CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209299Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review

NDA/BLA Multi-disciplinary Review and Evaluation

Application Type	New Drug Application (NDA)
Application Number	209299
Priority or Standard	Standard
Submit Date	April 15, 2017
Received Date	April 17, 2017
PDUFA Goal Date	April 17, 2018
Division/Office	Division of Hematology Products Office of Hematology and Oncology Products
Review Completion Date	February 28, 2018
Established Name	Fostamatinib
(Proposed) Trade Name	Tavalisse™
Pharmacologic Class	Kinase inhibitor
Code name	R935788 (or R788)
Applicant	Rigel Pharmaceuticals, Inc.
Formulation	Tablet
Dosing Regimen	The initial dose of fostamatinib is 100 mg orally twice daily. After 4 weeks increase to 150 mg twice daily if platelet count has not increased to at least 50 x 10^9/L
Applicant Proposed Indication(s)/Population(s)	Treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.
Recommendation on Regulatory Action	Regular Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Glossary

AC	advisory committee
ADaM	Analysis Data Model
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASH	American Society of Hematology
AST	aspartate aminotransferase
BID	twice daily
CDER	Center for Drug Evaluation and Research
CDTL	Cross-Discipline Team Leader
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DILI	drug-induced liver injury
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
DBP	diastolic blood pressure
ECG	electrocardiogram
EDR	electronic document room
eCTD	electronic common technical document
FDA	Food and Drug Administration
GCP	good clinical practice
GRMP	good review management practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IBLS	ITP Bleeding Score
ICH	International Conference on Harmonization
IND	Investigational New Drug
INR	International Normalized Ratio
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITP	immune thrombocytopenia
ITT	intent to treat
IVIG	immune globulin
IWG	International Working Group
IWRS	Interactive Web Response System

KPS	Karnofsky performance status
LDH	lactate dehydrogenase
LFT	liver function test
LOCF	last observation carried forward
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	per oral
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
REMS	risk evaluation and mitigation strategy
RR	reference range
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SBP	systolic blood pressure
SF-36	short form-36 (36-item short form health survey)
SOC	standard of care
SOC	System Organ Class
SRC	Safety Review Committee
STDM	Study Data Tabulation Model
SYK	spleen tyrosine kinase
TEAE	treatment emergent adverse event
TBL	total bilirubin level
TPO	thrombopoietin
ULN	upper limit normal
WHO	World Health Organization

1 Executive Summary

1.1. Product Introduction

The drug product, TAVALISSE™ (fostamatinib) Tablets is proposed for approval for the treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. Fostamatinib is a new molecular entity (NME) that was granted orphan designation in August 2015 for this use. The drug product is presented as 100 and 150 mg immediate release, film-coated tablets.

Fostamatinib disodium is a prodrug that converts *in vivo* to its active metabolite, R406. R406 is an orally active, ATP competitive, small molecule inhibitor of spleen tyrosine kinase (SYK). SYK plays a role in the immune system by mediating signal transduction of Fc-activating receptors and is involved in B-cell maturation. In ITP, platelet elimination is primarily mediated through the formation of immune complexes by autoantibodies that target the cells for phagocytosis and elimination. The phagocytosis of platelet immune complexes is mediated through FcγR activation on macrophages. The applicant hypothesizes that the inhibition of SYK has therapeutic potential in patients with ITP through the reduction of FcγR-mediated platelet destruction and elimination.

The established pharmacological class for fostamatinib is kinase inhibitor.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Efficacy of fostamatinib for the treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment was demonstrated in two identical randomized, double-blind, placebo-controlled clinical studies (C788-047 trial [FIT-1] and C788-048 trial [FIT-2]) augmented by additional efficacy data was provided from an extension study (C788-049 [FIT-3]). An initial dose of 100 mg twice daily which may be increased to 150 mg twice daily to achieve a platelet count of 50,000/mcL is supported based on dosing used in the clinical trials.

Studies C788-047 and C788-048 were designed to assess the efficacy of 24 weeks of treatment with fostamatinib versus placebo in achieving a stable platelet count in patients with ITP who had received at least one prior systemic treatment. Enrolled patients were consenting adult (age ≥18 years) males or females with diagnosis of ITP for at least 3 months and no known etiology for thrombocytopenia, average baseline platelet count <30, 000/mcl and who had previously received at least 1 typical regimen for the treatment of ITP. Fostamatinib (or matching placebo) dose was initiated at 100 mg PO BID and starting at Week 4 could be

increased to 150 mg PO BID if the platelet count remained <50,000/mcL and the study drug had been well tolerated. The primary efficacy endpoint was achievement of a stable platelet response by Week 24, defined as having a platelet count of at least 50,000/mcL on at least 4 of the last 6 scheduled visits between Weeks 14-24. Patients who discontinued treatment prior to Week 24 due to lack of efficacy or due to an adverse event, or who received rescue treatment after 10 weeks, were considered non-responders. Study C788-047 randomized 76 patients (51 to fostamatinib; 25 to placebo) and Study C788-048 randomized 74 patients (50, fostamatinib; 24 placebo). In Study C788-047, a total of 9 patients (17.6%) in the fostamatinib arm and no patient (0%) in the placebo arm achieved this endpoint. The difference of response between the arms was 17.6% [95% CI (-6.1%, 40.3%), exact confidence interval], [95% CI (7.2%, 28.1%), normal approximation], Fisher's exact test p-value: 0.03, favoring fostamatinib. In Study C788-048, this endpoint was achieved in a total of 8 patients (16.0%) in the fostamatinib arm and 1 patient (4.2%) in the placebo arm. The difference between the arms was 11.8% [95% CI (-13.0%, 35.7%), exact confidence intervals], [95% CI (-1.1%, 24.8%), normal approximation], Fisher's exact test p-value: 0.26. Severe bleeding-related adverse events (requiring hospitalization) occurred in 1 fostamatinib-treated patient and 3 placebo-treated patients in these studies.

Study C788-049 was an open-label extension study that enrolled 123 patients who had participated in Study C788-047 or Study C788-048. Upon ending participation in Study C788-047 or C788-048, patients who had completed the study or discontinued early (starting at 12 weeks) due to lack of response were eligible to continue into the extension study (Study C788-049). Patients remained blinded to their treatment assignment from C788-047 or C788-048 trials. Patients designated as responders in the prior study (defined as achievement of platelet count of at least 50 x 10^9/L) at the time of roll over continued in the extension study at their current trial dose and regimen. Patients who entered the extension study as non-responders (defined as platelet count less than 50 x 10^9/L) received TAVALISSE 100 mg twice daily regardless of their dose and regimen in the prior study. A total of 123 patients enrolled in the study. Among 44 patients who had received placebo in the prior study 10 subjects achieved a stable response (defined as no 2 visits, at least 4 weeks apart, with a platelet count less than 50 x 10^9/L, without an intervening visit with a platelet count of at least 50 x 10^9/L [and unrelated to rescue therapy], within a period of 12 weeks following initial achievement of the target platelet count). It should be noted that these 10 included the 1 placebo-responder from Study C788-048.

Considered as a whole, these studies provide adequate evidence of effectiveness for fostamatinib for the treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a prior therapy to support approval for the indication.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

The benefit-risk of fostamatinib for treatment of thrombocytopenia in adult patients with persistent or chronic ITP who have had an insufficient response to a previous treatment is favorable.

Efficacy of fostamatinib for the indication was demonstrated based on results of 2 randomized, placebo-controlled, (2:1, fostamatinib:placebo) studies and an open-label extension study as described in Section **1.2. Conclusions on the Substantial Evidence of Effectiveness** above.

The safety review of fostamatinib was primarily based on a total of 150 patients with ITP (fostamatinib: 102 patients, placebo: 48 patients) who participated in the two identical phase 3, registrational trials (C788-047 and C788-048); and on the 44 patients who received placebo during the C788-047 and C788-048 trials and continued on the open-label, extension trial (C788-049) and received treatment with fostamatinib. Patients who received treatment with fostamatinib initially were dosed on the 100 mg twice daily regimen and in majority of patients (87%) the dose was increased to 150 mg twice daily starting at Week 4. The median average daily dose of fostamatinib was 248 mg. The median duration of study treatment was 85 days (fostamatinib: 86 days, placebo: 85 days) during the placebo-controlled period. Based on the total of 146 patients who received fostamatinib throughout the placebo-controlled and the extension trials, the median duration of fostamatinib exposure was 179 days (range, 8 to 712 days). In the ITP double-blind studies, serious adverse drug reactions were febrile neutropenia, diarrhea, pneumonia, and hypertensive crisis, which each occurred in 1% of patients receiving TAVALISSE. Also, severe adverse reactions observed in patients receiving fostamatinib included dyspnea and hypertension (both 2%); and neutropenia, arthralgia, chest pain, diarrhea, dizziness, nephrolithiasis, pain in extremity, toothache, syncope, and hypoxia (all 1%). Diarrhea and hypertension were the two most common adverse reactions occurring in 31% and 28%, respectively, of fostamatinib-treated patients as compared to in 15% and 13%, respectively, of patients who received placebo. Febrile neutropenia was reported in 6% of fostamatinib-treated patients and in no patients who received placebo in the studies.

Animal studies identified embryofetal lethality and decreased fetal weights at high doses. Teratogenic effects were observed in both species in the form of soft tissue and skeletal abnormalities (variations and malformations). Consequently, the drug label will advise females of reproductive potential to use effective contraception during treatment and for at least 1 month following the last dose of the drug.

The Clinical Pharmacology review of pharmacokinetic data concluded that a dose reduction is recommended when concomitantly taking a strong CYP3A inhibitor and avoidance of concomitant use with fostamatinib is recommended when concomitantly taking a strong CYP3A

inducer.

Pharmacology/Toxicology review, Clinical Pharmacology review, and Clinical/Statistical review (in this **NDA Multi-disciplinary Review and Evaluation)** and CMC review (separate review documents) did not identify any issues that would preclude approval of fostamatinib for the indication. Based on results of the reviews, fostamatinib may be approved for the indication for treatment of thrombocytopenia in adult patients with persistent or chronic ITP who have had an insufficient response to a previous treatment. The final wording of the labeling should be agreed upon with the sponsor.

The safety and effectiveness of fostamatinib in pediatric patients have not been evaluated. No pediatric patients with ITP were enrolled in fostamatinib studies. Fostamatinib has been granted Orphan Drug Designation for treatment of ITP in adult patients. Therefore, requirements for studies under the Pediatric Research Equity Act do not apply for this application.

Chemistry, Manufacturing, and Controls (CMC) post marketing commitments are recommended as follows (See separate CMC Reviews):

- Develop a test method for (b) (4) and hardness for the drug product and submit the validation data to the FDA. Include tests for (b) (4) and hardness for drug product release and stability specifications with adequate justification.
- Test (b) (4) for elemental impurities and submit the data to FDA. (b) (4)

There were no other recommendations for post-marketing commitments/requirements.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Immune thrombocytopenia (ITP), also known as immune or idiopathic thrombocytopenic purpura, is an autoimmune disorder characterized by immunologic destruction of platelets and decreased platelet production. • The resulting thrombocytopenia predisposes to bleeding, bruising or	• ITP is an uncommon autoimmune disorder that may result in bleeding.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	petechiae. • The estimated incidence of ITP among adults in the US is 3.3/100,000 per year.	
Current Treatment Options	• Romiplostim (Nplate) (intravenous administration) • Eltrombopag (Promacta) (oral administration) • Splenectomy • Corticosteroids • Immunoglobulins	• There is no cure for ITP. • Although there are other treatment options for patients with ITP, there remain patients for who these therapies are not effective or not sustained. Additional, treatment options are needed for these patients.
Benefit	• In clinical trials in patients with ITP who had insufficient response to previous treatment fostamatinib produced a modest increase in patients having a stable platelet response to the therapy when compared to placebo.	• Fostamatinib provides an important additional treatment option to the therapeutic armamentarium for ITP.
Risk	• Patients treated with fostamatinib may experience hypertension (including hypertensive crisis), elevated liver function tests (LFTs), and neutropenia, with or without fever. • Diarrhea was the most common adverse reaction in clinical trials occurring in 31% of patients and was severe in 1% of patients. • Based on findings from animal studies and its mechanism of action, fostamatinib can cause fetal harm when administered to a pregnant woman. • The safety database for fostamatinib for treatment of ITP is small with only 102 patients treated in the controlled trials and additional 44 in the extension study. Therefore, the safety data currently available may not reflect very uncommon and rare events that may occur with fostamatinib treatment.	• Adverse reactions seen in the clinical trials were generally manageable with monitoring, dose adjustment and appropriate clinical management. • Following approval, the post-marketing reporting database should be examined on a regular basis for any serious but rare adverse reactions that may emerge.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Although ITP treatment may be lifelong, treatment duration in the clinical trials did not exceed 6 months and was about 3 months in most patients.	
Risk Management	• The safety data do not indicate need for a special risk evaluation and mitigation strategy (REMS). Adequate provisions for safe use of fostamatinib are incorporated into the draft labeling. • There are two CMC post-marketing commitments (PMC) (See separate CMC Review)	• Post-approval safety reporting for adverse reactions should be done per 21 CFR 314.80 and 314.81. The two CMC PMCs should be completed as agreed.

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Kathy Robie Suh, MD, PhD
Cross-Disciplinary Team Leader

2 Therapeutic Context

Analysis of Condition

Immune thrombocytopenia (ITP), also known as immune or idiopathic thrombocytopenic purpura, is an autoimmune disorder characterized by immunologic destruction of platelets and decreased platelet production. This results in thrombocytopenia and a predisposition to bleeding, bruising or petechiae. The estimated incidence of ITP among adults in the US is 3.3/100,000 per year and is approximately equal between the sexes except it is more prevalent in females during middle-age (30-60 years).

The diagnosis of ITP relies on the exclusion of other causes of thrombocytopenia that includes certain disorders or medications. Necessary evaluation includes a careful history, physical examination, review of the complete blood count and peripheral blood smear and if necessary, a bone marrow examination. ITP may occur as primary or secondary to other disorders, including autoimmune diseases, infections, lymphoproliferative disorders, and certain drugs. Primary ITP is defined by the International Working Group (IWG) as platelet count less than 100 x 10^9/L in the absence of other causes. In some adults, the disorder may resolve spontaneously. The decision to start treatment is determined by severity of bleeding, bleeding risk, activity level, and patient preference. However, for newly diagnosed patients, treatment is usually administered with a platelet count <30 x 10^9/L. Corticosteroids and/or intravenous infusions of immune globulin (IVIg) or Anti-D (also known as Rho(D) immune globulin intravenous or anti-D IGIV) is used for initial treatment. Second line therapies include rituximab and splenectomy. Thrombopoietin (TPO) mimetics (romiplostim and eltrombopag) are approved for the treatment of patients with chronic ITP who had insufficient responses to corticosteroids, IVIg, or splenectomy. For patients who relapse or are refractory to available therapies, treatment options are limited. Other safe and effective therapies are needed for this patient population.

2.2. Analysis of Current Treatment Options

Therapies for ITP that were approved within the last 10 years are summarized in the table below.

