamatinib group (fostamatinib 26.5%; placebo 20.8% during the placebo-controlled period), that was primarily caused by higher incidence of local infections (e.g., upper respiratory tract infections, lower respiratory tract infections, urinary tract infections) without any systemic opportunistic infections [m2.5]. In the RA observational report (Real World Evidence [RWE]177), sensitivity analyses with additional standardisation to HAQ score have identified comparable incidence rates for infection mortality and hospitalisation in the fostamatinib and registry cohorts [Nyberg, 2013]. Infections are listed in Section 4.4 and Section 4.8 of the SmPC for fostamatinib. The risk can be adequately minimised with advice provided in the Patient Information Leaflet on initial symptoms of infections and recommendation to contact the treating health care provider.

Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; ITP=immune thrombocytopenia; RA=rheumatoid arthritis; SmPC=Summary of Product Characteristics

Table 14 : Justification for risk-benefit impact of important potential risk

Important potential risk	Justificaiton for risk benefit impact
Off label use in paediatrics (effect of fostamatinib during bone formation and regrowth during development)	Based upon the chondrodystrophy/growth plate dysplasia seen in juvenile animals (rodents and rabbits) in non-clinical studies, which may be related to off-target inhibition of VEGFR by R406 in growing animals, fostamatinib is not for use in patients <18 years of age [m2.5]. Section 4.2 of the SmPC states that fostamatinib should not be used in children because of safety concerns (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)	Since fostamatinib was shown in vitro to not only target SYK but 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.

Abbreviations: EMA=European Medicines Agency; ITP=immune thrombocytopenia; PPND=post-natal developmental study; SmPC=Summary of Product Characteristics; VEGFR: Vascular endothelial growth factor receptor.

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

There are no new safety concerns that should be considered in addition to the information included in product labelling.

2.7.3 Details of important identified risks, important potential risks, and missing information

The primary basis of the evaluation of safety in subjects with ITP is derived from the following 3 studies:

- Study C788-047: Phase 3, randomised study in subjects with chronic ITP (N=76)
- Study C788-048: Phase 3, randomised study in subjects with chronic ITP (N=74)
- Study C788-049: Phase 3, open-label extension study in subjects with chronic ITP participating in Study C788-047 or Study C788-048 (N=123; interim data cut-off 08 March 2018).

The subjects participating in Studies C788-047, C788-048, and C788-049 had previously treated, persistent or chronic ITP. The identical designs of Study C788 047 and Study C788-048 allowed pooling of data to assess the short-term safety and tolerability profile of fostamatinib in a placebo-controlled safety population. To assess the long-term safety and tolerability profile of fostamatinib, data from all subjects receiving fostamatinib in Studies C788-047, C788-048, and C788-049 were pooled in the fostamatinib treated population.

Two treatment periods were defined as follows:

- Placebo-controlled period: Time on treatment during Studies C788-047 and C788-048 (i.e., placebo controlled). Data obtained after subjects enrolled in Study C788-049 were excluded, regardless of randomised treatment. This treatment period was used for analyses of the placebo-controlled safety population.
- Fostamatinib exposure period: Time on fostamatinib, regardless of randomised treatment, including both double-blind fostamatinib data (from Study C788-047 or Study C788-048) and open-label fostamatinib data (from Study C788-049). Subjects randomised to placebo in Studies C788-047 or C788-048 were included after switching to fostamatinib in Study C788-049. This treatment period was used for analyses of the fostamatinib treated population.

2.7.3.1 Presentation of important identified risks and important potential risks

Information on important identified and potential risks for fostamatinib is summarised in Table 15 (Diarrhoea), Table 16 (Hypertension), Table 17 (Hepatotoxicity), Table 18 (Neutropenia), and Table 19 (Infections); Table 20 (Off label use in paediatrics [effect of fostamatinib during bone formation and regrowth during development]); Table 21 (Use in patients with osteoporosis, patients with fractures, or young adults where epiphyseal fusion has not yet occurred).

For the ITP indication, it is worth noting that AEs and laboratory findings reported in the Fostamatinib Exposure Period include events already described for fostamatinib subjects treated in the Placebo-Controlled Period, who are referred to as "Fos-PCP" in the Fostamatinib Exposure Period summaries below.

The frequently reported ADRs from the lymphoma studies are consistent with the frequently reported ADRs from the ITP studies. It is important to note differences in reported adverse events in these lymphoma studies were often consistent with the clinical presentation of the underlying disease or prior treatment with systemic chemotherapy, radiotherapy, and transplant. In addition, the design of the oncology studies included the use of higher fostamatinib doses than those in the ITP trials and those intented for the marketed indication in ITP. Thus, these data should be interpreted carefully due to the underlying malignancy and the advanced nature of the disease in lymphoma patients.

Table 15: Important identified risk – Diarrhoea

Diarrhoea	
MedDRA Search Terms	SMQ Non infection diarrhea (narrow search). HLT Diarrhoea and other gastrointestinal complaints.
Potential mechanisms	Diarrhoea is amongst the most common extra-haematological adverse effects reported with tyrosine kinase inhibitors (Sodergren 2014), and the mechanism is not identified (Hartmann 2009). There is no known mechanism for fostamatinib to cause diarrhoea.
Evidence source and strength of evidence	Diarrhoea in the placebo-controlled period in the ITP studies was reported with a higher incidence in fostamatinib patients (31.4%) than placebo patients (14.6%) (m5, ISS-ITP, Appendix 2: Table 3.1.8.1.1). Most of the events of diarrhoea were treatment-related (87.5%of fostamatinib patients, 85.7% of placebo patients) (m5, ISS-ITP, Appendix 2: Table 3.1.17.1.1). Post-marketing data included three hundred eight (308) spontaneous cases since the product was first authorized potentially related to the use of fostamatinib that fall under the HLT of diarrhoea and other gastrointestinal complaints.
Characterisation of the risk	• **CLINICAL EXPERIENCE** **ITP:** *Placebo-controlled period:* Non-infectious diarrhoea SMQ was the most commonly reported GI complaint, occurring in 32 (31.4%) of subjects receiving fostamatinib and 7 (14.6%) of subjects ceiving placebo, and in most of these subjects, non infectious diarrhoea was mild (63.3% fostamatinib, 85.7% placebo) or moderate (30.0% fostamatinib, 14.3% placebo) (m5, ISS-ITP, Appendix 2: Table 3.1.15.1.1). Severe non-infectious diarrhoea was reported in 1 subject (3.1%) receiving fostamatinib and no subjects receiving placebo (m5, ISS-ITP, Appendix 2: Table 3.1.15.1.1). Non infectious diarrhoea was considered related to study drug in 28 of the 32 (87.5%) fostamatinib subjects and in 6 of the 7 (85.7%) placebo subjects experiencing the event (m5, ISS-ITP, Appendix 2: Table 3.1.17.1.1). Study drug was interrupted due to the preferred term of diarrhoea in 3 subjects (2.9%) receiving fostamatinib and no subjects receiving placebo (m5, ISS-ITP, Appendix 2: Table 3.1.11.1.1).

Diarrhoea	
	Study drug dose reductions due to diarrhoea were reported in 2 subjects (2.0%) receiving fostamatinib and no subjects receiving placebo. One subject in each treatment group discontinued study drug because diarrhoea (m5 ISS-ITP Table 19). Antidiarrhoeal medication was taken for diarrhoea in 13 subjects (12.7%) receiving fostamatinib and 5 subjects (10.4%) receiving placebo (m5, ISS-ITP, Appendix 2: Table 3.8.1). Among the subjects with moderate or severe diarrhoea (6 fostamatinib subjects, 1 placebo subject), the median (range) time to first use of antidiarrhoeal medication was 62 days (4 to 73), and median (range) duration of use was 5.5 days (1 to 98). The placebo subject with moderate diarrhoea initiated antidiarrhoeal medication on Day 26 and continued treatment for a total of 2 days (Appendix 2: Table 3.9.2). Diarrhoea was assessed by the investigator as serious in 1 (1.0%) patient who received fostamatinib (m5, C788-047 CSR, Table 12-5). Time to onset: Twenty-five subjects (24.5%) receiving fostamatinib and 7 subjects (14.6%) receiving placebo experienced diarrhoea (PT) within the first 12 weeks of the Placebo-Controlled Period (m5, ISS_ITP Appendix 2: Table 3.1.20.1.2). Among subjects receiving fostamatinib who had moderate or severe Non-Infectious Diarrhoea SMQ events (n = 11), the median (range) time to the first occurrence of moderate or severe (Grade 2 or greater) diarrhoea was 57 days (4 to 103), and the median (range) duration of each event was 15 days (1 to 89). Placebo subject with moderate or severe Non-Infectious Diarrhoea SMQ (n=1) had median time to first occurrence of 26 days and duration of 2 days. The median duration of the PT of Diarrhoea was 15 days in fostamatinib and 2 days in placebo group and were considered resolved within 2 to 4 weeks of onset. (m5, ISS_ITP Appendix 2: Table 3.9.2). *Fostamatinib exposure period:* During the Fostamatinib Exposure Period in the ITP studies, non-infectious diarrhoea was reported in a total of 51 subjects (34.9%), (32 subjects included in Fos-PCP) (m5, ISS-ITP, Appendix 2: Table 3.1.8.2.1). The non-infectious diarrhoea event was either mild or moderate in 49 of these subjects (33.5%); severe non-infectious diarrhoea was reported in 2 subjects (1.4%), 1 subject in Fos-PCP (m5, ISS-ITP Appendix 2: Table 3.1.15.2.1). Non-infectious diarrhoea was considered related to study drug in 46 subjects (31.5%) (m5, ISS-ITP, Appendix 2: Table 3.1.17.2.1). Study drug was interrupted due to the preferred term of diarrhoea in 5 subjects (3.4%), 3 subjects included in Fos-PCP (m5, ISS_ITP Appendix 2: Table 3.1.11.2.1). Study drug dose reductions due to the preferred term of diarrhoea were reported in 4 subjects (2.7%), 2 subjects included in Fos-PCP (m5, ISS_ITP Appendix 2: Table 3.1.10.2.1). Study drug was discontinued due to the preferred term of diarrhoea in 6 subjects (4.1%), 1 subject included in Fos-PCP (m5, ISS_ITP Appendix 2: Table 3.1.12.2.1). No subject had a study drug interruption, dose reduction, or discontinued study drug due to frequent bowel movements, the only other preferred term within the Non-Infectious Diarrhoea SMQ.