Table 1 Promacta, Nplate and Octagam 10% Approvals

Drug/ Approval	Indication	Study Design and Patient Population	Efficacy Results
Promacta (eltrombopag)/ 2008 Accelerated	A TPO receptor agonist indicated for the treatment of thrombocytopenia in	Study 1 and 2: Randomized, double-blind, placebo-controlled trials.	Study 1 and 2: Response rate defined as shift from a baseline platelet count of <30 x 10^9/L to ≥50 x 10^9/L at

approval	patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.	Patients received at least 1 prior ITP therapy (70% of patients had at least 2 prior ITP therapies and 40% had splenectomy) and had baseline platelet count <30 x 10^9/L.	any time during the treatment period. Study 1: Promacta 43/73 (59%); placebo 6/37 (16%), p<0.001. Study 2: Promacta 19/27 (70%); placebo 3/27 (11%), p<0.001. Platelet count response to Promacta was similar among patients who had or had not prior splenectomy in both studies.
Promacta (eltrombopag)/ 2011 Regular Approval	For the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy	Study 3: Randomized, double-blind, placebo-controlled trial. Approximately half of the patients were receiving concomitant ITP medication at randomization and had baseline platelet counts ≤15 x 10^9/L. Similar percentage of patients treated with Promacta and placebo (37% and 34%, respectively) had a prior splenectomy. Study 3 enrolled a total of 197 patients (Promacta: 135 patients, placebo: 62 patients).	Study 3: -Assessed odds of achieving platelet count ≥50 x 10^9/L and ≤ 400x x 10^9/L for patients receiving Promacta relative to placebo and was based on response throughout the 6-month treatment period: the odds were 8 times greater in the Promacta group than placebo group, the difference was significant (P<0.001) at the 1% level. -Sustained platelet response (platelet count ≥50 x 10^9/L for 6 out of the last 8 weeks of the 26-week treatment period in the absence of rescue medication at any time) was achieved by 60% of patients treated with Promacta and 10% of patients in the placebo arm (splenectomized patients: Promacta 51%, placebo 8%; non-splenectomized patients: Promacta 66%, placebo 11%). - Mean number of weeks

			with platelet counts ≥50 x 10^9/L was 11 for Promacta and 2 for placebo arm.
Nplate (romiplostim)/ 2008 Regular Approval	A TPO receptor agonist indicated for the treatment of thrombocytopenia in patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.	Two randomized, double-blind, placebo-controlled trials. Patients had completed at least one prior treatment and had a platelet count of ≤ 30 x 10^9/L. -Study 1 evaluated patients who had not undergone a splenectomy. Patients had received a median of three prior ITP treatments. -Study 2 evaluated patients who had undergone a splenectomy. Patients had received a median of six prior ITP treatments.	Study 1 and 2: Durable platelet response was the achievement of a weekly platelet count ≥ 50 x 10^9/L for any 6 of the last 8 weeks of the 24-week treatment period in the absence of rescue medication at any time. -Study 1: Nplate 26/41 (61%), placebo 1/21 (5%), p<0.05. Average number of weeks with platelet ≥ 50 x 10^9/L: Nplate 15 wks, placebo 1 wk. -Study 2: Nplate 16/42 (38%), placebo 0/21 (0%), p<0.05. Average number of weeks with platelet ≥ 50 x 10^9/L: Nplate 12 wks, placebo 0.
Octagam 10% 2014 Regular Approval	Immune globulin intravenous (IGIV) for the treatment of chronic immune thrombocytopenic purpura (ITP) to rapidly raise platelet counts to control or prevent bleeding in adults.	One open-label, single arm trial in patients with newly diagnosed or chronic ITP with a platelet count of ≤ 20 x 10^9/L.	-Response rate (% subjects with an increase of platelet count to ≥ 50 x 10^9/L within 7 days after the first infusion): 82%. -Median duration of response: 12 days (range 1-79) -Median maximum platelet count: 212 x 10^9/L. -In 35 of the 45 patients (78%) who had bleeding at baseline, hemorrhages had completely resolved by Day 7.

[Source: FDA compilation]

Other drug products indicated for ITP treatment include WinRho and various other brands of

IVIgs. Alternative treatments for ITP include corticosteroids, vinca alkaloids, danazol, azathioprine, cyclophosphamide, cyclosporine A, dapsone, rituximab and splenectomy.

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Fostamatinib is a new molecular entity (NME) and has not been and is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

The table below summarizes the relevant regulatory history pertaining to this NDA.

Table 2 Regulatory History

June 30, 2006	IND 074939 was opened for R935788 (R788) for ITP. Rigel Pharmaceuticals submitted protocol C-935788-007 entitled "A Phase 2, Single Center, Open Label, Efficacy and Safety, Ascending Dose, Pilot Study of R935788 for the Treatment of Adult Refractory Immune Thrombocytopenic Purpura."
April 16, 2010	The sponsorship of IND 074939 was transferred from Rigel Pharmaceuticals to AstraZeneca Pharmaceuticals.
February 2010	AstraZeneca signed a global license agreement with Rigel Pharmaceuticals Inc. to develop and commercialize fostamatinib.
October 8, 2013	End of Phase 2 meeting was held. Key clinical/statistical communications were as follows: - Regarding the proposed dose, the applicant stated that a dose of 50 mg daily has minimal activity based on human biomarker data. The 100 mg bid dose was chosen because it had a demonstrated activity. The applicant proposed to conduct two studies with one study having a lower starting dose. The FDA commented that for interpretation it would be preferable to have the same starting dose and escalation in both studies. FDA agreed that for the Phase 3 study it does not seem scientifically reasonable to start at a dose likely to be ineffective. - Regarding the efficacy endpoint of the proposed Phase 3 double-blind study C788-047, the applicant proposed that the durability of response will be assessed through a primary endpoint such as achieving a platelet count ≥50,000/mcL for any 4 out of the last 6 visits of a 24 week treatment period. The FDA stated that this appears reasonable but will need to review the protocol. - The FDA expressed concerns regarding the clinical meaningfulness of the WHO Bleeding scale due to its subjective nature and the unclear clinical meaning of small incremental changes between bleeding levels.

	-The FDA agreed with the proposed safety endpoint focus on blood pressure effects, liver function tests, gastrointestinal tolerability, infectious complications, neutrophil counts and adverse events. - The applicant proposed a sample size of approximately 150 patients (100:50 [active:placebo]) with an alpha level of 0.0025 for the phase 3 study C788-047. The FDA commented that the sample size should consider dropout rate. Too much missing data undermine the reliability and confidence of the results. The applicant understood the issue of missing data and stated that they would provide sensitivity analyses. - The applicant proposed that the double-blind study be followed by a Phase 3 open-label extension trial to gain additional efficacy information from placebo patients who crossover to active drug and to evaluate the long-term efficacy and safety of fostamatinib. FDA agreed that an extension study is an important component for the development of the drug and to provide a clear definition of the primary endpoint for this study. The applicant proposed a primary endpoint for the extension study of patients having platelet counts above 50,000 greater than 50% of the time and that they would provide additional bleeding scale data. The FDA reiterated these bleeding scales have not been validated. - The FDA stated that for a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. Two adequate and well-controlled trials should be conducted to support the proposed indication. Approval for marketing based on a single study will require highly compelling results in both efficacy and safety. Safety information from the non-ITP studies for this drug could be considered supportive. The applicant accepted the FDA's recommendation to conduct two efficacy studies. - The applicant proposed to stratify on splenectomy/no splenectomy and platelet count above and below 15,000. The applicant would conduct a secondary analysis of the frequency of response in patients with a platelet count below 15,000 with regard to achieving a count greater than 30,000 and increased at least 20,000 from baseline as a secondary endpoint. The FDA stated that utility of the analysis would be a review issue. - The FDA stated that the applicant should address a pediatric development plan.
November 1, 2013	The sponsorship of IND 074939 was transferred from AstraZeneca Pharmaceuticals back to Rigel Pharmaceuticals.
March 26, 2014	The following statistical comments were sent to the applicant. For study C-935788-047: - FDA does not consider the proposed three secondary endpoints acceptable for regulatory labeling purpose. Specifically, the secondary endpoints based

	on the rate of platelet response at Weeks 12 and 24 and the percentage of patients with a baseline platelet count < 15,000/mcL, achievement of a count ≥ 30,000/mcL, and at least 20,000/mcL above baseline, at Weeks 12 and 24, are not acceptable due to the concern of the variability of the platelet assessments at a specific time point. Both ITP Bleeding Score (IBLS) and WHO Bleeding scale cannot be considered as acceptable regulatory endpoints due to its subjective nature and the unclear clinical meaning of small incremental changes between bleeding levels. - FDA does not agree that the last observation carried forward (LOCF) method be applied for missing data imputation for the primary efficacy endpoint analysis. Please refer to statistical review for Nplate (romiplostim) from DRUGS@FDA for details of missing data handling strategies. LOCF method could be used for the sensitivity analysis. - Provide additional sensitivity analyses for the primary efficacy endpoint, specifically, to take account of different missing data imputation strategies. For Study C-935788-049: - The results of efficacy analyses will be considered exploratory.
August 25, 2015	Orphan drug designation was granted for “treatment of adult ITP”.
April 5, 2016	A pre-NDA meeting was held. The relevant clinical /statistical discussions were as follows: - The FDA urged that the sponsor should complete the phase 3 studies (C-935788-047 and C-935788-048) in order to enhance the fostamatinib safety and efficacy database for the proposed indication. The results of these controlled, randomized trials may qualify fostamatinib for a regular approval. The applicant clarified that the NDA will contain the two Phase 3 trials. The enrollment is complete for those trials with the last patient visit scheduled for near the end of summer 2016. - The applicant proposal for the NDA safety database will include data from all ITP studies, as well as all completed studies for other indications. The FDA commented that the proposed safety database appears to be acceptable in terms of numbers of subjects exposed. However, there is little information for the ITP population. - The FDA stated that the ISS should contain an integrated summary of all safety data pertaining to fostamatinib. The FDA emphasized that the safety database will need to adequately reflect the population to be labeled including dose information and duration of exposure. - The FDA stated that the SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the submission. All programs involving data analysis and the creation of derived datasets should be

	submitted. The location of the SAS dataset, the names of the variables used and the programs used to get every new value that will appear in the label should be provided. - The FDA clarified that the program involving data analysis and the creation of derived datasets is only for the Phase 3 ITP studies. - The FDA clarified that studies which may have been terminated early, would still be considered covered studies, and as such financial disclosure information would be required. The Agency recommended the applicant to provide as complete financial disclosure information as possible. - A preliminary discussion on the need for a REMS was held and it was concluded that the applicant is not required to submit a REMS at the time of the application submission. The need for risk management activities will be a subject of discussion as the review of the application proceeds.

[Source: FDA compilation]

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The C788-047 and C788-048 trials are the pivotal trials to support efficacy and safety of fostamatinib for the proposed indication. One clinical site in each of the trials was chosen for Office of Scientific Investigations (OSI) inspections. The site selections were based on the consideration of the combination of the large numbers of patient enrollment, protocol violations and site-specific treatment effect.

Table 3 Requested OSI Clinical Site Audits for C788-047 and C788-048

Protocol ID	Site ID	Number of enrolled patients	Name of the Principal Investigator	Location
C788-047	063	7	James Bussel	Cornell Medical College 525 East 68th Street New York, NY USA 10065
C788-048	428	8	Jiri Mayer	Interni hematologicka a onkologicka klinika Jihalavska 20 Brno, Czech Republic 625 00

In addition to the two clinical sites (Drs. Bussel and Mayer), Rigel Pharmaceuticals, the applicant was also inspected. OSI's overall assessment of findings and general recommendations for these sites were as follows:

"The preliminary regulatory classification for Dr. Mayer is No Action Indicated (NAI). The final regulatory classification for Dr. Bussel is No Action Indicated (NAI). The preliminary regulatory classification for the inspection of Rigel Pharmaceuticals, Inc. is No Action Indicated (NAI)."

Therefore, the overall compliance with GCP is acceptable.

Refer to the OSI review dated September 14, 2017.

4.2. Product Quality

Novel excipients: No.
Any impurity of concern: No.

Refer to the Chemistry, Manufacturing and Controls (CMC) review dated January 29, 2018.

4.3. Clinical Microbiology

This section is not applicable.

4.4. Devices and Companion Diagnostic Issues

Not applicable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

Fostamatinib (also known as R935788 or R788) is a prodrug that rapidly metabolizes to the active compound R940406 (R406). R406 is an orally active, ATP competitive, small molecule inhibitor of spleen tyrosine kinase (SYK). SYK plays a role in the immune system by mediating signal transduction of Fc-activating receptors and is involved in B-cell maturation. In immune thrombocytopenia (ITP), platelet elimination is primarily mediated through the formation of immune complexes by autoantibodies that target the cells for phagocytosis and elimination. It has previously been shown that the phagocytosis of platelet immune complexes is mediated through FcγR activation on macrophages. The applicant hypothesizes that the inhibition of SYK has therapeutic potential in patients with ITP through the reduction of FcγR-mediated platelet destruction and elimination. The established pharmacological class for fostamatinib is kinase inhibitor.

In an in vitro fluorescence polarization assay, R406 was shown to inhibit in vitro biochemical SYK activity (Ki = 30 nM) in an ATP-competitive manner. Inhibition of SYK by R406 was further supported by an observed decrease in phosphorylation of proteins downstream of SYK signaling

but not upstream. Kinase inhibition was not specific to SYK, however, as activity was observed in numerous proteins at lower concentrations in kinase activity and competitive binding assays. A subset of the R406 targeted proteins were assessed in in vitro functional assays and R406 was generally more active against SYK by approximately 2 to 5-fold than against other kinases tested. In Caliper capillary electrophoresis assays, inhibition of SYK was similar between human, mouse and rat with IC50 values of 25, 20 and 30 nM, respectively.

The potential for fostamatinib to inhibit phagocytic clearance of platelets was assessed in an in vivo mouse model of ITP. In this model, platelet elimination was induced by injection of 2 µg anti-GPIIb antibody in CD-1 mice. Mean platelet counts were significantly decreased by 24-hours post-antibody injection. Pretreatment with 30.8 or 49.4 mg/kg fostamatinib resulted in a protective effect against antibody mediated platelet elimination and significantly increased platelet counts that were approximately 2-fold higher than vehicle treated animals and 70% of naïve controls.

In safety pharmacology studies, no consistent effects of toxicological significance were observed.

Orally administered fostamatinib is rapidly converted to R406 in the gut within the first hour of exposure, with a bioavailability of 42-54% in rats and 43% in monkeys. Following absorption, R406 is widely distributed with the greatest concentrations occurring in the small intestines at levels approximately 5-fold higher than other tissues. Other tissues with relatively high concentrations of R406 include the liver, cecum, white adipose, eye (uveal tract), kidney cortex and the urinary bladder. R406 is readily metabolized by liver microsomes of human, monkey and rat with an O-demethylated R406 being the primary metabolite, which is subsequently conjugated to glucuronic acid. R406 has a relatively short half-life (< 4 hours) and its metabolites are primarily eliminated through biliary secretion into the intestines and excretion through feces.

Exposure to R406 was dose related and generally greater than dose-proportional. There were sex related differences in exposure that were not consistent between rats and monkeys. In both species, females typically had a higher exposure than males apart from the mid dose groups. In rats, the sex differences were most pronounced at high doses, whereas the low doses were more pronounced in monkeys. There were no apparent signs of accumulation in either sex or species.

In a 9-month repeat-dose study, male and female monkeys were dosed orally, twice per day, at doses of 0, 5, 17, and 60 mg/kg/day. The high dose was lowered to 34 mg/kg/day after 13 weeks due to the premature deaths of 2 males. Both animals had evidence of severe anemia which appeared to be related to blood loss from hemorrhage in the GI tract, which was the main organ of toxicity. Additional target organs of toxicity in animals surviving to study completion included bone marrow, thymus, and prostate. Reductions in lymphocytes in high

dose animals along with hematopoietic hypocellularity were observed but are consistent with the pharmacodynamic effects of R406.

In 1- and 6-month repeat dose studies in Sprague Dawley rats, observed toxicities were similar to those reported in monkeys. In the 1-month study, administration of R406 at ≥ 30 mg/kg/day resulted in increased liver transaminases that were not observed in monkeys. In the 6-month study, a premature death of a male in the high dose group (60/40 mg/kg/day) occurred on Day 150 with macroscopic findings in the GI tract. In both studies, animals had hypocellularity of femur and sternum marrow and reduced white blood cell counts.

In a 1-month repeat dose study, juvenile rabbits were orally administered fostamatinib at 10, 30 or 60 mg/kg/day. Administration of fostamatinib resulted in growth plate dysplasia of the proximal femur and femoro-tibial joint at doses ≥ 30 mg/kg/day. Dysplasia was characterized by thickening, fissuring and fracturing of the growth plate due to hypertrophic chondrocytes that was accompanied by hemorrhage into the bone marrow in severe cases. A prematurely sacrificed male in the high dose group was found *in extremis* condition that was attributed to fractured femur heads due to growth plate dysplasia.

Fostamatinib and R406 were not mutagenic in the in vitro bacterial reverse mutation (Ames) assay and not clastogenic in the in vitro human lymphocyte chromosomal aberration assay, and were not genotoxic in an in vivo mouse bone marrow micronucleus assay. In 104-week carcinogenicity studies conducted in rats and mice, fostamatinib did not result in any tumor findings that met the threshold for statistical significance in either sex or species.

In a fertility and early embryonic development (FEED) study in rats, fostamatinib was administered orally at 5, 14, or 40 mg/kg/day (males) and 5, 11, or 25 mg/kg/day (females). Females were treated 15 days before mating through Gestation Day 7 (GD 7) and cohabitated with a treated male. Treatment resulted in a decrease in pregnant dams in the high dose group and an increase in preimplantation loss in all dose groups. There were no significant treatment related effects on male sperm count or motility. In the toxicokinetic evaluation, there were insufficient data points to calculate area under the curve (AUC) values, thus the drug label will use dose comparisons between animal data and the maximum recommended human dose (MRHD).

Embryo-fetal development (EFD) studies were conducted in rats and rabbits. Female rats were orally administered fostamatinib at 5, 12.5, or 25 mg/kg/day from GD 6 - GD 17. Female rabbits were orally administered fostamatinib at 10, 22, or 50 mg/kg/day from GD 7 – GD 19. In both studies, the high dose resulted in embryofetal lethality and decreased fetal weights. Teratogenic effects were observed in both species in the form of soft tissue and skeletal abnormalities (variations and malformations). Affected tissues/structures include the heart, kidneys, ureter, uterus, vas deferens, vertebrae, ribs and skull. Based on these findings and the mechanism of action of fostamatinib, the drug label will advise females of reproductive potential to use effective contraception during treatment and for at least 1 month following the

last dose of the drug. The EFD summary in the label will use exposure multiples based on AUCs from animal data and the MRHD.

A peri and postnatal development (PPND) study was conducted in female rats. Fostamatinib was orally administered at doses of 2.5, 12.5, and 25 mg/kg/day from gestation day 7 until lactation day 20. Maternal doses of ≥ 12.5 mg/kg/day resulted in F1 generation effects that included increased neonatal mortality, and a reduction in pup body weights. At 25 mg/kg/day F1 progeny exhibited urogenital malformations and delayed sexual maturation. Additionally, maternal toxicities of reduced body weight gains and feed consumption was observed at 25 mg/kg/day. There were no dose-dependent or significant findings in the F2 generation fetuses. In the toxicokinetic evaluation of plasma and maternal milk, concentrations of fostamatinib were found to be 5- to 10-fold higher in milk; however, there were insufficient data points to determine AUCs. The drug label will use dose comparisons between animal data and the MRHD and advise women not to breastfeed during treatment and for at least 1 month following the last dose of the drug.

The nonclinical pharmacology and toxicology data submitted to this NDA are adequate to support the approval of fostamatinib for the proposed indication.

5.2. Referenced NDAs, BLAs, DMFs

None

5.3. Pharmacology

Primary pharmacology

Table 4 Summary of Primary Pharmacology Studies

Study No.	Study title	Findings
N-935788-0010	Efficacy of R935788 in a Mouse Model of Immune Thrombocytopenic Purpura (ITP)	Platelet elimination was induced by the injection of 2 µg anti-GPIIb antibody. Pretreatment with 30.8 or 49.4 mg/kg fostamatinib resulted in a protective effect with statistically significant higher platelet counts.
B040007	R940406 Inhibits FcεRI-Dependent Activation of Cord-Blood Derived Primary Human Mast Cells (CHMC)	R940406 inhibited mast cell degranulation induced by FcεRI crosslinking, but not ionomycin indicating that it acts upstream of calcium mobilization.
B040008	R940406 Mechanism of Action: Inhibition of Syk Kinase	R940406 is an ATP competitive inhibitor of Syk kinase activity (Ki = 30 nM) and the downstream phosphorylation of signaling molecules (LAT, PLCγ, PKB, ERK, JNK, p38) but not upstream of SYK.

B040009	R940406 Inhibits Syk-Dependent FcγR Signaling and B-Cell Receptor Signaling	"R940406 specifically inhibits FcγR signaling in mast cells, macrophages, and neutrophils and B-cell receptor signaling in B-cells."
B040010	R940406 Effects on Macrophage and Neutrophil Function	R940406 did not have any significant effects on leukocyte phagocytosis (50 µM), oxidative burst (> 30 µM), chemotaxis (10 µM), and microbicidal activity (20 µM).
B040011	R940406 Effects on Platelet Function	R940406 inhibited collagen-, but not ADP induced platelet activation (42% at 5 µM). At 100 mg/kg (oral), no effect on bleeding time was observed in mice.
B040012	R940406 Selectivity: Cell-Based Assays	R940406 was significantly more potent in Syk-dependent pathways in cultured human mast cell assays compared to Syk independent pathways in 12 cell-based assays.
B040006	R940406 Selectivity: Biochemical Assays Screen	R940406 showed significant antagonistic activity on adenosine A3 receptor activity among the 140 targets screened.
B040013	R940406 Selectivity: In Vitro Kinase Selectivity	R940406 (0.3, 1, and 3 µM) showed activity against 28 kinases (> 50% inhibition) in in vitro kinase assays. However, three selected kinases (from 28) were not significantly affected in cellular assays. This was unlike Syk kinase which showed similar potency in both in vitro and cellular assays.
E14378-71	Effect of R940406 on Human Spleen Tyrosine Kinase (SYK) Phosphorylation of Peptide EEPLYWSFPAKKK CONH2 In Vitro	As measured by a caliper capillary electrophoresis assay R406 inhibited SYK activity with a pIC_{50} value 7.60 ± 0.09 (mean ± SEM), which correlates to an IC_{50} value of 25 nM.
E14378-72	Effect of R940406 on Mouse Spleen Tyrosine Kinase (SYK) Phosphorylation of Peptide EEPLYWSFPAKKK CONH2 In Vitro	As measured by a caliper capillary electrophoresis assay R406 inhibited SYK activity with a pIC_{50} value 7.69 ± 0.07 (mean ± SEM), which correlates to an IC_{50} value of 20 nM.
E14378-73	Effect of R940406 on Rat Spleen Tyrosine Kinase (SYK) Phosphorylation of Peptide EEPLYWSFPAKKK CONH2 In Vitro	As measured by a caliper capillary electrophoresis assay R406 inhibited SYK activity with a pIC_{50} value 7.53 ± 0.08 (mean ± SEM), which correlates to an IC_{50} value of 30 nM.

Secondary Pharmacology

In studies 1062SY and 2983SV, R406 was evaluated for in vitro kinase inhibition activity (IC_{50}) and competitive binding (K_d), respectively. Kinases where R406 was active at lower concentrations than SYK are tabulated below.

Table 5 Kinase Profiling of R406

Kinase	IC_{50} (nM)
FLT3	3
FLT4	4
FLT1	4
MAP3K9	5
JAK2	7
RET	10
TNK2	20
SRC	20
TBK1	20
ULK3	20
CSF1R	20
AURKB	30
BMX	30
NTRK1	30
FGFR1	30
KDR	30
LCK	30
FGFR3	40
LYN	40
MAPK10	40
YES1	40
TSSK1B	50
FYN	50
PLK3	50
SYK	**50**

Kinase	K_d (nM)
STK16	0.6
JAK2	0.78
FLT3	0.97
PDGFRB	2.6
MLK2	3
NEK6	3.6
GCN2	3.7
PLK4	5
IRAK3	5
RET	5.6
KIT	8.1
NEK5	8.5
PLK3	9.8
JAK3	10
MLK1	10
MLK3	12
SYK	**12**

Safety Pharmacology

Safety pharmacology was reviewed under IND by Dr. Hamid R. Amouzadeh.

Neurological Effects: (Study No. 940406-002, GLP-compliant) Male Sprague- Dawley rats were treated with a single oral dose of 0, 5, 15 or 50 mg/kg of R940406 besylate. Chlorpromazine (20 mg/kg) was used as the positive control. Behavioral parameters (Irwin test) were evaluated 30, 60, 90 and 120 minutes after dosing. No consistent gross behavioral or physiological effects were observed at 5 or 15 mg/kg. At 50 mg/kg, inconsistent signs of mild general depression

including decreased startle response, locomotion and grooming were observed at all time points.

Cardiovascular Effects: (Study No. 940406-001, GLP-compliant) Monkeys were treated with single oral doses of 0, 5, 15, or 50 mg/kg of R940406 besylate and arterial blood pressure (systolic and diastolic), heart rate and ECG were measured by telemetry. Blood samples were collected approximately 6 hours after dosing. Mean arterial blood pressure and QTcF (Fridericia's formula) intervals were calculated. No toxicologically significant effects were observed.

Effects on hERG Channel: (Study No. N-940406-003, Non-GLP) R940406 (2 µM) had no effect on the hERG currents.

Pulmonary Effects: (Study No. 940406-003, GLP compliant) Male Sprague- Dawley rats were treated with a single oral dose of 0, 5, 15 or 50 mg/kg of R940406 besylate and respiration rate and tidal volume were measured at approximately 60 and 240 minutes post-dose. Baclofen (20 mg/kg) was used as the positive control. No toxicologically significant effects were observed.

5.4. ADME/PK

Table 6 ADME and Toxicokinetic Summary

<table>
<tr><th>Type of Study</th><th>Major Findings</th></tr>
<tr><td colspan="2">Absorption</td></tr>
<tr><td>V040212: An Evaluation of the Absorption and First-pass Metabolism of R935788</td><td>Following oral administration of 4 mg/kg fostamatinb to rats with cannulated portal veins, concentrations of fostamatinib were below the limit of quantitation in the portal and jugular veins. R406 had a t_{max} of 0.25 and 0.33 h in the portal and jugular veins, respectively.</td></tr>
<tr><td colspan="2">Distribution</td></tr>
<tr><td>G-935788-0011: Quantitative Tissue Distribution of Drug-Related Material Using Whole-Body Autoradiography in Sprague-Dawley and Long-Evans Rats</td><td>Distribution was similar between rat strains. Highest concentrations of radioactivity (> 5 µg equiv/g) are tabulated below.
<table>
<tr><th>Tissue</th><th>Radioactivity (µg equiv/g)</th></tr>
<tr><td>Small intestine</td><td>53.8</td></tr>
<tr><td>Liver</td><td>11.5</td></tr>
<tr><td>Cecum</td><td>9.1</td></tr>
<tr><td>White adipose</td><td>7.6</td></tr>
<tr><td>Eye - uveal tract</td><td>7.4</td></tr>
<tr><td>Kidney cortex</td><td>6.4</td></tr>
<tr><td>Urinary bladder</td><td>5.9</td></tr>
</table></td></tr>
<tr><td colspan="2">Metabolism</td></tr>
</table>

N-940406-0019: Metabolite Profiling of Urine, Bile and Feces Samples Following a Single Intravenous Bolus or Oral Dose of [14C]R940406 to Male Rats

Metabolite Identification	
Peak Number	**Metabolite**
M1	Unknown
M2	Unknown
M3	Glucuronide of O-demethylated M7
M4	Glucuronide of O-demethylated M8
M5	Sulfate conjugate of O-demethylated M7
M6	Direct glucuronide
M7	O-demethylated metabolite
M8	O-demethylated metabolite
R940406	Parent

Relative abundance of metabolites in bile urine and feces (0-24 hr)			
Peak	**Bile**	**Urine**	**Feces**
M1	0.75%	30%	0%
M2	1.00%	6%	0%
M3	64.50%	23%	0%
M4	4.00%	3%	0%
M5/M6	29.00%	10%	8%
M7	-	0%	58%
M8	-	0%	6%
parent	-	1%	27%
others	0.75%	27%	1%

Excretion

N-935788-0037: Mass Balance and Metabolism of R935788 in Male Cynomolgus Monkeys

Biliary secretion of R406 into the intestines and excretion through feces is the primary route of elimination.

Cumulative recovery of radioactivity					
Bile duct	**Bile**	**Urine**	**Feces**	**Cage**	**Total**
Intact	-	3.1%	81.7%	4.4%	89.3%
Cannulated	68.9%	4.6%	17.7%	1.9%	93.1%

TK data from general toxicology studies

G-935788-001: R935788 (b) (4) -A 28-Day Repeat Dose Oral Toxicity Study Followed by a 14-Day Recovery Period in Sprague-Dawley Rats

Fostamatinib					
Day	Dose (mg/kg/day)	Sex	C_{max} (ug/mL)	T_{max} (hr)	AUC_{0-24} (ng*hr/mL)
1	2.5	M	0	ND	0
		F	4.5	24	27
	10	M	3.56	24	21.4
		F	4.66	12	50.6
	30	M	5.26	24	36.8
		F	6.21	24	37.2
	100	M	1.78	2	4.44
	100/50	F	12.9	6	68.5
28	2.5	M	49.7	6	217
		F	18.7	2	140
	10	M	18.1	1	40.7
		F	4.37	8	15.3
	30	M	8.51	2	47.6
		F	3.36	1	33.9
	100	M	21.0	6	103
	100/50	F	9.48	2	49.5

R406					
Day	Dose (mg/kg/day)	Sex	C_{max} (ug/mL)	T_{max} (hr)	AUC_{0-24} (ng*hr/mL)
1	2.5	M	228	1	1351
		F	270	1	1625
	10	M	1989	8	9535
		F	1388	1	8150
	30	M	1976	8	12222
		F	2090	1	16631
	100	M	12384	8	139286
	100/50	F	16134	8	288147
28	2.5	M	1626	8	1626
		F	1752	8	1752
	10	M	7752	1	7752
		F	10199	1	10199
	30	M	21281	1	21281
		F	12544	8	13544
	100	M	88005	8	88005
	100/50	F	88451	8	88451

G-940406-0005: A 28-Day Repeat Dose Oral Toxicity Study Followed by a 14-Day Recovery Period in Cynomolgus Monkeys

R406						
Day	Dose (mg/kg/day)	Sex	C_{max} (ug/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	AUC_{0-24} (ng*hr/mL)
1	10	M	148	8	-	873
		F	779	1	9.7	2562
	30	M	1454	8	2.2	10671
		F	1531	1	1.7	10898
	100	M	3823	8	3.4	30025
		F	4241	8	2.6	32921
28	10	M	323	1	2.8	1792
		F	488	1	2.4	3232
	30	M	1947	2	2.2	15615
		F	1544	8	2.5	11464
	100	M	2897	8	4.0	23094
		F	2669	1	3.8	27582

G-935788-0005: R935788 Sodium Salt: A 13 Week and 39 Week Repeat Rose Oral Toxicity Study, Including Toxicokinetics, Followed by 4-Week Recovery Periods in Cynomolgus Monkeys

			Fostamatinib		R406	
Day	Dose (mg/kg/day)	Sex	C_{max} (ng/mL)	AUC_{0-6} (ng*hr/mL)	C_{max} (ng/mL)	AUC_{0-24} (ng*hr/mL)
1	5	M	2.87	6.03	331	1902
		F	6.12	12	407	2095
	17	M	3.33	7.5	2026	12328
		F	3.44	8.47	2044	14586
	60	M	9.1	18.3	4410	36819
		F	16.8	23.7	5209	42471
91	5	M	4.52	12.2	271	1692
		F	4.42	13.2	478	2620
	17	M	6.55	10	1876	12607
		F	4.8	11.2	2359	15555
	60	M	7.41	15.3	4703	36030
		F	7.29	11.6	5751	50966
273	5	M	0.36	0.89	318	1770
		F	ND	ND	432	2378
	17	M	16.7	42.4	1422	9853
		F	1.77	1.77	1613	10251
	60/34	M	4.65	9.18	1549	11472
		F	6.12	11.3	2049	16547