Diarrhoea	
	RA: *Placebo-controlled period:* The preferred term most commonly reported in RA subjects was diarrhoea (13.6% vs 4.4%, respectively) (m5, ISS RA, Appendix 2: Table 4.1.10.1). Overall in this data set, 1.5% of subjects discontinued fostamatinib as a result of diarrhoea. *Fostamatinib exposure period:* Across both blinded and open-label fostamatinib RA treatment studies, the preferred term most commonly reported was diarrhoea (23.9%).(m5, ISS RA, Appendix 2: Table 4.1.10.2). **Oncology**: A total of 167 patients with lymphomas received fostamatinib in 3 studies which were designed as open-label studies. Therefore, the data presented below are from the fostamatinib-treated subjects. Gastro-intestinal safety profile of fostamatinib in ITP patients was in line with the one described in lymphoma patients where gastro-intestinal events were observed in 69.5% of patients. The gastrointestinal preferred term most commonly reported was diarrhoea (m5, ISS ONC, Appendix 2: Table 4.1.10). • **POST-MARKETING EXPERIENCE** A total of three hundred eight (308) spontaneous cases potentially related to the use of fostamatinib that fall under the HLT of diarrhoea and other gastrointestinal complaints such as diarrhoea infectious neonatal, diarrhoea infectious, viral diarrhea and bacterial diarrhoea have been received since the product was first authorized. Thus, the frequency is 0.00040 ICSRs per daily dose // 0.144 patient-year. The majority of the reported cases were considered nonserious. Only thirty-four (34) ICSRs that included diarrhoea events were considered serious. This is in line with all the observations found during clinical trials.
Risk factors and risk groups	No known risk factor or risk group for diarrhoea has been identified.
Preventability	Diarrhoea may be treated by dietary changes, hydration and/or anti-diarrhoeal medication. Section 4.2 of the SmPC includes recommendations for monitoring and dose modification for Diarrhoea.
Impact on the the risk-benefit balance of the product	Diarrhoea as observed in clinical trials and post-marketing was rarely severe. Therefore, the impact on the risk-benefit balance is minimal.
Public health impact	A potential impact on public health is not anticipated.

Source: m2.7.4, m5, ISS-ITP, ISS-RA and ISS-ONC.
Abbreviations: ITP=immune thrombocytopenia; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; RA=rheumatoid arthritis.

Table 16: Important identified risk – Hypertension

Hypertension	
MedDRA Search Terms	SMQ Hypertension
Potential mechanisms	Increased peripheral vascular resistance is a primary mechanism of fostamatinib-induced blood pressure elevation. Conceivably, the increased vascular resistance is a consequence of impaired vasorelaxation, resulting from reduced endothelial nitric oxide availability. This hypothesis is consistent with other kinase inhibitors whose hypertensive effects appear to be mediated by inhibition of VEGFR-2, which is an off-target effect of fostamatinib (m2.5).
Evidence source and strength of evidence	Most of the Hypertension AEs during the fostamatinib exposure period were treatment-related (in 18.5%; 27/146 patients) (m5, ISS-ITP Table 3.1.17.2.1). Changes in blood pressure are shown by shift analysis showed 44 subjects (43.1%) receiving fostamatinib and 28 subjects (58.3%) receiving placebo retained their baseline blood pressure status throughout the Placebo-Controlled Period. A one category increase in blood pressure was observed in 45 subjects (44.1%) receiving fostamatinib and 18 subjects (37.5%) receiving placebo. Two category increases were observed in 9 subjects (8.8%) receiving fostamatinib and 1 subject receiving placebo (2.1%). One subject receiving fostamatinib and no subjects receiving placebo had a 3 category increase in blood pressure. Post-marketing data included one hundred eighty-eight (188) spontaneous cases since the product was first authorized potentially related to the use of fostamatinib that fulfill the criteria of the SMQ for Hypertension.
Characterisation of the risk	• **CLINICAL EXPERIENCE** **ITP:** *Placebo-controlled period:* Hypertension (SMQ) AEs were reported for 27.5% of subjects receiving fostamatinib and 12.5% of subjects receiving placebo. Among subjects receiving fostamatinib, AEs of hypertension were mild (16.7% fostamatinib, 10.4% placebo) or moderate (8.8% fostamatinib, 0% placebo) in severity (m5, ISS-ITP, Appendix 2: Table 3.1.15.1.1). Two subjects receiving fostamatinib (2.0%) and one subject receiving placebo (2.1%) had severe hypertension. One of the two fostamatinib subjects had a hypertensive crisis that was considered severe and was serious. Hypertension AEs were considered related to study drug in 21.5% of fostamatinib subjects and 4.2% of placebo subjects (m5, ISS-ITP, Appendix 2: Table 3.1.17.1.1). Hypertension events led to study drug interruption in 2 subjects receiving fostamatinib and in none of the subjects receiving placebo. Dose reduction was required for 2 subjects receiving fostamatinib and none of the subjects receiving placebo. Study drug was withdrawn due to hypertension in 1 subject (2.1%) receiving placebo and none of the subjects receiving fostamatinib (m5 ISS-ITP Table 19). Twenty subjects (19.6%) receiving fostamatinib and 8 subjects (16.7%) receiving placebo required at least 1 intervention for hypertension. The dose of concomitant antihypertensive medication was increased in 10 subjects (9.8%) receiving fostamatinib and 3 subjects (6.3%) receiving placebo, and a new

Hypertension	
	antihypertensive medication was initiated in 17 subjects (16.7%) receiving fostamatinib and 6 subjects (12.5%) receiving placebo. *Fostamatinib exposure period:* Hypertension (SMQ) events were reported for a total of 41 subjects (28.1%) (28 subjects included in fos-PCP) (Appendix 2: Table 3.1.8.2.1). Most of the hypertension SMQ AEs were treatment-related (18.5%; 27/146) (m5, ISS-ITP, Appendix 2: Table 3.1.17.2.1) and mild (17.1%) or moderate (9.6%) in severity; 2 subjects (1.4%) had severe hypertension SMQ events (m5, ISS-ITP, Appendix 2: Table 3.1.15.2.1). Study drug was interrupted for 3 subjects (2.1%) with hypertension SMQ AEs, and the dose of fostamatinib was also reduced in 3 subjects (m5, ISS-ITP, Appendix 2: Table 3.1.11.2.1 and Table 3.1.10.2.1). No subject discontinued study drug due to hypertension SMQ events (m5, ISS-ITP, Appendix 2: Table 3.1.12.2.1). During the Fostamatinib Exposure Period, 43 subjects (29.5%) (20 included in Fos-PCP) received at least 1 intervention for hypertension; of these, 19 subjects (13.0%) were treated with an increased dose of a current antihypertensive medication and 38 subjects (26.0%) were started on a new antihypertensive medication (m5, ISS-ITP, Appendix 2: Table 3.5.7.2.1). Hypertension (PT) was reported in the first 12 weeks of study drug treatment by 21 (20.6%) fostamatinib subjects and 4 (8.3%) placebo subjects (m5, ISS-ITP, Appendix 2: Table 3.1.20.1.2). A post-hoc analysis of subjects with BP $\geq$ 140/90 mmHg showed that the median (range) time to first occurrence was 30 days (7 to 171) in the fostamatinib group and 43 days (14 to 70) in the placebo group (m5, ISS-ITP, Table 34). Median (range and Q1, Q3) duration of BP $\geq$ 140/90 mmHg was 15 days in both treatment groups (1 to 78 and 8 to 17 fostamatinib; 6 to 16 and 13 to 15 placebo). **RA:** Hypertension safety profile of fostamatinib in RA patients was consistent with the one described in ITP patients. *Placebo-controlled period:* In the placebo-controlled safety data set consisting of approximately 3500 patients, hypertension (representing the predominant AE in the Vascular SOC) was reported in 13.5% vs. 4.5% (fostamatinib vs. placebo, respectively), also reported as increased blood pressure (3.3% vs 2.0%) (m5, ISS-RA, Appendix 2: Table 10). Two patients in the fostamatinib group (0.9%) were reported to have hypertension or hypertensive crisis that was considered serious (m5, ISS-RA, Appendix 2: Table 4.2.2.1). In the placebo group, 67.3% of patients either retained their baseline blood pressure status - mostly normal or prehypertensive - or improved from baseline during treatment. A total of 28.7% patients became more hypertensive by 1 grade during treatment, 3.9% by 2 grades, and 0.2% by 3 grades. Only 1 patient who received placebo had treatment-emergent Stage 3 hypertension and no event of hypertension was considered serious by the investigator (m2.7.4.3.4.2.2.2.3). Fewer than 1% of treated subjects must discontinue fostamatinib for reasons related to BP elevation. The rate of adjudicated cardiovascular events was similar between placebo and fostamatinib