TK data from reproductive toxicology studies

<table>
<tr><td>G-935788-0007: Oral Gavage Study for Effects on Embryo-Fetal Development and Toxicokinetic Study with R935788 Na in Rats</td><td>Rat
<table>
<tr><th>Gestation Day</th><th>Dose (mg/kg/day)</th><th>C_{max} (ng/mL)</th><th>AUC_{0-t} (ng*h/mL)</th></tr>
<tr><td>6</td><td>5</td><td>388</td><td>943</td></tr>
<tr><td></td><td>12.5</td><td>1503</td><td>3396</td></tr>
<tr><td></td><td>25</td><td>2529</td><td>8336</td></tr>
<tr><td>17</td><td>5</td><td>323</td><td>992</td></tr>
<tr><td></td><td>12.5</td><td>1416</td><td>3763</td></tr>
<tr><td></td><td>25</td><td>3741</td><td>10505</td></tr>
</table></td></tr>
<tr><td>G-935788-0006: Embryo-Fetal Developmental Study in Rabbits via Oral Administration</td><td>Rabbit
<table>
<tr><th>Gestation Day</th><th>Dose (mg/kg/day)</th><th>C_{max} (ng/mL)</th><th>AUC_{0-t} (ng*h/mL)</th></tr>
<tr><td>7</td><td>10</td><td>3985</td><td>36613</td></tr>
<tr><td></td><td>22</td><td>8825</td><td>92919</td></tr>
<tr><td></td><td>50</td><td>19121</td><td>161095</td></tr>
<tr><td>19</td><td>10</td><td>4336</td><td>38228</td></tr>
<tr><td></td><td>22</td><td>9663</td><td>111105</td></tr>
<tr><td></td><td>50</td><td>26901</td><td>248369</td></tr>
</table></td></tr>
<tr><td>G935788-0014: Developmental and Perinatal/Postnatal Reproduction Toxicity Study of R935788 Na Administered Orally (Gavage) (b.i.d.) in Rats</td><td>
<table>
<tr><th colspan="4">R406 in milk and plasma on Lactation Day 14</th></tr>
<tr><th>Dose (mg/kg/day)</th><th>Plasma</th><th>Milk</th><th>Milk/Plasma Ratio</th></tr>
<tr><td>2.5</td><td>32</td><td>312.1</td><td>9.9</td></tr>
<tr><td>12.5</td><td>254.8</td><td>1566.4</td><td>6.9</td></tr>
<tr><td>25</td><td>1149.5</td><td>6461.6</td><td>5.5</td></tr>
</table></td></tr>
<tr><td>G-935788-0008: Fertility and General Reproduction Toxicity Study of R935788 Na Administered Orally (Gavage) (b.i.d.) in Rats</td><td>Insufficient data points to calculate an AUC.</td></tr>
<tr><td colspan="2">TK data from Carcinogenicity studies</td></tr>
</table>

G-935788-0015: 104-Week Oral Gavage Carcinogenicity Study in Mice G-935788-0013: A 104-Weeek Oral Gavage Carcinogenicity Study in Rats	Higher doses in both studies were discontinued due to toxicity prior to study completion. Mouse

R406				
Day	Dose (mg/kg/day)	Sex	C_{max} (ng/mL)	AUC_{0-6h} (ng*h/mL)
1	50	M	2785	4437
		F	534	779
	150	M	9558	22821
		F	6563	10608
364	50	M	3410	6296
		F	880	1465
	150	M	5998	16008
		F	8032	12560

Rat

R406				
Day	Dose (mg/kg/day)	Sex	C_{max} (ng/mL)	AUC_{0-6h} (ng*h/mL)
1	10	M	636	1550
	25	M	2082	4350
728	10	M	678	2299
	25	M	1774	6442
1	5	F	320	885
	12	F	1026	2836
728	5	F	1317	934
	12	F	911	4137

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: R935788 Sodium Salt: A 13 and 26-Week Repeat Dose Oral Toxicity Study, Including Toxicokinetics, Followed by 4 Week Recover Periods in Sprague Dawley Rats/ G-935788-0003

Key Study Findings

- Primary target of toxicity was the lymphohematopoietic system in the form of hypocellularity with associated changes in hematological parameters. Minimal hypocellularity was present after recovery in the 26-week study but to a lesser degree

than the main study, suggesting the changes were reversible.

- A statistically significant increase in liver transaminases were reported without any associated histopathological findings.
- Incidence and severity of vacuolar changes to the adrenal glands increased at 26-weeks in high dose animals when compared to controls.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 2.5, 8.5 and 30 mg/kg twice daily
Route of administration: Oral gavage
Formulation/Vehicle: Vehicle: Aqueous solution containing (w/w):
0.1% sodium carboxymethylcellulose
0.1% methylparaben sodium
0.02% propylparaben sodium and water.
Species/Strain: Sprague Dawley rats
Number/Sex/Group: 13-week: 10/sex/group
26-week: 20/sex/group
Age: 7-8 weeks
Satellite groups/ unique design: 4-week recovery of 5/sex/group (13-week) or 8/sex/group (26-week) and TK treatment groups of 10/sex/group
Deviation from study protocol affecting interpretation of results: High dose was lowered from 60 mg/kg/day to 40 mg/kg/day (males) or 30 mg/kg/day (females) on Days 12-27. Deviations did not affect the interpretation of study results.

Table 7 Observation and Results of Fostamatinib in Sprague Dawley Rats at 13/26 Weeks

Parameters	Major findings
Mortality	No unscheduled deaths were considered test article related.
Clinical Signs	Clinical signs related to the oral administration of R935788 included skin tugor, loose fur/fur loss and dry material that varied in color (i.e., red, brown, yellow or black), palor and thin body condition. Thin body condition resulted in a dose reduction from 60 mg/kg/day to 40 mg/kg/day (males) or 30 mg/kg/day (females) between Days 12 and 27. Changes in the teeth were also noted in the animals treated with the high dose of R935788. Misaligned, loose, missing, and broken teeth and malocclusion was

	noted in up to two-third of the female and one-third of the males in the high dose group. Problems with the teeth began to abate at Week 12 of the study; however they persisted throughout the study at a reduced incidence rate.
Body Weights	Week 13 HD females had a statistically significant decrease of 12.2% in mean body weight on Day 92 relative to Day 1. Week 26 HD females had a statistically significant decrease of 8.7% and 11.0% in mean body weight on Days 92 and 183 when compared to Day 1, respectively.
Ophthalmoscopy	Unremarkable
Hematology	Week 13 Findings at 13 weeks were similar to observations in Week 26 Week 26

Week 26 hematology (% change from control)

Parameter	Males			Females		
Dose (mg/kg/day)	5	17	60/40	5	17	60/30
WBC	-14	**-27**	**-47**	-21	**-31**	**-59**
RBC	1	**-10**	**-23**	-3	**-12**	**-18**
Hemoglobin	1	-3	**-10**	-2	**-5**	**-7**
Hematocrit	2	-2	**-11**	-3	**-3**	**-5**
Mean cell volume	0	**8**	**18**	1	**8**	**15**
Mean cell hemoglobin	0	8	**17**	2	**7**	**14**
Red cell distribution width	0	7	14.5	0	6	**10**
Hemoglobin distribution width	0	7	**10**	2	0	3
Platelets	1	**16**	**39**	2	**17**	**36**
Plateletcrit	0	**14**	**43**	0	**33**	**50**
Absolute lymphocytes	-14	**-42**	**-66**	-26	**-58**	**-73**
Relative lymphocytes	-9	**-18**	**-34**	-6	**-22**	**-36**
Absolute eosinophils	-6	**-31**	**-63**	**-20**	**-40**	**-60**
Relative eosinophils	0	0	**-24**	0	0	-14
Basophils	-17	**-50**	**-50**	-50	-50	**-50**
Neutrophils	16	**52**	**103**	22	**77**	**129**
Absolute reticulocytes	4	**23**	**26**	-7	-4	-4
Relative reticulocytes	4	**38**	**67**	-5	-5	-14

Bold = p < 0.05

Clinical Chemistry	

Clinical chemistry (% change from control)

Parameter	Week	Males	Females

	Dose (mg/kg/day)	60/40	60/30
Albumin	13	-	-9.5
	26	-	10.8
Glucose	13	-	-12.7
	26	-	-11.4
Total protein	13	-5.0	-9.5
	26	-	11.1
Globulin	13	-18.0	-
	26	-	-11.9
A/G ratio	13	26.9	-
	26	13.5	-
Calcium	13	-	-5.7
	26	-	-5.7
Phosphorus	13	14.5	-
	26	18.8	-
AST	13	31.7	41.5
	26	-	39.7
ALT	13	33.3	-
	26	45.9	60.0
ALP	13	-	91.4
	26	-	-
Total cholesterol	13	-21.5	-
	26	-	-
Triglycerides	13	-	-
	26	-	-61.1
Potassium	13	-	-
	26	-	9.6

Urinalysis: Unremarkable

Gross Pathology

Week 13

Small thymus was observed in 1/10 high dose males and 4/10 high dose females.

Week 26

	Male				Female			
Dose (mg/kg/day)	**0**	**5**	**17**	**60/40**	**0**	**5**	**17**	**60/30**
No. Animals	**20**	**20**	**20**	**18**	**20**	**20**	**20**	**19**
Adrenal								

Discoloration, dark	0	0	2	3	0	0	3	5
Discoloration, pale	0	0	0	1	0	0	1	1
Cyst	0	0	0	1	0	0	1	2
Enlargement	0	0	0	0	0	0	0	1
Thymus								
Small	0	0	5	11	0	0	6	19

Organ Weights

Week 26 organ weights (% change from control relative to body weight)						
Organ	**Males**			**Females**		
Dose (mg/kg/day)	**5**	**17**	**60/40**	**5**	**17**	**60/30**
Liver	4.2%	**7.9%**	**11.6%**	4.5%	**17.3%**	**17.0%**
Spleen	9.8%	21.2%	24.8%	9.4%	**25.3%**	**26.5%**
Thymus	7.6%	20.4%	**26.7%**	-2.1%	6.0%	**42.6%**
Thyroid & Parathyroid	0.0%	0.0%	-2.4%	4.8%	9.7%	11.3%

Bold = p < 0.05

Histopathology Adequate battery:

Yes

Week 13

Microscopic findings at Week 13 were similar to those observed in Week 26.

Week 26

	Male				**Female**			
Dose (mg/kg/day)	**0**	**5**	**17**	**60/40**	**0**	**5**	**17**	**60/30**
No. Animals	**20**	**20**	**20**	**18**	**20**	**20**	**20**	**19**
Femur and Marrow								
Hypocellularity, hematopoietic								
minimal to moderate	0	0	4	9	0	0	15	18
Hypoplasia, femoral head								
moderate	0	0	0	0	0	0	0	2
Recovery (+4 weeks, n = 8/sex)								
Hypocellularity, hematopoietic								
minimal	0	0	0	3	0	0	3	6
Sternum and Marrow								
Hypocellularity, hematopoietic								
minimal to mild	0	0	7	19	0	0	10	17

	Recovery (+4 weeks, n = 8/sex)							
	Hypocellularity, hematopoietic							
	minimal	0	0	0	5	0	0	2	5
	mild	0	0	0	1	0	0	0	0
	Thymus								
	Hypocellularity/atrophy, lymphoid								
	minimal to mild	2	4	4	13	6	5	6	19
	moderate	0	0	0	1	0	0	0	2
	Additionally, vacuolar change of the adrenal gland was observed after 26-weeks and was not present in the 13-week study. This finding is considered a common occurence in ageing rats with a sex-related bias towards females; however, an increase in severity (moderate to severe) was observed in 7/20 females and 3/20 males that is potentially drug related.							
Bone Marrow Cell Counts	The M:E ratio was lower in HD males and female rats compared to controls after 26 weeks of dosing due to higher erythroid and lower myeloid counts.							

Study title/ number: R935788 Sodium Salt: A 13 Week and 39 Week Repeat Rose Oral Toxicity Study, Including Toxicokinetics, Followed by 4-Week Recovery Periods in Cynomolgus Monkeys/ G-935788-0005

Key Study Findings

- Treatment related premature deaths of 2 HD (60 mg/kg/day) males occurred on days 69 and 87 that were potentially drug related as a result of hemorrhage in the GI tract, which appeared to be the main organ of toxicity.
- Mild-moderate hematopoietic hypocellularity of the bone marrow was observed in MD and HD males and females at 13 weeks.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: 2.5, 8.5 and 30 mg/kg twice daily
Route of administration: Oral gavage
Formulation/Vehicle: Vehicle: Aqueous solution containing (w/w):

	0.1% sodium carboxymethylcellulose 0.1% methylparaben sodium 0.02% propylparaben sodium and water.
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	13-week: 3/sex/group 39-week: 4/sex/group
Age:	Males: 2 years 6 months – 3 years 9 months Females: 2 years 9 months – 4 years 6 months
Satellite groups/ unique design:	4-week recovery for control and high dose groups: 2/sex/group
Deviation from study protocol affecting interpretation of results:	High dose was lowered from 60 mg/ to 34 mg/kg at week 13. Deviations did not affect the interpretation of study results.

Table 8 Observation and Results of Fostamatinib in Cynomolgus Monkeys at 13/39 Weeks

Parameters	Major findings
Mortality	**60 mg/kg:** 2 animals were prematurely sacrificed due to poor clinical condition. Animals experienced blood loss from GI tract lesions that resulted in severe anemia as evidenced by an 8-fold decrease in RBCs.
Clinical Signs	Observations of thin body condition were made in 3/7 MD females and 2/11 HD females.
Body Weights	HD females had a 6.9% decrease in mean body weight at week 13 relative to study day 1.
Ophthalmoscopy	Unremarkable
ECG	

Heart rate (BPM, % change from control)					
Animal (HD)	**Pre-treatment**	**Week 6**	**Week 13**	**Week 26**	**Week 39**
4103B[a]	-2	-33	-15	-	-
4010H*	6	1	-24	-	-
4111K	-2	-28	-18	0	-7

[a]sacrificed on Day 87 (4103B) and Day 69 (4010H)

Hematology

Findings at 13 weeks were primarily in the HD group and consistent with observations of blood loss and anemia (↓RBC, ↓hemoglobin, ↓hematocrit, ↑platelets, ↑reticulocytes).

Hematology (Week 39, % change from control)					
Parameter	Sex	5	17	60/34	60/34 (recovery)
WBC	M	-4	12	70	29
	F	-16	6	31	-36
RBC	M	-7	-10	-10	-12
	F	1	1	-4	6
Hemoglobin	M	-4	-7	-12	-8
	F	1	1	-4	2
Platelets	M	14	2	31	23
	F	8	1	38	-13
Neutrophil	M	15	55	236	74
	F	-17	24	79	-25
Lymphocyte	M	-17	-19	-49	-8
	F	-18	-18	-28	-43
Reticulocyte	M	-19	19	44	-36
	F	7	17	1	-22

Clinical Chemistry

Week 13: Unremarkable

Week 39: Unremarkable

Urinalysis

Week 39: HD females had increased bacteria, RBCs and protein present in the urine. No correlating histopathological findings in the kidneys were observed.

Gross Pathology

<u>13 week study</u>

HD male 4005C had a small thymus – this correlated with histopathology findings of hypocellularity and atrophy as well as decreased thymus weight. There were no relevant gross pathology findings in 13 week recovery males.

HD F (4607L) had uterus in estrus. This provides evidence that the microscopic finding of interstitial hemorrhage in the ovaries is not adverse in this animal. HD Female 4505C had small thymus but no correlating microscopic findings.

<u>39 week study</u>

HD male 4103B died prematurely on day 87. Gross pathology examination of this animal revealed small thymus along with pale discoloration of multiple organs including kidney, pituitary, cecum, colon, lungs, pancreas, duodenum, ileum and jejunum.

HD Female 4511I had small thymus, which correlated with lymphoid atrophy in the cortical thymus.

Organ Weights

Mean thymus weights (% bodyweight)

Dose (mg/kg/day)	Week 13 M	Week 13 F	Week 39 M	Week 39 F
0	0.110	0.087	0.077	0.058
5	0.152	0.068	0.089	0.075
17	0.171	0.063	0.083	0.066
60/34	0.049	0.047	0.061	0.027
Recovery (+4 weeks)				
0	0.153	0.038	0.054	0.063
60/34	0.129	0.060	0.293	0.070

Histopathology
Adequate battery: Yes

Week 13

	Male				Female			
Dose (mg/kg/day)	**0**	**5**	**17**	**60**	**0**	**5**	**17**	**60**
No. Animals	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**
Femur and Marrow								
Hypocellularity, hematopoietic								
mild	0	0	0	1	0	0	1	2
moderate	0	0	1	1	0	0	0	1
Recovery (+4 weeks, n = 2/sex)								
Hypocellularity, hematopoietic								
minimal	0	-	-	1		-	-	0
mild	0	-	-	1		-	-	2
Ovaries								
Interstitial hemorrhage, multifocal, unilateral								
mild	-	-	-	-	0	0	0	1
Skin and Subcutis								
Thoracic, cyst, multiple								
mild	0	0	0	1	0	0	0	0
Tail, inflammation, subacute, multifocal, with bacteria								
moderate	0	0	0	1	0	0	0	0
Thymus								
Cyst, multiple								
mild	0	0	0	0	0	0	0	1
Hypocellularity/atrophy, lymphoid								
minimal	0	0	0	1	0	0	0	0
Recovery (+4 weeks, n = 2/sex)								
Cyst, multiple								
mild	0	-	-	0	1	-	-	0

Hypocellularity/atrophy, lymphoid								
minimal	0	-	-	0	0	-	-	1

Week 39

	Male				Female			
Dose (mg/kg/day)	**0**	**5**	**17**	**60/34**	**0**	**5**	**17**	**60/34**
No. Animals	**4**	**4**	**4**	**4**	**4**	**4**	**4**	**4**
Colon								
Necrosis, glandular, mucosal, multifocal								
mild	0	0	0	0	0	0	0	1
Pigmented material, luminal, crystalline to proteinaceous								
mild	0	0	0	1	0	0	0	0
Femur and Marrow								
Hypocellularity, hematopoietic								
minimal	0	0	0	0	0	0	0	1
mild	0	0	0	0	0	0	0	1
Liver								
Histiocytic accumulation, intrasinusoidal, multifocal								
mild	0	0	0	0	0	0	0	1
Ovaries								
Cyst, paraovarian, unilateral								
mild	-	-	-	-	0	0	0	1
Prostate								
Inflammation, interstitial, subacute, multifocal								
mild	0	0	0	1	-	-	-	-
Inflammation, intra-acinar, acute, multifocal								
mild	0	0	0	1	-	-	-	-
Duodenum								
Lacteal dilation								
moderate	0	0	0	1	0	0	0	0
Recovery (+4 weeks, n = 2/sex)								
Lacteal dilation								
moderate	0	-	-	1	0	-	-	0

Ileum								
Lacteal dilation								
moderate	0	0	0	1	0	0	0	0
Recovery (+4 weeks, n = 2/sex)								
Lacteal dilation								
moderate	0	-	-	1	0	-	-	0
Jejunum								
Lacteal dilation								
moderate	0	0	0	1	0	0	0	0
Recovery (+4 weeks, n = 2/sex)								
Lacteal dilation								
moderate	0	-	-	1	0	-	-	0
Thymus								
Atrophy, lymphoid, cortical								
minimal	0	0	0	1	0	0	1	1
mild	0	0	0	0	1	0	0	1
Hemorrhage, focal, acute								
minimal	0	1	0	1	0	0	0	0
Hemorrhage, multifocal, acute								
minimal	0	0	0	1	0	0	0	0
Transformation, cystic, medullary, focal								
mild	0	0	0	0	0	0	0	1
Recovery (+4 weeks, n = 2/sex)								
Atrophy, lymphoid, cortical								
moderate	0	-	-	1	0	-	-	0

Bone Marrow Cell Counts

	Mean total cell count ($x10^6$)			
	Week 13		Week 39	
Dose (mg/kg/day)	M	F	M	F
0	234	387	128	236
5	369	221	142	71
17	128	96*	79	141
60/34	76	21**	55	56
Recovery (+4 weeks)				
0	145	142	96	14
60/34	69	67	88	29

*p < 0.05; **p < 0.01

LD: low dose; MD: mid dose; HD: high dose.
-: indicates reduction in parameters compared to control.

General toxicology; additional studies

Study title/ number: R940406 Besylate: A 28-Day Repeat Dose Oral Toxicity (Including Immunotoxicology Assessment) Study Followed by a 14-Day Recovery Period in Sprague-Dawley Rats/ G-940406-0004

R406 was administered to Sprague-Dawley rats at 10, 30, or 100 mg/kg/day in a single daily dose by oral gavage for 28 consecutive days with a 14 day recovery period. At 30 and 100 mg/kg/day, reduction the WBC and lymphocyte absolute and relative counts (more pronounced in females), elevation of AST and ALT, decreased CD3+ and CD45RA+ cell numbers, decreased spleen and thymus weight, minimal to mild hypocellularity of femur and sternum marrow, reduced bone marrow cell counts were observed.

Study title/ number: Fostamatinib disodium (R935788): One Month Toxicity Study in the Juvenile Rabbit/ 0306JB

R788 was administered to New Zealand white rabbits at 10, 30 or 60 mg/kg/day by oral gavage twice daily for 1 month. An HD male was prematurely sacrificed *in extremis* and was found to have fractured femur heads due to growth plate dysplasia. Growth plate dysplasia was observed in the proximal femur and femoro-tibial joint of animals treated with ≥ 30 mg/kg/day fostamatinib. Dysplasia was characterized by thickening, fissuring and fracturing of the growth plate due to hypertrophic chondrocytes that was accompanied by hemorrhage into the bone marrow in severe cases.

Females presented with degenerate/necrotic ovarian follicles at all dose levels. Other study findings were consistent with previously described toxicities of the lymphohematopoietic system (reduced spleen and thymus weights, reduced lymphocytes, and femur and sternum marrow hypocellularity).

5.5.2. Genetic Toxicology

<u>In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)</u>
Study title/ number: GLP Bacterial Reverse Mutation Assay of R788 Sodium Salt/ G-935788-0009
Key Study Findings:

- Compound was negative for mutagenicity in all strains at concentrations from 50 to 5000 µg/plate with and without S9 metabolic activation.

GLP compliance: Yes
Test system: TA98, TA100, TA1535, TA1537, and WP2 uvrA up to 5000 ug/plate; +/- S9
Study is valid: Yes

Study title/ number: GLP Bacterial Reverse Mutation Assay of R940406 Besylate / G-940406-0006

Key Study Findings:

- Compound was negative for mutagenicity in all strains at concentrations from 50 to 5000 µg/plate with and without S9 metabolic activation.

GLP compliance: Yes
Test system: TA98, TA100, TA1535, TA1537, and WP2 uvrA up to 5000 ug/plate; +/- S9
Study is valid: Yes

In Vitro Assays in Mammalian Cells

Study title/ number: LP In Vitro Mammalian Chromosome Aberration Test of R940406 Besylate / G-940406-0007

Key Study Findings:

- R940406 besylate was negative for the induction of structural and numerical chromosome aberrations at concentrations from 50 to 500 µg/mL with and without S9 metabolic activation.

GLP compliance: Yes
Test system: Human peripheral blood lymphocytes up to 500 µg/mL ± rat S9.
Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: Mammalian Erythrocyte Micronucleus Test with R940406 Besylate / G-940406-0008

Key Study Findings:

- R940406 besylate did not induce a biologically significant increase in the number of micronucleated polychromatic erythrocytes in bone marrow of male and female ICR mice at doses of 20, 60, or 200 mg/kg. In this regard, R940406 besylate did not demonstrate evidence of clastogenic activity and was concluded to be negative in the mouse micronucleus test.

GLP compliance: Yes
Test system: Cells of the bone marrow from the femur (5 per sex per treatment) of mice (ICR) were assessed for micronuclei in 2000 polychromic erythrocytes 24-48 hours after the oral administration of a single dose at 0, 20, 60 or 200 mg/kg of R406.
Study is valid: Yes

5.5.3. Carcinogenicity

The carcinogenic potential of fostamatinib was investigated in 104-week studies conducted in Crl:CD1(ICR) mice and Crl:CD(SD) rats. In mice, fostamatinib was administered at doses of 50, 150, 500/250, or 1200 mg/kg/day. In rats, fostamatinib was administered at doses of 10, 25, 45, and 80 mg/kg/day in males and 5, 12, 24 and 40 mg/kg/day in females. The studies were conducted under a special protocol agreement (SPA) with concurrence from the executive carcinogenicity advisory committee (ECAC). In both species, the FDA survival analysis showed a statistically significant dose response relationship in mortality in males and females when compared to controls. No tumor findings achieved statistical significance in either sex or species.

5.5.4. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: Fertility and General Reproduction Toxicity Study of R935788 Na Administered Orally (Gavage) (b.i.d.) in Rats/ G-935788-0008

Key Study Findings

- A decrease in the number of pregnancies in HD (25 mg/kg/day) female rats (-20% vs. controls).
- In female rats, pre-implantation loss percentage was increased vs. controls at all dose levels.
- Decreased fertility rates were attributed to female rats. No effects of toxicological significance were observed in males and sperm parameters were unaffected by drug administration.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	Animals were dosed twice daily. Total dose levels were 5, 14, or 40 mg/kg/day (males) and 5, 11, or 25 mg/kg/day (females).
Route of administration:	Oral gavage
Formulation/Vehicle:	0.1% Carboxymethylcellulose Na 0.1% Methylparaben Na 0.02% Propylparaben Na
Species/Strain:	Sprague-Dawley rats; Crl:CD(SD)
Number/Sex/Group:	25/sex/group
Satellite groups:	Toxicokinetic animals, n = 4/sex/group
Study design:	(1) Treated animals were mated with treated

animals. 1 male rat was coupled with 1 female rat in the cohabitation phase.
(2) Male rats: Test article was administered 2x daily starting 28 days before cohabitation and continued through the cohabitation period until the day before sacrifice.
(3) Female rats: Test article was administered 2x daily starting 15 days before cohabitation and continued through day 7 of presumed gestation (DG7).
(4) Cohabitation period consisted of a maximum of 11 days.
(5) Female rats with spermatozoa observed in a smear of the vaginal contents and/or a copulatory plug in situ were considered to be at DG0 and assigned to individual housing.
(6) Female rats were sacrificed on DG13 and offspring removed by Caesarean section.

Deviation from study protocol affecting interpretation of results: No

Table 9 Observations and Results of FEED Study in Rats

Parameters	Major findings
Mortality	One control female rat was sacrificed on study day 17 due to a fractured hard palate.
Clinical Signs	Apparent treatment related clinical signs in males included chromorhinorrhea, chromodacryorrhea and dehydration. Potential treatment related clinical signs in females were limited to misaligned and missing/broken incisors in HD females only.
Body Weights	Unremarkable
Necropsy findings	There were no significant treatment related effects on male sperm count or motility. A decrease in pregnant dams was observed at the HD and an increase in preimplantation loss was observed at all doses when compared to control and was statistically significant at the MD (p≤0.01).

Litter data (mean ± SD)				
Dose (mg/kg/day)	0	5	11	25
Pregnant	24/24	25/25	24/25	20/25
Corpora Lutea	16.0 ± 1.8	17.0 ± 1.5	17.0 ± 2.3	17.2 ± 1.5
Implantations	15.7 ± 1.6	16.0 ± 1.4	15.7 ± 2.0	16.4 ± 1.5
Preimplantation loss	2.0 ± 3.3	5.6 ± 7.5	7.6 ± 7.5*	4.3 ± 3.2
Postimplantation loss	10.0 ± 11.4	4.2 ± 4.4	9.2 ± 7.8	14.4 ± 11.4

Embryo-Fetal Development

Study title/ number: Oral Gavage Study for Effects on Embryo-Fetal Development and Toxicokinetic Study with R935788 Na in Rats/ G-935788-0007

Key Study Findings

- R935788 Na was teratogenic in rats based upon soft tissue malformations in the heart and kidneys at the HD and skeletal malformations in the vertebrae at the MD and HD and ribs at the HD.
- R935788 Na caused embryofetal lethality and decreased fetal body weight at the HD.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	Animals were dosed twice daily. Total dose levels were 5, 12.5, or 25 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	0.1% carboxymethylcellulose sodium salt 0.1% methylparaben sodium 0.02% propylparaben sodium
Species/Strain:	Premated Female Crl:CD®(SD) IGS BR rats
Number/Sex/Group:	25/F/group
Satellite groups:	Toxicokinetics 6/F/group
Study design:	(1) Time-mated female rats were mated at the Supplier (b) (4) The day that each female was confirmed to be sperm positive was designated as Gestation Day 0 (GD 0). Females were received at the testing laboratory ((b) (4) prior to GD 4. (2) Animals were dosed twice daily from GD 6 – GD 17 (3) On GD 20, main study females were sacrificed and the fetuses removed by Caesarean section.
Deviation from study protocol affecting interpretation of results:	No

Table 10 Observations and Results of EFD Study in Rats

Parameters	Major findings
Mortality	Unremarkable
Clinical Signs	Unremarkable
Body Weights	A significant decrease in maternal body weight gain was observed in the HD group that is potentially driven by a significant decrease in gravid uterus weight.

Uterine and body weight (% relative to control)			
Dose (mg/kg/day)	**5**	**12.5**	**25**
Body weight gain	100%	101%	88%
Gravid uterus weight	97%	95%	78%
Body weight (-uterus)	99%	101%	98%

Necropsy findings Cesarean Section Data

Dose (mg/kg/day)	0	5	12.5	25
Pregnant at C-section	25	24	22	23
Resorptions				
Total (Mean ± SD)	0.6 ± 0.7	0.5 ± 1.0	1.0 ± 1.5	2.2 ± 2.6
Early (Mean ± SD)	0.5 ± 0.7	0.5 ± 1.0	0.9 ± 1.5	2.1 ± 2.6
Late (Mean ± SD)	0.0 ± 0.2	0.0 ± 0.0	0.0 ± 0.2	0.1 ± 0.3
Nonviable fetuses (Total)	0	0	0	0
Postimplantation loss (Mean % ± SD)	3.9 ± 4.9	3.3 ± 7.4	6.8 ± 11.3	15.1 ± 18.3

Necropsy findings Offspring

Fetal weights (Mean ± SD)				
Dose (mg/kg/day)	**0**	**5**	**12.5**	**25**
Male	3.97 ± 0.28	3.85 ± 0.36	3.84 ± 0.29	3.35 ± 0.24**
Female	3.75 ± 0.31	3.65 ± 0.30	3.63 ± 0.24	3.16 ± 0.22**

**p < 0.01 for covariate adjusted mean v. control

Significant fetal soft tissue variations (%)				
Dose (mg/kg/day)	**0**	**5**	**12.5**	**25**
Absent innominate artery				
Fetal incidence	0.0	1.2	0.7	7.9**
Litter incidence	0.0	8.3	4.5	35**
Increased renal pelvic cavitation				
Fetal incidence	0.0	0.0	0.0	18**
Litter incidence	0.0	0.0	0.0	65**
Dilated ureter				
Fetal incidence	1.2	0.0	0.7	23**

Litter incidence	8.0	0.0	4.5	74**
Total variations				
Fetal incidence	1.2	1.2	1.4	32**
Litter incidence	8.0	8.3	9.1	78**

**p < 0.01

Significant fetal head variations (%)				
Dose (mg/kg/day)	0	5	12.5	25
Dilated lateral ventricle				
Fetal incidence	1.2	3.7	2.7	8.6**
Litter incidence	8.0	21.0	18.0	43**

**p < 0.01

Significant fetal soft tissue malformations (%)				
Dose (mg/kg/day)	0	5	12.5	25
Heart and/or great vessel malformations				
Fetal incidence	0.0	0.0	0.0	16**
Litter incidence	0.0	0.0	0.0	65**
Renal agenesis				
Fetal incidence	0.0	0.0	0.0	16**
Litter incidence	0.0	0.0	0.0	57**
Total malformations				
Fetal incidence	0.0	0.6	0.0	27**
Litter incidence	0.0	4.2	0.0	74**

**p < 0.01

Significant fetal skeletal variations (%)				
Dose (mg/kg/day)	0	5	12.5	25
25 presacral vertebrae				
Fetal incidence	0.0	0.6	4.3**	5.1**
Litter incidence	0.0	4.2	18**	22**
13th rudimentary rib				
Fetal incidence	0.0	3.1*	5.0**	12**
Litter incidence	0.0	21*	32**	57**
Wavy/bent ribs				
Fetal incidence	0.6	1.9	6.4**	5.8**
Litter incidence	4.0	8.3	14.0	35**

*p < 0.05; **p < 0.01

Significant fetal skeletal malformations (%)				
Dose (mg/kg/day)	0	5	12.5	25
Vertebral anomaly				
Fetal incidence	0.0	0.6	2.1	2.9*

	Litter incidence	0.0	4.2	14	17*
	Total malformations				
	Fetal incidence	0.6	1.3	2.8	5.1*
	Litter incidence	4.0	8.3	18	30*

*p < 0.05

LD: low dose; MD: mid dose; HD: high dose

Study title/ number: R935788 Na: Embryo-fetal developmental study in rabbits via oral administration/ G-935788-0006

Key Study Findings

- R935788 Na was teratogenic in rabbits based upon soft tissue malformations that included absent kidney, ureter, uterus, and vas deferens at the MD and/or HD and skeletal malformations in the skull at the HD.
- R935788 Na caused embryofetal lethality and decreased fetal body weight at the HD.
- One HD female died prematurely on GD16 and 2 HD females delivered their litters prematurely (prior to euthanasia on GD29).