Hypertension	
	groups, supporting the fact that increases in BP are manageable, transient, and do not affect cardiovascular outcomes. *Fostamatinib exposure period*: The Fostamatinib Safety Analysis was highly consistent with the observations of the placebo-controlled set. BP related SAEs were reported infrequently: hypertensive crisis (3 subjects) and hypertension, essential hypertension, and malignant hypertension (1 subject each). Treatment-Emergent hypertension was managed through the administration of antihypertensive medications, fostamatinib dose modifications (2.2%), and treatment discontinuation (0.7%). Summary statistics on SBP and DBP over time (m5, ISS RA, Appendix 2: Table 5.1.1.2) revealed no clinically significant increases from baseline in the fostamatinib group, with median SBP at approximately 124 - 126 mmHg during the earlier time points and decreasing to 122 - 123 mmHg later during treatment, perhaps due to the effects of subject attrition. Median DBP fluctuated between approximately 78 - 80 mmHg - similar to what was seen for the fostamatinib group in the Placebo-Controlled Period. Summary statistics were prepared examining hypertensive events spanning consecutive time points (m5, ISS RA, Appendix 2: Table 5.1.4.2), which were between 1 and 4 weeks apart through Week 76. Of the 12.5% of subjects receiving fostamatinib with Stage 2 or greater hypertension at any point during treatment, 2.2% had a consecutive reading of the same grade. Likewise, of the 1.5% of subjects with Stage 3 hypertension, only 0.1% had a consecutive reading. Although absolute duration of hypertensive events cannot be inferred from this analysis, it does indicate that the majority of hypertensive events were effectively managed as outlined above. By the last on-treatment observation, 82.3% of subjects had a BP reading of baseline or better; the remaining subjects had residual treatment-emergent hypertension of the following grades: Prehypertensive - 11.0%, Stage 1 - 5.3%, Stage 2 - 0.9%, and Stage 3 - 0.4% (m5, ISS RA, Appendix 2: Table 5.1.4.2). **Oncology:** A total of 167 patients with lymphomas received fostamatinib in 3 studies which were designed as open-label studies. Therefore, the data presented below are from the fostamatinib-treated subjects. Hypertension demonstrated possible fostamatinib dose relationships in lymphoma patients. Overall 22.8% patients experienced hypertension, none of which were serious. Treatment-related hypertension AE occurred in 17.4% patients, whereas 5.4% patients experienced severe hypertension (ISS-ONC). • **POST-MARKETING EXPERIENCE** A total of one hundred eighty-eight (188) spontaneous cases potentially related to the use of fostamatinib that fulfill the criteria of the SMQ for Hypertension have been received since the product was first authorized. Thus, the frequency is 0.00024 ICSRs per daily dose // 0.088 patient-year.

Hypertension	
	The majority of the reported cases were considered nonserious. Only twenty (20) ICSRs were considered serious. However, of these twenty (20) cases only eight (8) were serious due to hypertension events and two (2) of them included hypertensive crisis.
Risk factors and risk groups	Patients with pre-existing hypertension may be more susceptible to the fostamatinib blood pressure effects.
Preventability	Most subjects with clinically important changes in blood pressure can be successfully managed with standard doses of conventional anti-hypertensive medications. Blood pressure must be regularly monitored during treatment with fostamatinib. Rarely dose adjustments of fostamatinib are needed. Section 4.2 of the SmPC includes recommendations for monitoring and dose modification of fostamatinib in case of onset of hypertension.
Impact on the risk-benefit balance of the product	As shown in the clinical studies, prompt initiation or adjustment of anti-hypertensive medication can minimise the risk for serious blood pressure elevation. Therefore, the impact on the risk-benefit balance is minimal.
Public health impact	A potential impact on public health is not anticipated.

Source: m2.7.4, m5, ISS-ITP, ISS-RA and ISS-ONC.
Abbreviations: ITP=immune thrombocytopenia; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; RA=rheumatoid arthritis.

Table 17: Important identified risk – Hepatotoxicity

Hepatotoxicity	
MedDRA Search Terms	SMQ Drug related hepatic disorders. SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions. SMQ Hepatitis, non-infectious.
Potential mechanisms	Transaminase elevations are a common side effect of tyrosine kinase inhibitors (Bunchorntavakul and Reddy, 2017). The interpretation of the significance of transaminase elevations by fostamatinib can be clouded by its separate, innocuous inhibition of bilirubin conjugation, which results in increased indirect bilirubin: Fostamatinib inhibits UGT1A1, the sole enzyme responsible for bilirubin conjugation; this may increase unconjugated bilirubin levels in some subjects. Hence, an isolated increase in blood bilirubin (without an increase in another liver function test) may represent the enzyme inhibition activity of the drug (m2.5).
Evidence source and strength of evidence	Fostamatinib administration can result in blood transaminase (ALT and/or AST) elevations that may necessitate drug dose reduction or discontinuation (m2.5). During the placebo-controlled period, 16 patients (15.7%) treated with fostamatinib and 1 placebo patient (2.1%) had an AE coded under the SMQ Drug-related hepatic disorder. Review of liver function laboratory testing showed that maximum ALT levels were > 3 x the ULN in 9 subjects (8.8%) receiving fostamatinib and no subjects receiving placebo. Of the 9 fostamatinib subjects with ALT levels > 3 x ULN, 3 subjects had ALT levels between > 3 and ≤ 5 x ULN, 5 subjects (4.9%) had ALT levels > 5 and ≤ 10 x ULN, and 1 subject (1.0%) had an ALT level > 10 x ULN. Maximum AST levels among subjects receiving fostamatinib were > 3 x ULN in 2 subjects (2.0%), including 1 subject (1.0%) with AST > 5 x ULN; no subjects receiving placebo had an AST increase ≥ 3 x ULN. Transaminases recovered to baseline levels within 2 to 4 weeks of dose modification. Post-marketing data included eleven (11) spontaneous cases since the product was first authorized potentially related to the use of fostamatinib that fulfill the conditions of the SMQ for Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions and SMQ for Hepatitis, non-infectious.
Characterisation of the risk	• **CLINICAL EXPERIENCE** Of the more than 4600 people treated with fostamatinib in the entire clinical development programme, no subject met the Hy's law criteria for drug-induced liver injury (ALT or AST >3 x upper limit of normal (ULN), concurrent total bilirubin >2 x ULN, and alkaline phosphatase <2 x ULN with no other cause for liver toxicity) (m5, ISS ITP, Appendix 2: Table 3.4.2.1.1). **ITP:** In the ITP program, there was no simultaneous 2-fold increase in bilirubin levels associated with any of the transaminase elevations described below. *Placebo-controlled period:* A total of 16 subjects (15.7%) treated with fostamatinib and 1 placebo subject (2.1%) had a Drug-Related Hepatic Disorder SMQ AE. "Transaminase elevation AEs" included the following preferred terms: ALT increased (11 fostamatinib subjects (10.8%); 0 placebo subjects), AST increased

Hepatotoxicity	
	(9 fostamatinib subjects (8.8%); 0 placebo subject), hepatic enzyme increased (1 fostamatinib subject (1.0%); 0 placebo subjects), liver function test abnormal (1 fostamatinib subject (1.0%); 0 placebo subjects), and gamma glutamyltransferase increased (1 fostamatinib subject (1.0%); 0 placebo subjects). The only additional events included in the SMQ were hepatic cyst, which was reported in 1 fostamatinib-treated subject (1.0%), and ocular icterus, which was reported in 1 placebo-treated subject (2.1%) (m5, ISS-ITP, Appendix 2: Table 3.1.8.1.1). Six AEs of ALT increased (5.9%) and 4 AEs of AST increased (3.9%) were moderate in severity; all other transaminase elevations were mild in severity (m5, ISS-ITP, Appendix 2: Table 3.1.15.1.1). Most transaminase elevations were considered possibly or probably related to treatment (m5, ISS-ITP, Appendix 2: Table 3.1.17.1.1). Transaminase elevation AEs led to dose reduction in 2 fostamatinib subjects and dose interruption in 6 fostamatinib subjects; no placebo subjects had a dose reduction or dose interruption due to a transaminase elevation AE (m5, ISS-ITP, Appendix 2: Table 3.1.10.1.1 and Table 3.1.11.1.1). One subject (1.0%) in the fostamatinib group, [redacted] discontinued study drug due to a transaminase elevation AE (m5 ISS-ITP Table 19). Bilirubin elevation AEs (blood bilirubin increased) were noted in 2 subjects receiving fostamatinib and no subject receiving placebo (m5 ISS-ITP Table 21). In both subjects review of laboratory values available near onset of the AEs showed the increase in bilirubin was due almost exclusively to unconjugated bilirubin above the ULN (m5, C788 047 CSR, Listing 16.2.8.7.1). Both events were mild in severity, and were considered related to study drug. One subject had an interruption in study drug due to the event [redacted]. No subject required dose reduction or study drug discontinuation due to bilirubin elevation. Review of laboratory bilirubin values showed that total bilirubin was > 2 x ULN in 1 subject ([redacted] with AE of blood bilirubin increased) (1.0%) receiving fostamatinib and no subjects receiving placebo (m5, ISS-ITP, Appendix 2: Table 3.4.2.1.1). All of the increases in bilirubin for this subject were due to increases in indirect bilirubin and were not accompanied by increases in other LFT values (i.e., ALT or AST) (m5, 047 CSR Listing 16.2.8.7.3). *Fostamatinib exposure period:* A Drug-related Hepatic Disorder SMQ AE was reported for 26 subjects (17.8%) (16 included in Fos-PCP) (m5, ISS-ITP Appendix 2: Table 3.1.8.2.1). Of these, 15 subjects (10.3%) had ALT increased (11 in Fos-PCP), Section5.4.6.4.1.3), 11 subjects (7.5%) had AST increased (9 in Fos-PCP), 5 subjects (3.4%) had hepatic enzyme increased (1 in Fos-PCP), and 2 subjects (1.4%) had transaminases increased. The majority of transaminase elevation events were considered mild or moderate in severity; 3 subjects (2.1%) had severe events (hepatic enzyme increased (1 subject) and transaminases increased (2 subjects)) (m5, ISS-ITP Appendix 2: Table 3.1.15.2.1).