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Methods

Dose and frequency of dosing: Animals were dosed twice daily. Total dose levels were 10, 22, or 50 mg/kg/day

Route of administration: Oral gavage

Formulation/Vehicle: 0.1% carboxymethylcellulose sodium salt
0.1% methylparaben sodium
0.02% propylparaben sodium

Species/Strain: Time mated New Zealand White [Hra:(NZW)SPF] rabbits

Number/Sex/Group: 23/F/group

Satellite groups: Toxicokinetics 4/F/group

Study design: (1) Time-mated female rabbits ((b) (4)) were approximately 5-5.5 months of age upon arrival (GD0). Animals arrived on the day evidence of mating was observed.

(2) Animals were dosed twice daily from GD7 – GD19.

(3) TK animals were administered the first dose

only onGD29.

(4) On GD29, all main study animals were euthanized and immediately subject to Caesarean section.

Deviation from study protocol affecting interpretation of results: No

Table 11 Observations and Results of EFD Study in Rabbits

Parameters	Major findings
Mortality	One death in the HD group was considered potentially drug related. Two additional deaths, one in the HD group and one in the MD TK group were considered dosing-related errors.
Clinical Signs	Unremarkable
Body Weights	Gravid uterine weight in the HD group was significantly ($p < 0.05$) decreased when compared to controls (0.406 v. 0.479 kg)
Necropsy findings Cesarean Section Data	2/23 pregnant females in the HD group (#283 and #285) delivered their litters on GD29 prior to scheduled euthanasia.

Dose (mg/kg/day)	0	10	22	50
Pregnant at C-section	23	23	23	19
Resorptions				
Total (Mean ± SD)	0.3 ± 0.78	0.5 ± 1.5	0.4 ± 0.66	2.2 ± 1.98**
Early (Mean ± SD)	0.2 ± 0.65	0.5 ± 1.5	0.2 ± 0.52	0.6 ± 0.76
Late (Mean ± SD)	0.2 ± 0.49	0.0 ± 0.0	0.2 ± 0.52	1.5 ± 1.90*
Nonviable fetuses (Total)	0	0	0	0
Postimplantation loss (Mean % ± SD)	4.09 ± 9.03	5.61 ± 15.3	4.20 ± 6.15	22.3 ± 19.8**

Necropsy findings Offspring

Fetal weights (Mean ± SD)				
Dose (mg/kg/day)	0	10	22	50
Male	40.6 ± 5.0	40.2 ± 5.0	41.9 ± 3.8	35.1 ± 4.3**
Female	40.3 ± 5.1	39.6 ± 6.2	40.0 ± 5.0	34.0 ± 4.0**

**$p < 0.01$

Significant fetal soft tissue variations (%)				
Dose (mg/kg/day)	0	10	22	50
Innominate artery, absent				
Fetal incidence	0.0	0.0	8.7	26.3**
Litter incidence	0.0	0.0	1.0	12
Subclavian artery, retroesophageal				

Fetal incidence	0.0	0.0	17.4	42.1**
Litter incidence	0.0	0.0	2.4	18.3

**p < 0.01

Significant fetal visceral malformations (%)				
Dose (mg/kg/day)	**0**	**10**	**22**	**50**
Kidney, absent				
Fetal incidence	0.0	0.0	8.7	52.6**
Litter incidence	0.0	0.0	1.0	15.5
Ureter, absent				
Fetal incidence	0.0	0.0	8.7	57.9**
Litter incidence	0.0	0.0	1.0	16.9
Uterus, absent				
Fetal incidence	0.0	0.0	4.3	42.1**
Litter incidence	0.0	0.0	0.5	9.2
Vas deferens, absent				
Fetal incidence	0.0	0.0	0.0	26.3*
Litter incidence	0.0	0.0	0.0	5.6

*p < 0.05; **p < 0.01

Significant fetal skeletal variations (%)				
Dose (mg/kg/day)	**0**	**10**	**22**	**50**
Cervical vertebrae, centra, hemicentric				
Fetal incidence	0.0	4.3	8.7	36.8**
Litter incidence	0.0	0.5	1.0	7.0
Skull, frontal bone, additional ossification center				
Fetal incidence	0.0	0.0	13.0	31.6**
Litter incidence	0.0	0.0	1.4	5.6

**p < 0.01

Significant fetal skeletal malformations (%)				
Dose (mg/kg/day)	**0**	**10**	**22**	**50**
Skull, frontal bone, accessory skull bone				
Fetal incidence	0.0	0.0	0.0	21.1*
Litter incidence	0.0	0.0	0	2.8

*p < 0.05

LD: low dose; MD: mid dose; HD: high dose

Prenatal and Postnatal Development

Study title/ number: Developmental and Perinatal/Postnatal Reproduction Toxicity Study of R935788 Na Administered Orally (Gavage) (b.i.d.) in Rats, Including a Postnatal Behavioral/Functional and Developmental Immunotoxicity Evaluation/ G-935788-0014

Key Study Findings

- Maternal toxicity in the F0 generation was evidenced by dehydration, decreased bodyweights, and decreased feed consumption in the 25 mg/kg/day group.
- At maternal doses ≥ 12.5 mg/kg/day, F1 generation toxicities included neonatal mortality, decreased body weights, and decreased feed consumption, with delayed sexual maturation and urogenital malformations observed at maternal doses of 25 mg/kg/day.
- There were no adverse findings in behavioral/functional or immunotoxicological evaluations of the F1 progeny.

Conducting laboratory and location:	(b) (4)
GLP compliance:	Yes

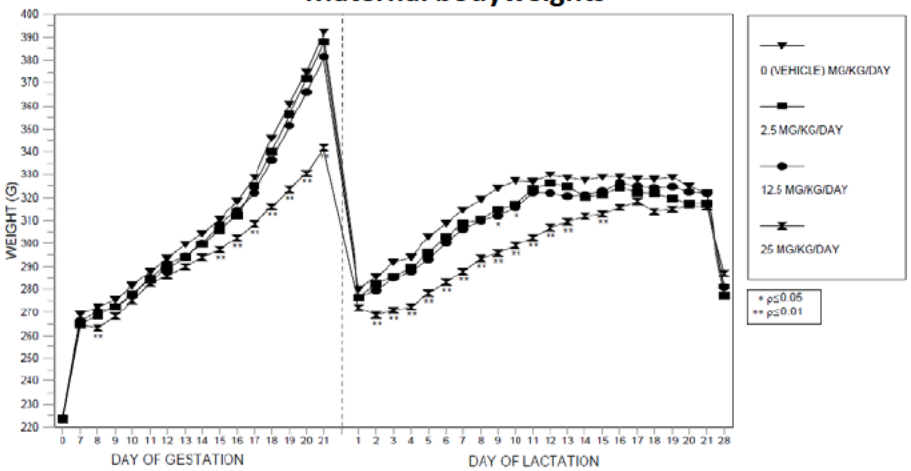
Methods

Dose and frequency of dosing:	Animals were dosed twice daily. Total dose levels were 2.5, 12.5, or 25 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	0.1% carboxymethylcellulose sodium salt 0.1% methylparaben sodium 0.02% propylparaben sodium
Species/Strain:	Crl:CD(SD) Rats
Number/Sex/Group:	25/F/group
Satellite groups:	Toxicokinetics 4/F/group
Study design:	(1) F0 generation rats were dosed twice daily from GD 7 – Day of Lactation (DL)_20 and sacrificed on DL 28. (2) F1 generation pups were not directly administered fostamatinib or vehicle. (3) F1 generation pups designated for histopathology or not selected for further evaluation were sacrificed on DL 14 and gross necropsy of the thoracic, abdominal and pelvic viscera was performed. (4) F1 generation dams were sacrificed on GD 21 and Caesarean-sectioned. (5) F2 fetuses were weighed and examined for gross external and soft tissue alterations and sex.
Deviation from study protocol affecting interpretation of results:	No

Table 12 Observation and Results of PPND Study in Rats

Generation	Major Findings
F0 Dams	

Maternal bodyweights



Feed consumption (mean ± SD)				
Dose (mg/kg/day)	**0**	**2.5**	**12.5**	**25**
Absolute (g/day)				
GD 0-20	24.8 ± 2.0	24.5 ± 1.8	24.0 ± 1.6	23.4 ± 1.7**
DL 1-14	52.9 ± 5.7	50.7 ± 7.7	48.9 ± 9.1	37.2 ± 9.9**
Relative (g/kg/day)				
GD 0-20	81.9 ± 3.9	81.9 ± 4.5	80.2 ± 2.8	81.2 ± 3.8
DL 1-14	170.1 ± 16.8	165.4 ± 21.1	160.9 ± 27.2	128.3 ± 33.5**

*p < 0.05; **p < 0.01 (throughout table)

F1 Generation

Pup Viability (%)				
Dose (mg/kg/day)	**0**	**2.5**	**12.5**	**25**
Pups delivered (mean ± SD)	13.9 ± 1.8	13.8 ± 2.4	13.7 ± 1.8	10.2 ± 4.0**
Viability index[a]	98.9	99.2	97.9	74.3**
Lactation index[b]	99.4	99	94.34	86.6**

[a]Number of live pups on day 4 postpartum/number of liveborn pups on day 1 postpartum

[b]Number of live pups on day 21 (weaning) postpartum/number of live pups on day 4 postpartum

Bodyweight (g, mean ± SD)				
Dose (mg/kg/day)	**0**	**2.5**	**12.5**	**25**
Day 1	6.9 ± 0.6	6.8 ± 0.7	6.3 ± 0.5**	6.2 ± 0.8**
Day 21	43.0 ± 6.0	40.0 ± 6.7	37.9 ± 7.4*	34.6 ± 7.8**

Clinical observations (total frequency / litters with observations)

Dose (mg/kg/day)	0	2.5	12.5	25
Edema	0/0	0/0	0/0	2665/23**
White or purple	5/3	0/0	1/1	173/16**
Dehydration, total	4/3	5/3	47/4	104/10**
mild	3/3	1/1	16/4	27/7
moderate	1/1	2/2	31/4	40/6
severe	0/0	2/2	0/0	37/2
Cold to touch	5/2	0/0	7/3	23/6**
Whole body, pale	0/0	0/0	1/1	22/7**
Discoloration	0/0	0/0	0/0	5/3**

Necropsy observations (%)				
Dose (mg/kg/day)	0	2.5	12.5	25
Kidney, left, absent				
Litter incidence	0	0	0	23.1**
Pup incidence	0	0	0	9.8**
Kidney, pelvis, extreme dilation				
Litter incidence	0	0	0	23.1**
Pup incidence	0	0	0	7.3**
Kidney, right, cysts				
Litter incidence	0	0	0	7.7
Pup incidence	0	0	0	2.4**
Ureter, marked dilation				
Litter incidence	0	0	0	23.1**
Pup incidence	0	0	0	7.3**
Diaphragmatic hernia				
Litter incidence	0	0	0	7.7
Pup incidence	0	0	0	2.4**

Sexual maturation (mean ± SD)				
Dose (mg/kg/day)	0	2.5	12.5	25
Preputial separation	45.5 ± 2.7	45.5 ± 2.0	45.7 ± 2.0	48.3 ± 3.8**
Bodyweight at separation (g)	235.4 ± 17.4	226.4 ± 18.0	220.5 ± 22.5	220.6 ± 28.8
Vaginal patency	33.5 ± 1.5	33.7 ± 1.6	34.8 ± 2.1	36.2 ± 3.5**
Bodyweight at patency (g)	109.0 ± 13.2	106.3 ± 9.4	107.0 ± 13.4	99.9 ± 11.0*

F2 Generation

Litter observations (mean ± SD)				
Dose (mg/kg/day)	0	2.5	12.5	25
Implantation	14.5 ± 3.7	15.8 ± 2.4	14.1 ± 3.2	11.9 ± 3.7*
Live fetuses	13.9 ± 3.8	14.9 ± 2.9	13.3 ± 3.3	11.4 ± 3.6**
Fetal bodyweight (g)	5.33 ± 0.26	5.32 ± 0.33	2.39 ± 0.25	5.61 ± 0.27**

5.5.5. Other Toxicology Studies

Impurity Qualification

Based on the 39-week repeat dose toxicity study conducted in cynomolgus monkeys, the following impurities were qualified above the ICH Q3A qualification threshold of ≤ 0.15% for new drug substances.

Table 13 Drug Substance Impurity Qualification

Impurities	Impurity level in tox study batch	Qualified percentage of impurity at MRHD
		(b) (4)

X X

Brian Cholewa, PhD
Primary Reviewer

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Team Leader

6 Clinical Pharmacology

6.1. Executive Summary

Fostamatinib (fostamatinib disodium hexahydrate) is an immediate-release tablet intended for the treatment of immune thrombocytopenic purpura (ITP). It is a prodrug that is converted into the major active metabolite, R406. The proposed indication is to treat adult patients with persistent or chronic ITP who have had an insufficient response to a previous treatment. The proposed dosing regimen is 100 mg taken orally twice daily (BID) initially. Dose can be increased to 150 mg BID after 4 weeks if platelet count has not increased to ≥ 50 x 10^9/L (or 50,000/µL).

The clinical efficacy is demonstrated by the data obtained from three phase 3 studies, where a consistent stable platelet response rate (18%) was observed across studies for the fostamatinib-treated subjects comparing to placebo arm. Exposure-response (E-R) relationship for Week 12 response (platelet count ≥50 x 10^9/L) supported the effectiveness of fostamatinib in patients with ITP. Fostamatinib-induced hypertension was observed and it has a significant relationship with R406 exposure.

Fostamatinib dose should be reduced when concomitantly used with a strong CYP3A inhibitor due to the potential safety concern as the mean exposure (AUC) of R406 was doubled when fostamatinib was co-administered with ketoconazole. Avoid concomitant use of strong CYP3A inducer due to the concern of loss of efficacy as the mean AUC of R406 was decreased by 75% when fostamatinib was co-administration with rifampicin.

6.1.1. Recommendations

The Office of Clinical Pharmacology Division of Clinical Pharmacology V and Pharmacometrics have reviewed the information contained in NDA 209299. This NDA is approvable from a clinical pharmacology perspective, and the Applicant and the Agency come to a mutually satisfactory agreement regarding the labeling language.