Hepatotoxicity	
	Transaminase elevations resulted in study drug interruption in 8 subjects (5.5%) (6 in Fos-PCP), and dose reduction in 4 subjects (2.7%) (2 in Fos PCP) (m5, ISS-ITP Appendix 2: Table 3.1.11.2.1 and Appendix 2: Table 3.1.10.2.1). Four subjects (2.7%) discontinued study drug due to transaminase elevations (1 in Fos-PCP) (m5, ISS-ITP, Appendix 2: Table 3.1.12.2.1). In total 2 subjects (1.4%) experienced serious event of transaminase increased (m5 ISS-ITP Table 41). Seventeen subjects (11.8%) (9 included in Fos-PCP) had a maximum ALT value > 3 x ULN, and 10 subjects (6.9%) (6 in Fos-PCP) had a maximum ALT value > 5 x ULN (Appendix 2: Table 3.4.2.2.1). In 2 subjects [redacted] (1.4%), the maximum ALT and AST values were > 10 x ULN, and in one of them [redacted] (0.7%) the maximum ALT and AST values were > 20 x ULN (transaminase elevation secondary to obstructive cholelithiasis). Maximum AST values were > 3 x ULN in 6 subjects (4.3%) and > 5 x ULN in 2 subjects (1.4%). Out of the 10 subjects with maximum ALT values > 5 x ULN, 3 of these subjects also had slight increases in indirect bilirubin leading to increases in total bilirubin that were less than 2 x ULN (Appendix 2: Table 3.4.2.2.1). One subject [redacted] had both ALT elevation > 3 x ULN and bilirubin elevation > 2 x ULN, but these events did not occur concurrently (m5, ISS-ITP, Appendix 2: Table 3.4.2.2.1). Bilirubin increase: during the Fostamatinib Exposure Period, 3 subjects (2.1%) had AEs of blood bilirubin increased: [redacted] included in Fos-PCP , 047-063-009 who had 2 events, one in Fos-PCP and one in the 049 extension period, and [redacted] (m5, ISS-ITP, Appendix 2: Table 3.1.8.2.1). In addition, 1 subject (0.7%) had an AE of hyperbilirubinemia [redacted]. Laboratory results near the time of the AEs showed predominantly indirect bilirubin. All of the bilirubin elevations were mild to moderate in severity (m5, ISS-ITP, Appendix 2: Table 3.1.15.2.1). Study drug was interrupted for 1 subject with an increase in bilirubin (m5, ISS-ITP, Appendix 2: Table 3.1.11.2.1). No bilirubin elevation resulted in a dose reduction (m5, ISS-ITP, Appendix 2: Table 3.1.10.2.1). Study drug was discontinued in one subject due to an elevation in bilirubin [redacted] (m5, ISS-ITP, Appendix 2: Table 3.1.12.2.1). Laboratory results at the time of discontinuation showed that the bilirubin was predominantly indirect and showed no liver transaminase elevation, a profile consistent with the known effects of fostamatinib on UGT1A1 (m5, 049 CSR, Listing 16.2.8.7.1). **RA:** In the placebo-controlled period, 6.8% fostamatinib-treated patients vs 3.4% placebo-treated patients reported Drug-related hepatic disorders including ALT increased (3.1% vs 1.5%), AST increased (2.0% vs 1.2%), and Transaminases increased (1.0% vs 0.3%). Of these, 0.6% fostamatinib-treated vs 0.3% placebo-treated patients reported severe events, including Liver disorder (0.2% vs 0%), Drug-induced liver injury (0.1% vs 0.2%), and Hepatic steatosis (0.1% vs 0%) (m2.7.4.3.1.4.3.2; m5, ISS-RA, Appendix 2: Table 4.1.10.1).

Hepatotoxicity	
	In both blinded and open-label fostamatinib exposure, 13.2% of RA patients reported Drug-related hepatic disorders including ALT increased (5.8%), AST increased (3.5%), Hepatic enzyme increased (2.2%), and Transaminases increased (2.2%). Of these, 1.7% of RA patients reported severe events including Hepatic steatosis (1.0%), Liver disorder (0.2%), and Drug-induced liver injury (0.1%). Increases in bilirubin were rare, as assessed through the PTs Blood bilirubin increase (0.4%), Hyperbilirubinaemia (0.1%), Conjugated bilirubin increased (0.0%, 1 patient), and Unconjugated bilirubin increased (0.0%, 1 patient) (m2.7.4.3.1.4.3.2; m5, ISS-RA, Appendix 2: Table 4.1.10.2). **Oncology:** A total of 167 patients with lymphomas received fostamatinib in 3 studies which were designed as open-label studies. Therefore, the data presented below are from the fostamatinib-treated subjects. In lymphoma patients, hepatic toxicity manifested largely through elevations in standard serum chemistry analytes ALT, AST, and bilirubin (ISS-ONC Appendix 2: Table 4.1.10). There was 1 report of hepatic failure that was fatal but unrelated to fostamatinib. This patient had displayed simultaneous elevations in ALT, AST, and bilirubin and was determined to have lymphomatous involvement in the liver. • **POST-MARKETING EXPERIENCE** A total of eleven (11) spontaneous cases potentially related to the use of fostamatinib that fulfill the conditions of the SMQ for Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions and SMQ for Hepatitis, non-infectious have been received since the product was first authorized. Thus, the frequency is 0.00001 ICSRs per daily dose // 0.005 patient-year. Only four (4) out of the eleven (11) ICSRs cumulatively reported for this risk have been considered serious. Two (2) of them included the event of hepatic cirrhosis and two (2) included the event of hepatotoxicity. The remaining seven (7) ICSRs were assessed as nonserious and included the event of liver disorder. One (1) of these seven (7) nonserious cases also included the event term of hepatic enzyme increased.
Risk factors and risk groups	Patients receiving concomitant medications known to frequently produce transaminase elevations. Patients with a history of hepatic impairment or hepatotoxicity.
Preventability	In clinical studies, the ALT and/or AST elevations were reversible upon discontinuation of the drug (m2.5). If ALT or AST increase more than 3 x ULN, hepatotoxicity should be managed by treatment interruption, reduction or discontinuation (SmPC Section 4.2 and Section 4.4). A concomitant total bilirubin increase greater than 2 x ULN should lead to treatment discontinuation.
Impact on the risk-benefit balance of the product	Fostamatinib administration can result in transaminase elevations that have been uniformly and without exception reversible upon discontinuation of the drug.

Hepatotoxicity	
	Frequent monitoring and appropriate dose reduction, interruption and/or discontinuation allowed fostamatinib to be safely administered in the study population, notwithstanding this adverse effect. Therefore, the impact on the risk-benefit balance is minimal.
Public health impact	A potential impact on public health is not anticipated.

Source: m2.7.4, m5, ISS-ITP, ISS-RA and ISS-ONC.
Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ITP=immune thrombocytopenia; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; RA=rheumatoid arthritis; SOC=System Organ Class; SMQ=standardised MedDRA Query; ULN=upper limit of normal.

Table 18: Important identified risk – Neutropenia

Neutropenia	
MedDRA Search Terms	Selected PTs: Neutropenia, Neutrophil Count Decreased, Febrile Neutropenia, Pancytopenia, Bicytopenia and Cytopenia. SMQ Haematopoietic leukopenia.
Potential mechanisms	Although the precise mechanism of neutropenia is unclear, it may relate at least in part to the off-target inhibitory effects on some kinases reported to be involved in haematopoiesis such as VEGF (Turner, 1995; m2.4).
Evidence source and strength of evidence	Early in clinical development, fostamatinib was recognised to produce reductions in neutrophils that were rapidly reversible upon discontinuation of therapy. During Placebo-Controlled Period, neutropenia was considered to be treatment-related in 6 patients (5.9%) (m5, ISS-ITP, Appendix 2: Table 3.1.17.1.1). Post-marketing data included fifty-nine (59) spontaneous cases since the product was first authorized potentially related to the use of fostamatinib that fulfill the conditions of the SMQ for Haematopoietic leukopenia and/or included the PTs of pancytopenia, bicytopenia and cytopenia.
Characterisation of the risk	• **CLINICAL EXPERIENCE** **ITP:** *Placebo-controlled period:* Neutropenia events were reported for 7 subjects (6.9%) in the fostamatinib group and no subject in the placebo group. The majority of these subjects (5/7) reported events that were mild or moderate in severity. Two neutropenia events were severe, one of these, in subject [redacted], was an SAE of neutropenic fever that was attributed to an unknown infection (brief narrative in Section 5.4.6.2). Neutropenic events were considered related to study drug in 6 subjects (85.7%). One subject, [redacted] had an interruption in study drug due to neutropenia. Two subjects had a reduction in study drug dose due to neutropenia events, and in one subject study drug was discontinued due to neutropenia. Neutropenia was rarely associated with infection. In addition to the event of neutropenic fever, one subject developed an upper respiratory tract infection approximately 10 days following the onset of neutropenia.

Neutropenia	
	One event of febrile neutropenia was assessed as serious and related to study drug by the investigator. A complete blood count, including ANC, was obtained regularly during the Phase 3 studies. In most subjects (91% in the fostamatinib group and 97.9% in the placebo group) neutrophil counts remained ≥ 1.5 x 10^9/L (m5 ISS-ITP Table 29). There was no decrease in neutrophils below 0.5 x 10^9/L. Two subjects (2.0%) receiving fostamatinib and no subjects receiving placebo had a decrease in neutrophils to between ≥ 0.5 and < 1.0 x 10^9/L. Seven subjects receiving fostamatinib (7.0%) and 1 subject (2.1%) receiving placebo had neutrophil counts decreased to between ≥ 1.0 and < 1.5 x 10^9/L. *Fostamatinib exposure period:* Neutropenia was reported for 10 subjects (6.8%) (7 included in Fos-PCP) (m5, ISS-ITP Appendix 2: Table 3.1.8.2.1). Two neutropenia events were considered severe, as described in the Placebo-Controlled Period, including a SAE of febrile neutropenia (in Fos-PCP) (Section 3.1.3.2.1) (m5, ISS-ITP, Appendix 2: Table 3.1.15.2.1). Decreases in neutrophil counts led to dose reduction and study drug interruption in 2 subjects (neutrophil count decreased and febrile neutropenia, in Fos-PCP) (m5, ISS-ITP, Appendix 2: Table 3.1.11.2.1 and m5, ISS-ITP, Appendix 2: Table 3.1.10.2.1). Study drug was discontinued in 3 subjects (2.1%) with a preferred term of "neutropenia"; 1 in Fos-PCP and the other 2 were cases of "moderate" neutropenia (m5, ISS-ITP, Appendix 2: Table 3.1.12.2.1). A review of ANC laboratory results showed that for most subjects (87.3%), neutrophil counts remained ≥ 1.5 x 10^9/L (m5, ISS-ITP, Appendix 2: Table 3.2.2.2.1). Two subjects (2.0%) receiving fostamatinib and no subjects receiving placebo had a decrease in neutrophils to between ≥ 0.5 and < 1.0 × 10^9/L. During the Fostamatinib Exposure Period, neutrophil counts remained ≥ 1.5 x 10^9/L in most subjects (87.3%). Neutrophil counts were decreased to between ≥ 0.5 to < 1.0 x 10^9/L in 5 subjects (3.5%) and to between ≥ 1.0 to 1.5 x 10^9/L in 13 subjects (9.2%). No subject had a decrease in neutrophils to < 0.5 × 10^9/L. **RA:** In the fostamatinib analysis set, the pattern of neutropenia in RA patients was similar. The overall incidence of treatment-emergent Grade 3/4 toxicity for fostamatinib vs placebo was 1.1% vs. 0.2%, respectively. By the time of the final on-treatment blood count, 94.0% of fostamatinib patients were at their baseline or better (m5, ISS-RA, Appendix 2: Table 6.2.2.1), indicating that the neutropenia generally resolved while still on treatment (m2.7.4.3.4.5.2). Treatment discontinuation due to neutropenia occurred in 0.2% of patients receiving fostamatinib and 0.1% of patients receiving placebo (m5, ISS-RA, Appendix 2: Table 4.1.7.1). Approximately 0.7% of patients discontinued therapy as a result of neutropenia and just below 5% had it reported as an AE. About 2% of RA patients had a nadir of <1000/mm3. Dose interruption, or reduction, or discontinuation uniformly was followed by recovery to the baseline range (m2.7.4.3.4.5.2).

Neutropenia	
	Oncology: A total of 167 patients with lymphomas received fostamatinib in 3 studies which were designed as open-label studies. Therefore, the data presented below are from the fostamatinib-treated subjects. Neutropenia (29.9%) was among the most commonly reported AEs in lymphoma population after fatigue (43.7%), diarrhea (40.1%) and nausea (30.5%). Of which 22.2% was treatment related whereas 18.0% were severe events. Grade 3 or 4 neutropenia was common. Hematologic AEs (including neutropenia) displayed no evidence of a dose-response. There were also 7 episodes of febrile neutropenia, all of which were considered related to fostamatinib (m5 ISS-ONC). The most commonly occurring AEs were generally mild to moderate, reversible, and easily managed, allowing the majority of patients to receive their full dose for the intended duration. • **POST-MARKETING EXPERIENCE** A total of fifty-nine (59) spontaneous cases potentially related to the use of fostamatinib that fulfill the conditions of the SMQ for Haematopoietic leukopenia and/or included the PTs of pancytopenia, bicytopenia and cytopenia have been received since the product was first authorized. Thus, the frequency is 0.00008 ICSRs per daily dose // 0.028 patient-year. Thirty (30) out of the fifty-nine (59) ICSRs cumulatively reported including neutropenia events were considered serious, of these, twenty-one (21) cases included serious neutropenia events.
Risk factors and risk groups	Patients with a history of bone marrow depression; combination therapy with myelotoxic agents; low white blood cell at the onset of the treatment.
Preventability	Clinical haematology tests should be monitored regularly throughout fostamatinib treatment. If absolute neutrophil count (Maison-Blanche et al.) decreases (ANC less than 1.0 x 109/L) and remains low after 72 hours, fostamatinib should be interrupted until ANC is greater than 1.5 x 10^9/L. Section 4.2 and Section 4.4 of the SmPC includes recommendations for monitoring and dose modification of fostamatinib in case of onset of neutropenia, and reference to treating health care provider.
Impact on the risk-benefit balance of the product	Reductions in neutrophils were rapidly reversible upon discontinuation of fostamatinib treatment. Therefore, the impact on the risk-benefit balance is minimal.
Public health impact	A potential impact on public health is not anticipated.

Source: m2.7.4, m5, ISS-ITP, ISS-RA and ISS-ONC.
Abbreviations: AE=adverse event; ANC=absolute neutrophil count; ITP=immune thrombocytopenia; MedDRA=Medical Dictionary for Regulatory Activities; NDA=New Drug application; PT=preferred term; RA=rheumatoid arthritis; VEGF=vascular endothelial growth factor.

Table 19: Important identified risk – Infections

Infections	
MedDRA Search Terms	SOC Infections and infestations. HLGT Microbiology and serology investigations.
Potential mechanisms	The primary mechanism of action of R406 is inhibition of SYK activity (Ki=30 nM), which plays a critical role in Fcγ receptor signalling, but it does not play a role in the other pathways initiating innate immune responses (m2.4.5.1). However, the immunomodulatory effect of fostamatinib is sometimes accompanied by an effect on neutrophil cell counts, with approximately 1% of patients having a nadir count <1000/mm3 at some point during treatment, and more than 5% having a nadir count <1500/mm3 at some point (m2.7.4.3.4.6).
Evidence source and strength of evidence	Fostamatinib administration has been associated with a slightly increased risk of routine/local infections (but not opportunistic infections) although the effect may deserve further analysis. The infections do not appear to be associated with neutropenia, with some exceptions (m2.7.4.3.4.6). Most of the Infection events were assessed by the investigator as unrelated to treatment; 2.9% of fostamatinib subjects and no placebo subjects experienced treatment-related Infection events (m5, ISS-ITP, Appendix2: Table 3.1.17.1.1). Post-marketing data included one hundred sixty-five (165) spontaneous cases since the product was first authorized potentially related to the use of fostamatinib that fall under the SOC of Infections and infestations and fall under the HLGT for Microbiology and serology investigations.
Characterisation of the risk	• **CLINICAL EXPERIENCE** **ITP:** *Placebo-controlled period:* Adverse events categorized as infection were reported in 30.4% (31/102) of subjects receiving fostamatinib and 20.8% (10/48) of subjects receiving placebo. The most frequently reported preferred term included in this category was upper respiratory tract infection (5.9% fostamatinib, 4.2% placebo) (m5, ISS-ITP, Appendix 2: Table 3.1.8.1.1). Infections involving the respiratory tract accounted for 60% of the infection events in the fostamatinib group and 40% of the events in the placebo group. Severe infection events, pneumonia and influenza-like illness, were reported for one subject each in the fostamatinib group, and 1 severe event of sepsis was reported for the placebo group. No systemic opportunistic infections were reported in the program. Oral herpes (reported as "fever blister") and oral candidiasis (reported as "oral thrush") were reported for 1 subject each in the fostamatinib group (m5, ISS-ITP, Appendix 2: Table 3.1.8.1.1). Both of these subjects had prior bacterial infections and were receiving antibiotics shortly before these viral and fungal infections occurred. Infection-related SAEs were rare: 2 fostamatinib subjects (2.0%) (bronchitis, pneumonia) vs 2 placebo subjects (4.2%) (infection, sepsis) (m5, ISS-ITP, Appendix 2: Table 3.1.3.1.1). One subject in the fostamatinib group discontinued study treatment due to an Infection event (pneumonia) (m5, ISS-ITP, Appendix 2: Table 3.1.12.1.1).