Review Issue	Recommendations and Comments
Pivotal and Supportive evidence of effectiveness	The primary efficacy results from two randomized phase 3 Studies C788-047 and C788-048 showed a stable platelet response rate (18%) for the fostamatinib-treated subjects. Moreover, extension phase 3 Study C788-049 showed a consistent stable response rate of 19.5% for 40 placebo non-responders that rolled over from Studies C788-047 and C788-048. Of note, the treatment difference was statistically significant in Study C788-047 but not in Study C788-048 as

	there was one responder in the placebo arm in the later study.
General dosing instructions	The clinical efficacy of the proposed dose of fostamatinib was supported by E-R relationship for Week 12 response (platelet count ≥50 x 10^9/L). Daily AUC following 100 mg BID is projected to have response in ~20% of subjects.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• A dose reduction is recommended when concomitantly taking a strong CYP3A inhibitor. • Avoiding concomitant use with fostamatinib is recommended when concomitantly taking a strong CYP3A inducer.
Bioequivalence between the tablets used in phase 3 studies and the commercial tablets	The commercial 150 mg orange film coated (OFC) fostamatinib tablets manufactured by Patheon are bioequivalent to the 150 mg OFC-I fostamatinib tablets manufactured by AZ used in efficacy and safety Studies C788-047 and C788-048.

6.1.2. Post-Marketing Requirements and Commitments

None

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Fostamatinib is a kinase inhibitor with demonstrated activity against spleen tyrosine kinase (SYK). Fostamatinib is a prodrug that is converted to the major active metabolite, R406, in the gut. R406 reduces antibody-mediated destruction of platelets.

Fostamatinib tablet formulations are available at 100 mg or 150 mg for oral administration. The commercial 150 mg OFC tablet is bioequivalent to the 150 mg OFC-I tablet manufactured by AZ. The mean ratios (90% CI) of Cmax and AUC0-inf comparing the commercial vs. AZ tablet were 94.27 (82.23, 108.08) and 99.11 (91.42, 107.45), respectively.

Absorption: The median Tmax is 1.5 hours with a range of 0.5 to 6 hours after a single 150 mg dose. R406 exposure was approximately dose proportional in the single dose range of fostamatinib 50 to 300 mg and repeated dose up to 200 mg BID. The accumulation ratio of approximately 2 to 3 folds was observed at steady state following BID dosing at 50-160 mg. A high fat meal did not significantly alter the exposure to R406.

Distribution: The mean (±SD) apparent volume of distribution is 256 (±92) L at steady state. In vitro protein binding is approximately 98%.

Metabolism: Fostamatinib is metabolized in the gut by alkaline phosphatase to the major active metabolite, R406. R406 is extensively metabolized, primarily through pathways of CYP3A4 and glucuronidation by UGT1A9.

Excretion: The mean (± SD) elimination half-life is 15 ± 4.3 hours after a single dose of fostamatinib 150 mg. Approximately 80% of the R406 metabolite is excreted in feces with 20% excreted in the urine.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The proposed initial fostamatinib dose is 100 mg BID, orally, without regard to food. If platelet count is increased to ≥ 50 x 109/L at after 4 weeks of treatment, dose is to increase to 150 mg BID. The clinical efficacy of fostamatinib based on the data from 3 Phase 3 studies (Study C788-047, C788-048 and C788-049) showed a consistent stable platelet response rate of 18% across studies. Half of the stable responders continually received the initial dose 100 mg BID without dose escalation, although dose was increased to 150 mg BID in 86% of patients after Week 4. In addition, exposure-response analysis showed that the R406 exposure following fostamatinib 100 mg BID has approximately 20% of probability of increasing platelet count to ≥ 50 x 109/L. A significant relationship between R406 exposure and fostamatinib-induced hypertension was observed in the E-R analysis for blood pressure.

Therapeutic Individualization

Hepatic Impairment: Based on the results of a dedicated hepatic impairment (HI) study, no dose adjustment is required for patients with mild (Child-Pugh class A), moderate (Child-Pugh class B) and severe (Child-Pugh class C) HI.

Renal Impairment: Based on the results of a dedicated renal impairment (RI) study with reduced design, no dose adjustment is required for patients with RI including patients with end stage renal disease (ESRD).

CYP3A Inhibitors: Based on the clinical data, it is recommended to reduce the fostamatinib dose if a strong CYP3A inhibitor must be co-administered.

CYP3A Inducers: Based on the clinical data, it is recommended to avoid concomitant use of strong CYP3A inducers as decreased efficacy can occur.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

The clinical pharmacology and pharmacokinetics characteristics of fostamatinib tablet formulation are summarized in the following table.

Pharmacology	
Mechanism of Action	Fostamatinib is a kinase inhibitor with demonstrated activity against spleen tyrosine kinase (SYK). The major active metabolite of fostamatinib, R406, inhibits signal transduction of Fc-activating receptors. R406 reduces antibody-mediated destruction of platelets.
QT Prolongation	Fostamatinib did not prolong the QT interval to a clinically relevant extent at two times the maximum recommended dose.
General Information	
Commercial 150 mg OFC tablet vs. AstraZeneca (AZ) manufacture 150 mg OFC-I tablet	The commercial 150 mg OFC tablet is bioequivalent to the 150 mg OFC-I tablet manufactured by AZ. The mean ratios (90% CI) of C_{max} and $AUC_{0\text{-}inf}$ comparing the commercial vs. AZ tablet were 94 (82, 108) and 99 (91, 107), respectively.
Drug exposure following a single dose and at steady state	Fostamatinib is a prodrug that is converted in the gut to the major active metabolite, R406. Mean exposure of R406 were 550 ng/mL for C_{max} and 7080 ng*h/mL for $AUC_{0\text{-}inf}$ after a single dose of 150 mg fostamatinib in healthy subjects. Mean $AUC_{0\text{-}12hour}$ and C_{max} of R406 at steady state were 769 ng/mL and 5120 ng*h/mL, respectively, after multiple doses of 150 mg fostamatinib BID in ITP patients.
Absorption	
T_{max} (oral)	Median value of 1.5 hours with a range of 0.5 to 6 hours following a single dose of 150 mg
Accumulation	Accumulation ratio of approximately 2 to 3 folds at steady state following BID dosing at 50-160 mg
Dose proportionality	R406 exposure is approximately dose proportional following a single dose ranging 50 to 300 mg of fostamatinib and multiples doses up to 200 mg BID of fostamatinib. C_{max} and AUC of R406 were slightly higher than dose proportional at fostamatinib doses above 200 mg BID.
Food effect	Mean (90% CI) AUC and C_{max} was increased by approximately 23% (2% to 49%) and 15% (-11% to 48%) after a high fat meal, while T_{max} was delayed by 1.5 hours.
Distribution	
Volume of Distribution	Mean (±SD) value of 256 ± 92 L at steady state
Plasma Protein Binding	~ 98%
Substrate transporter	R406 is a substrate of P-gp.

systems (*in vitro*)	
Elimination	
Terminal elimination half-life	Mean (± SD) half-life of 15 (±4) hours after a single dose of fostamatinib 150 mg
Clearance	Mean (± SD) clearance of 16 (±5) L/h
Metabolism	
Primary metabolic pathway (*in vitro*)	Fostamatinib is metabolized in the gut by alkaline phosphatase to the major active metabolite, R406. R406 is extensively metabolized, primarily through pathways of CYP3A4 and glucuronidation by UGT1A9.
Inhibitor/Inducer (*in vitro*)	• R406 can inhibit CYP3A4, BCRP, and UGT1A1, and can induce CYP2C8 activity. • Fostamatinib is an inhibitor of P-gp
Excretion	
Primary excretion pathways	Following a ^{14}C-fostamatinib oral dose of 150 mg, approximately 80% of the R406 metabolite is excreted in feces with 20% excreted in the urine. The major component excreted in urine was R406 N-glucuronide. The major components excreted in feces were R406, O-desmethyl R406 and a metabolite produced by gut bacteria from the O-desmethyl metabolite of R406.

Fostamatinib Formulation Development

A [redacted] (b) (4) oral solution of R406 was first developed and followed by the development of an oral suspension in orange juice of fostamatinib [redacted] (b) (4) in first-in-human studies. However, neither was suitable for phase 2 studies and beyond. Subsequently, tablet formulations with fostamatinib disodium were developed and used in all subsequent clinical programs.

Fostamatinib 25 mg [redacted] (b) (4)% w/w white [redacted] (b) (4) tablets were initially developed and used in the phase 2 studies of ITP and RA. Later, a 50 mg [redacted] (b) (4)% w/w blue film coated (BFC) tablet and a 100 mg [redacted] (b) (4)% w/w BFC tablet were developed in order to increase the drug load. Fostamatinib BFC tablets were also used in phases 2 and 3 studies for treatment of RA and bioequivalence (BE) studies. However, the 100 mg BFC tablets not only gave lower release than the 50 mg BFC tablets in the dissolution study but also had more variability from batch to batch that were manufactured by the same process with the similar process parameters and controls. Subsequently, a 50 mg [redacted] (b) (4)% w/w green film coated (GFC) tablet was developed and evaluated as attempts were made to further increase the drug load from [redacted] (b) (4)% w/w to [redacted] (b) (4)% w/w based on the 100 mg BFC tablet. In a relative bioavailability (BA) study C788-016, the GFC tablet showed a significantly reduced exposure compared to that of the 100 mg BFC tablet due to the extremely low release of drug substance from the tablet. [redacted] (b) (4)

The commercial formulation of an immediate release orange film coated (OFC) tablet with unit doses of 100 mg and 150 mg fostamatinib was developed [redacted] (b) (4) [redacted] (b) (4) Two types of OFC tablets were developed, manufactured, and used in clinical studies. One is the core tablet coated with the [redacted] (b) (4) [redacted] The other is the same core tablet formulation coated with the [redacted] (b) (4) [redacted] (b) (4) To differentiate the two OFC tablets, the tablets coated with [redacted] (b) (4) and manufactured by AZ and [redacted] (b) (4) are named as OFC-I tablets and were used in the phase 3 clinical studies. The tablets coated with [redacted] (b) (4) and manufactured by Patheon are named as OFC tablets and will be used commercially. The film coat was switched to the [redacted] (b) (4) because the [redacted] (b) (4) based film coat [redacted] (b) (4) [redacted] No difference in dissolution has been observed in the dissolution study between the OFC tablets and OFC-I tablets. Dissolution profiles of the OFC-I tablets were comparable to the 50 mg BFC tablets in various pH at the same doses. The bioequivalence (BE) study C788-054 showed that the commercial 150 mg OFC fostamatinib tablets manufactured by Patheon were bioequivalent to the 150 mg OFC-I fostamatinib tablets manufactured by AZ. Refer to Question 3.3.5 for detailed description of BE study C788-054.

Study D4300-020 assessed the BE between fostamatinib 100 mg and 150 mg OFC-I tablets and 50 mg [redacted] (b) (4) % w/w BFC tablets under fasted and fed conditions as the OFC-I tablet formulation was developed to match the exposure of the 50 mg BFC tablet formulation. Under fasted conditions, fostamatinib 100 mg and 150 mg OFC-I fostamatinib tablets were bioequivalent to two and three 50 mg [redacted] (b) (4) % w/w BFC tablets. When comparing OFC-I fostamatinib tablets with BFC fostamatinib tablets under fed conditions, the 90% CI for the GLS mean ratio of AUC fell entirely within the 80% to 125% bioequivalence window, but the 90% CI for C_{max} did not.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. Daily AUC at steady state ($DAUC_{ss}$) in ITP patients was used in the exposure-response (E-R) analyses to support the evidence of effectiveness.

$DAUC_{ss}$ was calculated using the final population PK model developed with data from two phase 3 Studies C788-047 and C788-048, where efficacy/safety of fostamatinib were evaluated in comparison with placebo for the treatment of thrombocytopenia in subjects with persistent/chronic ITP over 24 weeks (refer to the clinical review for the detailed study design and results). The mean (±SD) $DAUC_{ss}$ was 11,192 (±5,226) ng*hr/mL while the mean (±SD) daily dose was 218 (±39.6) mg. The calculated mean $DAUC_{ss}$ was close to the estimated EC_{50} for inhibition of SYK signaling in healthy volunteers, which could be generated by 100 mg BID in patients with ITP. In addition, there is a notable E-R relationship between R406 concentration and response for platelet count ≥ 50 x 10^9/L at Week 12. Even though dose was adjusted (mainly increased) based on platelet count from Week 4, the relationship was still meaningful

(refer to pharmacometrics review in the appendix for the detailed discussion of E-R analyses for efficacy and safety).

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed dosing regimen of fostamatinib appears acceptable as dose is titrated up based on the platelet response after Week 4. Of note, 50% of stable responders (4/9 in C788-47, 5/9 in C788-48) continued to receive the initial dose 100 mg BID without dose escalation, despite that dose escalation to 150 mg BID occurred in 86% of subjects due to the lack of response after Week 4.

An alternative to increase the initial dose to 150 mg BID could be considered for potential clinical benefit given the $DAUC_{ss}$ for either 100 mg BID or 150 mg BID is in the rising part of the E-R curve as shown in the Figure 1. From the reviewer's analysis, there is a significant difference in baseline platelet count between subjects who stayed at 100 mg BID (~22,000/uL) and those who increase dose to 150 mg BID (~15,000/uL) at Week 4 (Figure 2), which suggests there is a potential benefit of higher initial dose in patients with lower baseline platelet count. However, the benefit should be assessed in relation to potential risk associated with higher exposure.

Figure 1: Exposure-Efficacy Analysis for Response at Week 12

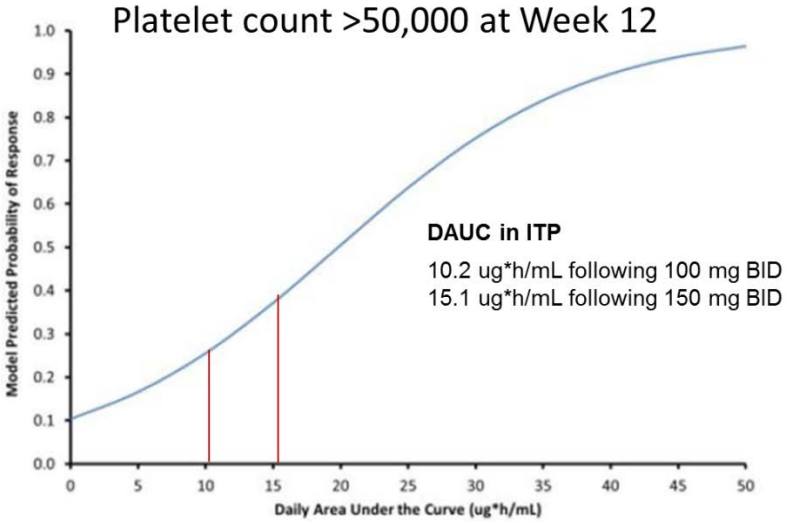
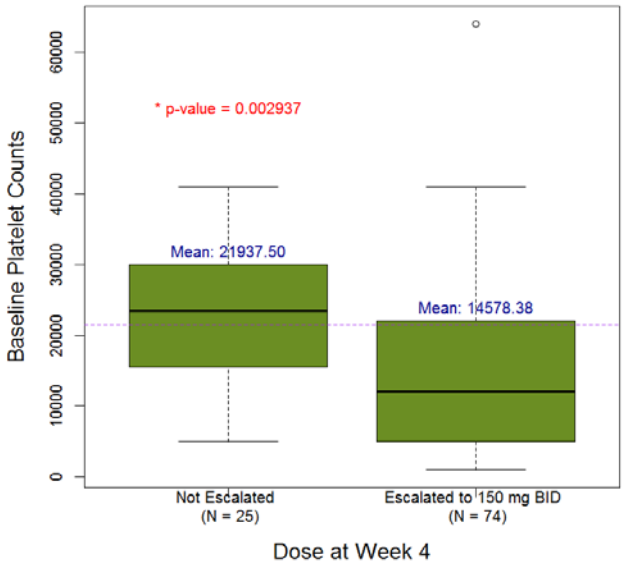


Figure 2: Distribution of Baseline Platelet Count



Higher incidence of hypertension was observed in fostamatinib arm (26%) compared to placebo arm (13%). In addition, exposure-safety analysis for blood pressure indicated that increases in both diastolic and systolic blood pressure are expected with increasing R406 concentration. Although the incidence of hypertensive crisis that required dose adjustment was rare (1%) in patients receiving fostamatinib, considering small number of subjects enrolled in the phase 3 studies, it is hard to predict the increased risk for hypertensive crisis by higher dose in the market setting, especially who are vulnerable to hypertensive crisis.