Infections	
	Fostamatinib exposure period: Sixty-two (62) subjects (42.5%) reported infection AEs (31 included in Fos-PCP) (m5, ISS-ITP, Appendix 2: Table 3.1.8.2.1). The most common infections reported were upper respiratory tract infection (16 subjects, 11.0%), nasopharyngitis (9 subjects, 6.2%), urinary tract infection (7 subjects, 4.8%), influenza-like illness, lower respiratory tract infection, and viral infection (6 subjects, 1.4% each). Six subjects (4.1%) had infection AEs which were considered severe: influenza-like illness, viral infection, sepsis (2 subjects), and pneumonia (2 subjects). Study drug was interrupted for 4 subjects (2.7%) with infection events (m5, ISS-ITP, Appendix 2: Table 3.1.11.2.1). One subject (0.7%) had a dose reduction due to an infection AE (respiratory tract infection) (m5, ISS-ITP, Appendix 2: Table 3.1.10.2.1). Fostamatinib was discontinued in 3 subjects (2.1%) with infection AEs, including 2 subjects with pneumonia (1 in Fos-PCP) and one subject with sepsis (m5, ISS-ITP, Appendix 2: Table 3.1.12.2.1). **RA:** Safety profile of infection-related SAEs in ITP and RA patients was similar. In the placebo-controlled analysis set of RA patients, 25.6% of fostamatinib patients and 20.1% of placebo patients experienced at least 1 AE in the Infections and infestations SOC (m5, ISS-RA, Appendix 2: Table 4.1.2.1). Nasopharyngitis and Upper respiratory infections were the only AEs reported in more than 2% of patients (3.8% and 2.4% in the fostamatinib group respectively; slightly lower that than the placebo group (2.1% and 1.9%, respectively)) (m5, ISS-RA, Appendix 2: Table 4.1.2.1). No SAE by PT was reported at a frequency exceeding 0.3% (m5, ISS-RA, Appendix 2: Table 4.2.2.1; m2.7.4.3.4.5.2). In the fostamatinib analysis set comprising the long-term extension studies, 45.1% of RA patients experienced at least 1 AE in the Infections and infestations SOC (m5, ISS-RA, Appendix 2: Table 4.1.2.2). Nasopharyngitis, Urinary tract infection, and Upper respiratory tract infection were reported at a 5% to 7% rate with an incidence per-patient exposure-year of 3.7-5.4. No Infection and infestations SAE by PT occurred at a frequency exceeding 0.7% (m5, ISS-RA, Appendix 2: Table 4.2.2.2; m2.7.4.3.4.5.2). In the RA observational report (RWE177), sensitivity analyses with additional standardisation to HAQ score have identified comparable incidence rates for infection mortality and hospitalisation in the fostamatinib and registry cohorts. **Oncology:** A total of 167 patients with lymphomas received fostamatinib in 3 studies which were designed as open-label studies. Therefore, the data presented below are from the fostamatinib-treated subjects. In lymphoma patients, infection was among the most commonly affected SOC (38.3%, ISS-ONC). Five deaths overall were related to infection (bacterial sepsis, sepsis, and pneumonia).

Infections	
	SAEs reported in > 2% of patients were all related to infection or its consequences: febrile neutropenia, pyrexia, pneumonia, and sepsis. 5.4% of the AEs that led to a fostamatinib dose reduction or interruption in oncology patients occurred in General, Infections, and Investigations SOC (m5 ISS-ONC). • **POST-MARKETING EXPERIENCE** A total of one hundred sixty-five (165) ICSRs potentially related to the use of fostamatinib that fall under the SOC of Infections and infestations and fall under the HLGT for Microbiology and serology investigations have been received since the product was first authorized. Thus, the frequency is 0.00021 ICSRs per daily dose // 0.077 patient-year. Ninety-three (93) out of the one hundred sixty-five (165) ICSRs cumulatively reported including any kind of infection were assessed as serious at case level. The most frequently reported preferred term included in this category was pneumonia. It was included in twenty-nine (29) ICSRs and was considered serious in twenty-eight (28) ICSRs. COVID-19 infection or COVID-19 pneumonia was reported in twenty-three (23) ICSRs which was considered serious in sixteen (16) ICSRs.
Risk factors and risk groups	Patients with conditions causing alterations in immune functions Patients with poor performance status.
Preventability	Patients should be advised on initial signs of infections and monitored regularly to identify adverse outcomes related to infections. In the event that concomitant neutropenia is present, a dose reduction or temporary cessation of fostamatinib therapy may be required to allow the white cell count to recover.
Impact on the risk-benefit balance of the product	Fostamatinib may be associated with a slightly increased risk of routine infections (but not opportunistic infections) although the effect is not clear. As most of the infection events were assessed by the investigator as unrelated to treatment, the impact on the risk-benefit balance of the product is minimal.
Public health impact	A potential impact on public health is not anticipated.

Source: m2.7.4, m5, ISS-ITP, ISS-RA and ISS-ONC.
Abbreviations: AE=adverse event; ITP=immune thrombocytopenia; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; RA=rheumatoid arthritis; SAE=serious adverse event; SOC=System Organ Class; SYK=spleen tyrosine kinase.

Table 20: Important potential risk – Off label use in paediatrics (effect of fostamatinib during bone formation and regrowth during development)

Off label use in paediatrics (effect of fostamatinib during bone formation and regrowth during development)	
MedDRA Search Terms	Relevant terms: Chondrodystrophy, growth plate thickening, odontodysplasia, vascular endothelial growth factor receptor (VEGFR) inhibition, juvenile toxicology findings, paediatric risk.
Potential mechanisms	Chondrodystrophy (growth plate thickening) has been observed in toxicology studies in mice, rats, and rabbits and is relevant to paediatric populations. Chondrodystrophy of the femoral head and sternum was observed in some animals in the higher fostamatinib dose groups in two 4-week studies as well as in the 26 week and 2-year carcinogenicity studies in the rat and in the 2-year mouse carcinogenicity study; it was not fully reversible by the end of the recovery period, when applicable. Chondrodystrophy/growth plate dysplasia was also seen in a 1-month juvenile toxicity study in rabbits. A related finding of odontodysplasia of the incisors was found in the rat chronic and carcinogenicity studies. The development of chondrodystrophy may be related to off target inhibition of VEGFR (Hall, 2006) and limited to actively growing bones (before growth plate closure). Indeed, effects on bone growth plates have been reported across several species for a range of agents that have VEGF inhibition characteristics (Gerber, 1999; Ryan, 1999; Wedge, 2000, Wedge, 2002; Beebe, 2003; Brown, 2005; Wedge, 2005; Hall, 2006; Patyna, 2008).
Evidence source and strength of evidence	Based on findings from several Good Laboratory Practice (GLP) toxicology studies in rodents and a GLP juvenile toxicology study in rabbits with fostamatinib there is potential for adverse bone development changes in paediatric populations. These changes may occur at dose levels at unity or below calculated margin of safety.
Characterisation of the risk	Not applicable. Patients under 18 years of age were excluded from the clinical trial development programme of fostamatinib. No pediatric cases involving bone formation/regrowth have been reported since the product was first authorized.
Risk factors and risk groups	Patients under 18 years old.
Preventability	Fostamatinib should not be used in patients under 18 years old because of adverse reactions on actively growing bones observed in nonclinical studies.
Impact on the risk-benefit balance of the product	The findings in bone should not be an issue in adult patients when growth plate closure has occurred but could pose a safety risk in children with actively growing bones which depend on the growth plate. Therefore, the impact on the risk-benefit balance of the product is minimal.
Public health impact	A potential impact on public health is not anticipated.

Source: As referenced in text.
Abbreviations: GLP=Good Laboratory Practice; VEGFR=vascular endothelial growth factor receptor.

Table 21: Important potential risk – 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)

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)	
MedDRA Search Terms	Relevant terms: Chondrodystrophy, growth plate thickening, odontodysplasia, vascular endothelial growth factor receptor (VEGFR) inhibition. SMQ Osteoporosis/osteopenia. PT Epiphyseal fracture and Epiphyseal injury.
Potential mechanisms	Chondrodystrophy (growth plate thickening) has been observed in toxicology studies in mice, rats, and rabbits and is relevant to patients with osteoporosis, patients with fractures, or young adults where epiphyseal fusion has not yet occurred. Chondrodystrophy of the femoral head and sternum was observed in some animals in the higher fostamatinib dose groups in two 4-week studies as well as in the 26 week and 2-year carcinogenicity studies in the rat and in the 2-year mouse carcinogenicity study; it was not fully reversible by the end of the recovery period, when applicable. Chondrodystrophy/growth plate dysplasia was also seen in a 1-month juvenile toxicity study in rabbits. A related finding of odontodysplasia of the incisors was found in the rat chronic and carcinogenicity studies. The development of chondrodystrophy may be related to off target inhibition of VEGFR (Hall, 2006) and limited to actively growing bones (before growth plate closure). Indeed, effects on bone growth plates have been reported across several species for a range of agents that have VEGF inhibition characteristics (Gerber, 1999; Ryan, 1999; Wedge, 2000, Wedge, 2002; Beebe, 2003; Brown, 2005; Wedge, 2005; Hall, 2006; Patyna, 2008).
Evidence source and strength of evidence	Since fostamatinib was shown in vitro to target SYK and 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. Post-marketing data included seven (7) spontaneous cases since the product was first authorized potentially related to the use of fostamatinib that fulfill the criteria of the SMQ for osteoporosis/osteopenia and/or included the PTs of epiphyseal fracture and epiphyseal injury.
Characterisation of the risk	• **CLINICAL EXPERIENCE** In the RA program, a total of 3437 subjects received fostamatinib with a mean duration of fostamatinib exposure of 546 days (approximately 78 weeks), ranging as high as 6.8 years. Dosing regimens ranging from 50 mg bid to 150 mg bid were studied. The incidences of adverse events (AEs) related to bone metabolism were low and comparable between treatment groups in the RA placebo-controlled studies: osteoporosis (0.3% incidence in both placebo [4/1169] and fostamatinib-treated [7/2414] RA subjects) and fractures (0.77% [9/1169] of subjects receiving placebo and 0.99% [24/2414 including 1 subject with osteoporotic fracture] of subjects receiving fostamatinib).

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)	
	The time to onset of first bone fracture event in the placebo-controlled RA studies was comparable between the fostamatinib and placebo treatment groups. The mean time to onset was 83.9 days vs. 86.6 days, and the median time to onset was 88 days vs. 106 days (fostamatinib vs placebo). The ranges (minimum – maximum number of days) also were comparable. An exposure adjusted analysis of all fostamatinib exposure subjects and placebo subjects showed the exposure period for fostamatinib was considerably longer (5150.2 patient years) than the exposure period for placebo (381.9 patient years). The exposure adjusted rate of any fracture was similar between the placebo-treated RA subjects (2.4 events per 100 subject years) and the fostamatinib-treated RA subjects for any time (2.6 events per 100 subject years). The exposure adjusted rates of fractures in the fostamatinib subjects decreased over time with rates as low as 0.4 events per 100 subject-years after 2 years of fostamatinib exposure; thus, there was no evidence of increased risk for fracture with long-term fostamatinib treatment. Importantly, there were no events of fracture delayed union, fracture nonunion, fracture malunion, or fracture infection in the RA safety population. Hence, there are no apparent complications of fracture healing in the extensive RA database, which is the only indication where the rare occurrence of fracture occurred. A separate analysis of serum bone marker assessments, serum osteocalcin (indicative of bone formation) and CTX (indicative of bone resorption), in 450 subjects, from placebo and 2 fostamatinib dose regimens, in the Phase 3 RA study favored a net gain in bone formation as shown by the CTX-I:osteocalcin ratio between baseline and Week 24 (Kjelgaard, 2018). In the ITP placebo-controlled studies (total 150 subjects), the incidence of osteoporosis was 1 subject receiving fostamatinib (none in placebo), and no subjects in either group experiencing bone fracture. While the size of this dataset limits the interpretation of the results, anticipated risks to bone formation or integrity (e.g., osteoporosis or fracture) are minimal. • **<u>POST-MARKETING EXPERIENCE</u>** A total of seven (7) spontaneous ICSRs potentially related to the use of fostamatinib that fulfill the criteria of the SMQ for Osteoporosis/osteopenia and/or included the PTs of epiphyseal fracture and epiphyseal injury have been received since the product was first authorized. Thus, the frequency is 0.00001 ICSRs per daily dose // 0.003 patient-year. Two (2) out of the seven (7) ICSRs involved the same patient. Since the medical history (e.g. osteoporosis) for the six (6) patients (either adult or elderly) is unknown, these ICSRs have been considered for this risk.
Risk factors and risk groups	Patients with osteoporosis, patients with fractures, or young adults where epiphyseal fusion has not yet occurred.
Preventability	Closer monitoring in these patients is recommended. The benefit risk of continuing therapy during the healing of a bone fracture should be thoroughly evaluated by the physician.

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)	
Impact on the risk-benefit balance of the product	The findings in bone should not be an issue in adult patients when growth plate closure has occurred but could pose a safety risk in patients with osteoporosis, patients with fractures, or young adults where epiphyseal fusion has not yet occurred. Therefore, the impact on the risk-benefit balance of the product is minimal.
Public health impact	A potential impact on public health is not anticipated.

Source: As referenced in text.
Abbreviations: GLP=Good Laboratory Practice; VEGFR=vascular endothelial growth factor receptor.

2.7.3.2 Presentation of the missing information

Long term safety data with fostamatinib is considered missing safety information.

2.8 Module SVIII - Summary of the Safety Concerns

A summary of the safety concerns for fostamatinib is presented in Table 22.

Table 22: Summary of 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

3 PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORISATION SAFETY STUDIES)

3.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities to report adverse reactions and perform signal detection will be performed in order to manage the important identified and potential risks.

3.2 Additional Pharmacovigilance Activities

A non-interventional post-authorisation study (PASS) will be conducted 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.

3.3 Summary Table of Additional Pharmacovigilance Activities

Table 23: Table of Additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
Post authorization safety surveillance study of fostamatinib in adult patients with chronic immune thrombocytopenia (ITP) who have received or are not candidates for three or more 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 have received or are not candidates for three or more 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: • Diaorrhea, • Hypertension • Hepatoxicity • Neutropenia • Infections	Protocol submission to EMA	on 24 April 2020
			Interim analysis:	In every PSUR
			Study Report submission to EMA:	6 months after last data collection

4 PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no plans for fostamatinib post-authorisation efficacy studies.

5 PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk minimisation plan

The safety information in the proposed product information is aligned to the reference medicinal product.

5.1 Routine Risk Minimisation Measures

Routine risk minimisation measures for fostamatinib are summarised in Table 24.

Table 24: Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Important Identified Risk	
Diarrhoea	*Routine risk communication:* Text in EU SmPC : Section 4.4 and Section 4.8 Text in EU PIL: Section 2 and Section 4 *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 EU 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:* Text in EU SmPC Section 4.4 and Section 4.8 Text in EU PIL: Section 2 and Section 4 *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 EU 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.

Safety concern	Routine risk minimisation measures
Hepatotoxicity	*Routine risk communication:* Text in EU SmPC Section 4.4 and Section 4.8 Text in EU PIL: Section 2 and Section 4 *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 EU SmPC Section 4.2 and Section 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:* Text in EU SmPC: Section 4.4 and Section 4.8 Text in EU PIL: Section 2 and Section 4 *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 10^9/L for at least 72 hours are included in EU 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.
Infections	*Routine risk communication:* Text in EU SmPC: Section 4.4 and Section 4.8. Text in EU PIL: Section 2 and Section 4 *Routine risk minimisation activities recommending specific clinical measures to address the risk:*

Safety concern	Routine risk minimisation measures
	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.
Important Potential Risk	
Off label use in paediatrics (effect of fostamatinib during bone formation and regrowth during development)	*Routine risk communication:* Text in EU SmPC: Section 4.2. Text in EU PIL: Section 2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Section 4.2 of the EU 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.
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)	*Routine risk communication:* Text in EU SmPC : Section 4.4. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Text in EU SmPC : Section 4.4 includes a warning not to use fostamatinib in patients with osteoporosis, patients with fractures, or young adults where epiphyseal fusion has not yet occurred. *Other routine risk minimisation measures beyond the Product Information:* Legal status: fostamatinib will be available as a prescription-only medicine.
Missing information	

Safety concern	Routine risk minimisation measures
Long term safety information	*Routine risk communication:* SmPC Section 4.2 *Routine risk minimisation activities recommending specific clinical measures to address the risk:* Section 4.2 of the EU SmPC states patients should discontinue fostamatinib after 12 weeks if no response. Benefit risk will be assessed on a regular basis (EU SmPC Section 4.2) by a prescriber who is experienced in the treatment of haematological diseases. *Other routine risk minimisation measures beyond the Product Information:* Legal status: fostamatinib will be available as a prescription-only medicine.

5.2 Additional Risk Minimisation Measures

There are no additional risk minimization measures for fostamatinib.

5.3 Routine risk minimisation activities as described in Part 5.1 are sufficient to manage the safety concerns of the medicinal product.Summary of Risk Minimisation Measures

Risk minimisation measures for the safety concerns are summarised in Table 23.

Table 25: Description of routine risk minimisation measures by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Diarrhoea	*Routine risk minimisation measures:* EU SmPC Section 4.8 EU SmPC Section 4.2 and Section 4.4 where advice is given on monitoring for diarrhoea, dose modification and interruption of fostamatinib treatment in case of a severe event. EU PIL Section 2 and Section 4 *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* PASS
Hypertension	*Routine risk minimisation measures:* EU SmPC Section 4.8 EU SmPC Section 4.2 and Section 4.4 where advice is given on monitoring for changes in blood pressure and administration of anti-hypertensive treatment (and interruption of fostamatinib) in case blood pressure remains 160/100 mmHg or higher for more than 4 weeks. EU PIL Section 2 and Section 4 *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* PASS
Hepatotoxicity	*Routine risk minimisation measures:* EU SmPC Section 4.8	

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
	EU SmPC Section 4.2 and Section 4.4 where advice is given on monitoring liver function tests monthly and considering interruption, dose reduction or discontinuation if ALT/ AST increase more than 3 x ULN and total bilirubin is greater than 2 x ULN. EU PIL Section 2 and Section 4 *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* PASS
Neutropenia	*Routine risk minimisation measures:* EU SmPC Section 4.8 EU SmPC Section 4.2 and Section 4.4 where advice is given on monitoring the ANC monthly and interrupt, reduce or discontinue fostamatinib if ANC decreases to less than 1.0 x 10^9/L for at least 72 hours. EU PIL Section 2 and Section 4 *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* PASS
Infections	*Routine risk minimisation measures:* EU SmPC Section 4.4 and Section 4.8 EU PIL Section 2 and Section 4 *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* PASS

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Potential risk		
Off label use in paediatrics (effect of fostamatinib during bone formation and regrowth during development)	*Routine risk minimisation measures:* EU SmPC Section 4.2 where warning is given not to use fostamatinib in children. EU PIL Section 2 *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* None
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)	*Routine risk minimisation measures:* EU SmPC Section 4.4 includes a warning not to use fostamatinib in patients with osteoporosis, patients with fractures, or young adults where epiphyseal fusion has not yet occurred. *Additional risk minimisation measures:* None	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* PASS
Missing Information		
Long term safety information	*Routine risk minimisation measures:* EU SmPC section 4.2 states patients should discontinue fostamatinib after 12 weeks if no response. Benefit risk is assessed on a regular basis (EU SmPC section 4.2) by a presecriber who is	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* PASS

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	experienced in the treatment of haematological diseases. *Additional risk minimisation measures:* None	

Abbreviations: ALT=alanine aminotransferase; ANC=absolute neutrophil count; AST=aspartate aminotransferase; SmPC=Summary of Product Characteristics; ULN=upper limit of normal.

6 PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

6.1 Summary of risk management plan for fostamatinib

This is a summary of the risk management plan (RMP) for fostamatinib. The RMP details important risks of fostamatinib, how these risks can be minimised, and how more information will be obtained about fostamatinib's risks and uncertainties.

Fostamatinib's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how fostamatinib should be used.

This summary of the RMP for fostamatinib should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of fostamatinib's RMP.

6.2 The Medicine and What it is Used For

Fostamatinib is authorised for the treatment of chronic immune thrombocytopenia (ITP) in adult patients who have received or are not candidates for three or more other treatments (see SmPC). It contains fostamatinib as the active substance and it is given orally in a film coated tablet.

Further information about the evaluation of fostamatinib's benefits can be found in fostamatinib's EPAR, including in its plain-language summary, available on the European Medicines Agency website, under the medicine's webpage.

6.3 Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of fostamatinib, together with measures to minimise such risks and the proposed studies for learning more about fostamatinib's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In addition to these measures, information about adverse reactions will be collected continuously and regularly analysed, including Periodic Safety Update Report assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

6.3.1 List of important risks and missing information

Important risks of fostamatinib are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of fostamatinib. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

The important risks and missing information for fostamatinib are listed in Table 26.

Table 26: Summary of important risks and missing information for fostamatinib

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

6.3.2 Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Summaries of the important risks and missing information for fostamatinib are provided in the following tables.

Table 27: Important identified risk of fostamatinib: Diarrhoea

Diarrhoea	
Evidence for linking the risk to the medicine	Diarrhoea is amongst the most common extra-haematological adverse effects reported with tyrosine kinase inhibitors Gastrointestinal complaints, specifically noninfectious diarrhoea events, were among the most common adverse reactions reported in patients treated with fostamatinib throughout the clinical development program. Non-infectious diarrhoea events are considered definitely related to fostamatinib treatment. Approximately 25% of patients receiving fostamatinib experienced noninfectious diarrhoea during the first 12 weeks of treatment during the placebo-controlled period. The events of diarrhoea in the placebo-controlled period in the ITP studies were reported with a higher incidence in fostamatinib patients (31.4%) than placebo patients (14.6%). Most of the events of diarrhoea were treatment-related (87.5% of fostamatinib patients, 85.7% of placebo patients).
Risk factors and risk groups	None identified
Risk minimisation measures	*Routine risk minimisation measures:* Adequately addressed in the EU SmPC : Section 4.8 Section 4.2 and Section 4.4 where advice is given on monitoring for diarrhoea, dose modification and interruption of fostamatinib treatment in case of a severe event. Adequately addressed in the EU PIL: Section 2 and Section 4*Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* PASS

Table 28: Important identified risk of fostamatinib: Hypertension

Hypertension	
Evidence for linking the risk to the medicine	Increased peripheral vascular resistance is a primary mechanism of fostamatinib-induced blood pressure elevation. Increases in blood pressure were dose dependent in early studies with fostamatinib in healthy subjects. In the ITP placebo-controlled population, hypertension-related adverse reactions were reported for 27.5% of patients receiving fostamatinib and 12.5% of patients receiving placebo in the placebo controlled studies.

Hypertension	
Risk factors and risk groups	Patients with pre-existing hypertension may be more susceptible to the fostamatinib blood pressure effects.
Risk minimisation measures	*Routine risk minimisation measures:* Adequately addressed in the EU SmPC: Section 4.8 Section 4.2 and Section 4.4 where advice is given on monitoring for changes in blood pressure and administration of anti-hypertensive treatment (and interruption of fostamatinib) in case blood pressure remains 160/100 mmHg or higher for more than 4 weeks. Adequately addressed in the EU PIL: Section 2 and Section 4 *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* PASS

Table 29: Important identified risk of fostamatinib: Hepatotoxicity

Hepatotoxicity	
Evidence for linking the risk to the medicine	Fostamatinib administration can result in blood transaminase (ALT and/or AST) elevations that may necessitate drug dose reduction or discontinuation. Mild to moderate increases in liver enzymes (ALT and AST) were observed in fostamatinib treated subjects in phase 1 studies in healthy volunteers, occurring more frequently at the higher doses tested (250 mg oral twice daily). These changes were mild and all were reversible. In the ITP placebo-controlled population, transaminase elevation adverse reactions (ALT increased and AST increased) were reported in 11% and 9% of patients receiving fostamatinib.
Risk factors and risk groups	Patients receiving concomitant medications known to frequently produce transaminase elevations. Patients with a history of hepatic impairment or hepatotoxicity.
Risk minimisation measures	*Routine risk minimisation measures:* Adequately addressed in the EU SmPC Section 4.8 Section 4.2 and Section 4.4 where advice is given on monitoring liver function tests monthly and considering interruption, dose reduction or discontinuation if ALT/ AST increase more than 3 x upper limit of normal (ULN). Adequately addressed in the EU PIL:

Hepatotoxicity	
	Section 2 and Section 4 *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* PASS

Table 30: Important identified risk of fostamatinib: Neutropenia

Neutropenia	
Evidence for linking the risk to the medicine	Early in clinical development, fostamatinib was recognised to produce reductions in neutrophils that were rapidly reversible upon discontinuation of therapy. In the initial Phase 1 human subject study, it was observed that at higher fostamatinib doses (up to 300 mg twice daily), the biologically active component of fostamatinib produced significant reductions in neutrophils, which were rapidly reversible upon discontinuation of therapy. In the placebo-controlled ITP population, neutropenia adverse reactions were reported for 7% of patients in the fostamatinib group and no patients in the placebo group. Most neutropenia adverse reactions were not associated with an infection and were mild or moderate in severity.
Risk factors and risk groups	Patients with a history of bone marrow depression; combination therapy with myelotoxic agents; low white blood cell at the onset of the treatment.
Risk minimisation measures	*Routine risk minimisation measures:* Adequately addressed in the EU SmPC : Section 4.8 Section 4.2 and Section 4.4 where advice is given on monitoring the absolute neutrophil count (Maison-Blanche et al.) monthly and interrupt, reduce or discontinue fostamatinib if ANC decreases to less than 1.0 x 10^9/L for at least 72 hours. Adequately addressed in the EU PIL: Section 2 and Section 4 *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* PASS

Table 31: Important identified risk of fostamatinib: Infections

Infections	
Evidence for linking the risk to the medicine	Fostamatinib administration has been associated with a slightly increased risk of routine/local infections (but not opportunistic infections) although the effect may deserve further analysis. The infections do not appear to be associated with neutropenia, with some exceptions. Most of the Infection events were assessed by the investigator as unrelated to treatment; 2.9% of fostamatinib subjects and no placebo subjects experienced treatment-related Infection events In the placebo-controlled ITP population, infection adverse reactions were reported in 30% of patients receiving fostamatinib and 20% of patients receiving placebo.
Risk factors and risk groups	Patients with conditions causing alterations in immune functions. Patients with poor performance status.
Risk minimisation measures	*Routine risk minimisation measures:* Adequately addressed in the EU SmPC : Section 4.4 and Section 4.8. Adequately addressed in the EU PIL: Section 2 and Section 4 *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* PASS

Table 32: Important potential risk of fostamatinib: Off label use in paediatrics (effect of fostamatinib during bone formation and regrowth during development)

Off label use in paediatrics (effect of fostamatinib during bone formation and regrowth during development)	
Evidence for linking the risk to the medicine	Based on findings from several Good Laboratory Practice (GLP) toxicology studies in rodents and a GLP juvenile toxicology study in rabbits with fostamatinib there is potential for adverse bone development changes in paediatric populations. These changes may occur at dose levels below those promoting maternal toxicity and at unity or below calculated margin of safety.
Risk factors and risk groups	Patients under 18 years old.
Risk minimisation measures	*Routine risk minimisation measures:* Adequately addressed in the EU SmPC : Section 4.2 where warning is given not to use fostamatinib in children. Adequately addressed in the EU PIL:

Off label use in paediatrics (effect of fostamatinib during bone formation and regrowth during development)	
	Section 2 *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* None

Table 33: Important potential risk of fostamatinib: 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)

Important potential risk of fostamatinib 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)	
Evidence for linking the risk to the medicine	Fostamatinib has shown in vitro to target SYK and other tyrosine kinases that are involved in the bone metabolism (e.g. VEGFR, RET), so 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. There was a low incidence of young adults enrolled in clinical studies and no data was collected on the development of growth plates in these patients. .
Risk factors and risk groups	Patients with osteoporosis, patients with fractures, or young adults where epiphyseal fusion has not yet occurred
Risk minimisation measures	*Routine risk minimisation measures:* Adequately addressed in the EU SmPC : Section 4.4 where warning is given not to use fostamatinib in patients with osteoporosis, patients with fractures, or young adults where epiphyseal fusion has not yet occurred. *Additional risk minimisation measures:* None
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* None

6.3.3 Post-authorisation Development Plan

6.3.3.1 Studies which are conditions of the marketing authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of fostamatinib.

6.3.3.2 Other studies in post-authorisation development plan

A non-interventional post-authorisation study (PASS) will be conducted 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.

7 PART VII: ANNEXES

7.4 Annex 4: Specific adverse drug reaction follow-up forms

No data.

7.6 Annex 6: Details of proposed additional risk minimisation activities (if applicable)

Not applicable.