Overall data suggest that the potential benefit from initiating treatment at 150 mg BID for the general patient population may not compensate the increased risk for hypertension compared to initiating treatment at 100 mg BID then escalating dose to 150 mg BID at Week 4 based on platelet count.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic factors?

Studies D4300C00010 (Study D4300-010) and D4300C00009 (Study D4300-009) evaluated the exposure of R406 in patients with hepatic and renal impairment. The review team agrees with the applicant that no dose adjustment is required for fostamatinib in such patient population.

<u>Hepatic Impairment (HI) Study D4300-010</u>
The HI study was an open-label, single center, single-dose, and parallel-group study in subjects with varying degrees of HI and in healthy volunteers. A single dose of 150 mg fostamatinib was administered on the first day and PK samples were collected up to 120 hours postdose. The degree of HI was categorized by Child-Pugh score: mild HI (Class A), moderate HI (Class B) and

severe HI (Class C). The PK parameters of R406 and the corresponding ratios of AUC and C_{max} between each HI group and volunteer with normal hepatic function are summarized in the Table 14.

Table 14: PK Parameters of R406 and Ratios of AUC and C_{max} between Each HI Group and Healthy Volunteer

	$AUC_{0\text{-}inf}$ (ng·h/mL) Mean (CV%)	C_{max} (ng/mL) Mean (CV%)	Comparison to Normal Hepatic Function Group	
			Ratio of $AUC_{0\text{-}inf}$ (90% CI)	Ratio of C_{max} (90% CI)
Mild HI (N=8)	6390 (21%)	615 (34%)	0.71 (0.51, 0.98)	0.89 (0.61, 1.31)
Moderate HI (N=8)	6860 (54%)	602 (39%)	0.76 (0.55, 1.06)	0.87 (0.59, 1.27)
Severe HI (N=8)	9490 (41%)	582 (71%)	1.06 (0.75, 1.46)	0.84 (0.57, 1.23)
Normal Hepatic Function (N=8)	8970 (37%)	692 (39%)	NA	NA

(Source: Table 6 on page 32 and Table 8 on page 35 in the CSR of Study D4300C00010)

The results showed that the mean AUC was similar between severe HI and normal hepatic function but lower for patients with mild HI (↓29%) and moderate HI (↓24%) after a single oral dose of fostamatinib 150 mg tablet, indicating inconsistent effect across various degree HI groups on R406 PK. The mean C_{max} values were lower for all HI groups compared to normal hepatic function (↓16% to ↓11%). All 90% CI intervals included 1 except the one for AUC comparing mild HI to normal hepatic function. The median t_{max} was 1.5 hours for the normal hepatic function and severe HI groups and 1.75 and 2.5 hours for the moderate and mild HI groups, respectively. The mean $t_{1/2}$ was similar between severe HI (19.2 hours) and normal hepatic function (19.4 hours) groups, while it was slightly shorter in mild (16.7 hours) and moderate HI (16.1 hours) groups. In addition, the AEs after a single dose of 150 mg forstamatinib are considered mild in all the HI groups. Altogether, the applicant proposed no dose adjustment of fostmatinib in patients with mild, moderate or severe HI. The review team agrees with the proposed no dose adjustment for patients with various degrees of HI.

Renal Impairment (RI) Study D4300-009

The RI study had a reduced design using an adaptive 2-stage approach as R406 is not substantially excreted renally. Stage 1 investigated the PK of R406 in 8 subjects with end stage renal disease (ESRD) requiring dialysis compared with 8 healthy subjects with normal renal function after a single oral dose of 150 mg fostamatinib. Subjects with ESRD received the single fostamatinib dose on Day 1 after completion of a dialysis session. R406 PK samples were

collected up to 72 hours postdose. Urine was collected from pre-dose to 48 hours postdose to determine R406 and its N-glucuronide metabolite urine concentrations. Subsequently, subjects with moderate RI were enrolled in Stage 2 to confirm whether there is any effect or not of RI on exposure of R406 as the applicant stated that unexpectedly lower exposure was observed for R406 in subjects with ESRD although the extent of low exposure did not warrant dosage adjustment. Similarly, a single oral dose of 150 mg fostamatinib was administered in subjects with moderate RI on Day 1 with PK samples collected up to 72 hours postdose.

In addition, subjects with ESRD requiring dialysis participated in 2 treatment periods in order to evaluate exposure of R406 under both non-dialysis and dialysis conditions. For period 1, subjects received a single oral dose of 150 mg fostamatinib on Day 1 after completion of a dialysis session with blood samples collected up to 72 hours postdose. For period 2, a single oral dose of 150 mg fostamatinib was administered 2 hours prior to the start of a dialysis session on Day 1 and blood samples were collected prior to, during and 72 hours post-dialysis.

The results in Table 15 showed that there was a decrease of 26% for mean AUC in patients with ESRD (Clcr= 9 to 44 mL/min) and 22% in patients with moderate RI (Clcr=33 to 50 mL/min) compared to normal renal function (Clcr = 89 to 193 mL/min) after a single oral dose of 150 mg fostamatinib. The decrease in mean C_{max} in patients with ESRD and moderate RI was 38% and 42%, respectively. However, the inter-subject variability for AUC and C_{max} was high in both RI groups. All 90% CI intervals contained 1 except the one for C_{max} comparing moderate RI to normal renal function. The median t_{max} was similar across groups (2.50 hours for the normal renal function group and moderate RI group and 2.25 hours for the ESRD group). The mean t1/2 was similar across groups and ranged from 19.6 to 23.8 hours. In addition, the mean values of AUC and C_{max} were higher in ESRD patients who were administered fostamatinib prior to dialysis than those had fostamatinib after completion of dialysis (Table 16). Similarly, the inter-subject variability was high in both groups and all 90% CI intervals included 1. In the urine PK analysis, removal of R406 through dialysis was less than 1% of the theoretical dose (0.22 ± 0.14 mg). Moreover, it was reported that a single dose of 150 mg fostamatinib was well tolerated in all RI groups, as well as healthy subjects.

Table 15: PK Parameters of R406 and Ratios of AUC and C_{max} between Each RI Group and Healthy Volunteer

	$AUC_{0\text{-}inf}$ (ng·h/mL) Mean (CV%)	C_{max} (ng/mL) Mean (CV%)	Comparison to Normal Renal Function Group	
			Ratio of $AUC_{0\text{-}inf}$ (90% CI)	Ratio of C_{max} (90% CI)
ESRD (N=8)	5450 (47%)	407 (60%)	0.74 (0.51, 1.07)	0.62 (0.38, 1.00)
Moderate RI (N=8)	5790 (53%)	425 (89%)	0.78 (0.52, 1.17)	0.58 (0.36, 0.93)

Normal Renal Function (N=8)	7380 (37%)	690 (33%)	NA	NA

(Data Source: Table 6 on page 38 and Table 8 on page 42 in the CSR of Study D4300C00009)

Table 16: PK Parameters of R406 and Ratios of AUC and C_{max} between ESRD with or without Dialysis

	$AUC_{0\text{-}inf}$ (ng·h/mL) Mean (CV%)	C_{max} (ng/mL) Mean (CV%)	Comparison to ESRD without Dialysis	
			Ratio of $AUC_{0\text{-}inf}$ (90% CI)	Ratio of C_{max} (90% CI)
ESRD requiring dialysis (N=8)	5450 (47%)	407 (60%)	0.80 (0.53, 1.22)	0.77 (0.49, 1.21)
ESRD without dialysis (N=8)	6810 (50%)	529 (50%)		

(Data Source: Table 6 on page 38 and Table 9 on page 43 in the CSR of Study D4300C00009)

Consequently, the applicant proposed no dose adjustment of fostamatinib in patients with mild, moderate, and severe RI including ESRD. The review team agrees with the proposed no dose adjustment for patients with various degrees of RI.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Food-Drug Interactions

Study D4300-019 was a randomized, open-label, two-part, single-center, phase 1 study. One of its objectives is to evaluate the effect of a high fat/high-calorie meal on the exposure of R406 when one single 150 mg OFC-I fostamatinib tablet was administered. Profiles in a total of 13 and 14 patients were evaluated for the fasted arm (Treatment C) and high fat fed arm (Treatment D), respectively. The applicant claimed that 12 volunteers would provide 80% power to detect a ratio of 0.75 or less in AUC and C_{max} using a 2-sided 5% significance test based on an intra-subject CV% of 33% for C_{max} in Study D4300-0018.

There was a mean increase of 23% in $AUC_{0\text{-}inf}$ and 15% in C_{max} in patients given high fat breakfast compared to those fasted (Table 17). The median t_{max} was delayed to 3 hours with food compared with the median t_{max} of 1.5 hours in fasted status. Therefore, the exposure of R406 following administration with food was slightly higher when compared to fasted state.

Table 17: PK Parameters of R406 and Ratios of AUC and C_{max} under Fed vs. Fasted Conditions

	$AUC_{0\text{-}inf}$ (ng*h/mL) Geo. Mean (CV%)	C_{max} (ng/mL) Geo. Mean (CV%)	Ratio (D/C) of $AUC_{0\text{-}inf}$ (90% CI)	Ratio (D/C) of C_{max} (90% CI)	T_{max} (hours) Median	$T_{1/2}$ (hours) Geo. Mean

					(min, max)	(CV%)
Treatment C (fasted) (N=13)	6560 (30.3%)	594 (48.4%)	123.26* (102.13, 148.77)	114.53* (88.68, 147.91)	1.50 (1.00, 4.00)	13.9 (29.5%)
Treatment D (fed) (N = 14)	8370 (32.2%)	697 (37.3%)			3.00 (2.00, 4.03)	13.4 (30.3%)

(Data Source: Table 13 on page 41 and Table 16 on page 46 in the CSR of Study D4300C00019)

In the two pivotal safety and efficacy studies 047 and 048, fostamatinib tablets were taken with or without food and the safety/tolerability profile was reported acceptable. Although both 90% CIs for $AUC_{0\text{-}inf}$ and C_{max} were not laid within the bounds of 0.80 to 1.25, food effect on exposure of R406 was not considered clinically meaningful. Therefore, the reviewer team agrees with the proposed labeling language that fostamatinib tablet can be given with or without food.

Drug-Drug Interactions

Fostamatinib as a victim of DDI	
R406 as a substrate of CYP3A	Strong CYP3A4 Inhibitor Study C788-001 evaluated the magnitude of the effect of multiple oral doses of ketoconazole on the single dose PK of fostamatinib and its metabolite R406 in 8 healthy subjects. Ketoconazole 200 mg or placebo was administered BID for 7 doses. Fostamatinib was administered 2 hours after the second dose of ketoconazole/placebo.PK samples of R406 were collected at pre-dose and up to 56 hours post-dose. Co-administration of ketoconazole increased mean C_{max} of R406 by 37% and mean $AUC_{0\text{-}inf}$ by 102%. The mean terminal $t_{1/2}$ increased from 14 hours to 18 hours. The PK parameters (mean ± SD) of R406 following a single oral administration of fostamatinib with or without ketoconazole were listed in the table below.

	80 mg fostamatinib + Placebo	80 mg fostamatinib + Ketoconazole	Mean Ratio (fostamatinib +Ketoconazole /fostamatinib)	90% CI
C_{max} (ng/mL)	328 ± 45.7	454 ± 83.7	1.37	1.23, 1.53
$AUC_{0\text{-}inf}$ (ng*h/mL)	3770 ± 735	7770 ± 2410	2.02	1.77, 2.30

(Data source: Table 11 on page 24 and Table 12 on page 25 in the Appendix 12 in the CSR of Study C-935788-001)

The review team recommends reducing the dose of fostamatinib when co-administering with a strong CYP3A inhibitor due to the potential safety concern instead of claiming that [redacted] (b) (4) proposed by the applicant.

<table>
<tr><td></td><td>
<u>Moderate CYP3A4 Inhibitor</u>
Study D4300-0011 evaluated the magnitude of the effect of multiple oral doses of verapamil on the single dose PK of fostamatinib and its metabolite R406 in 15 healthy subjects. Verapamil 80 mg was administered three times daily for 4 days. Fostamatinib 150 mg was administered on the second day with verapamil.PK samples of R406 were collected at pre-dose and up to 96 hours post-dose. Co-administration of verapamil increased mean C_{max} of R406 by 6% and mean $AUC_{0\text{-}inf}$ by 39%. The mean terminal $t_{1/2}$ increased from 14 hours to 19 hours. The mean PK parameters (CV%) of R406 following a single oral administration of fostamatinib with or without verapamil were listed in the table below.
<table>
<tr><td></td><td>150 mg fostamatinib alone</td><td>150 mg fostamatinib + verapamil</td><td>Mean Ratio (fostamatinib +verapamil /fostamatinib)</td><td>90% CI</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>588 (46%)</td><td>609 (73%)</td><td>1.06</td><td>0.78, 1.44</td></tr>
<tr><td>$AUC_{0\text{-}inf}$ (ng*h/mL)</td><td>6380 (36%)</td><td>9010 (50%)</td><td>1.39</td><td>1.08, 1.80</td></tr>
</table>
(Data source: Table 9 on page 33 and table 10 on page 38 in the CSR of Study D4300C00011)

The review team agrees with the applicant that no dose modification of fostamatinib is needed when co-administering with a moderate CYP3A inhibitor.

<u>Strong CYP3A4 Inducer</u>
Study D4300-0015 evaluated the magnitude of the effect of multiple oral doses of rifampicin on the single dose PK of fostamatinib and its metabolite R406 in 15 healthy subjects. Rifampicin 600 mg were administered once daily for 8 days. A single dose of 150 mg fostamatinib was administered on Day 6. PK samples of R406 were collected at pre-dose and up to 96 hours post-dose. Co-administration of rifampicin decreased mean C_{max} of R406 by 59% and mean $AUC_{0\text{-}inf}$ by 75%. The mean terminal $t_{1/2}$ decreased from 15 hours to 11 hours. The mean PK parameters (CV%) of R406 following a single oral administration of fostamatinib with or without rifampicin were listed in the table below.
<table>
<tr><td></td><td>150 mg fostamatinib alone</td><td>150 mg fostamatinib + rifampicin</td><td>Mean Ratio (fostamatinib +rifampicin/fostamatinib)</td><td>90% CI</td></tr>
<tr><td>C_{max} (ng/mL)</td><td>573 (59%)</td><td>234 (56%)</td><td>0.41</td><td>0.30, 0.56</td></tr>
<tr><td>$AUC_{0\text{-}inf}$ (ng*h/mL)</td><td>6540 (49%)</td><td>1610 (33%)</td><td>0.25</td><td>0.19, 0.32</td></tr>
</table>
(Data source: Table 7 on page 28 and table 8 on page 30 in the CSR of Study D4300C00015)

The review team recommended to avoid concomitant use of fostamatinib and strong CYP3A4 inducers due to the concern of potential lack of efficacy instead of claiming that (b) (4) proposed by the applicant.
</td></tr>
<tr><td>Fostamatinib concomitant with drugs altering gastric pH</td><td>
<u>Proton Pump Inhibitors (PPIs)</u>
Study D4300-0019 also evaluated the magnitude of the effect of co-administration of ranitidine on the PK of R406 in 13 healthy subjects in addition to food effect as fostamatinib demonstrated pH-dependent solubility with higher solubility at higher pH. A single dose of ranitidine 150 mg was administered with a single dose of 150 mg fostamatinib under the fasted condition. PK samples of R406 were collected at pre-dose and up to 96 hours post-dose. Co-administration of ranitidine slightly decreased mean C_{max} of R406 by 2% and mean $AUC_{0\text{-}inf}$ by 3%. The mean terminal $t_{1/2}$ changed slightly from
</td></tr>
</table>

14 hours to 16 hours. The mean PK parameters (CV%) of R406 following a single oral administration of fostamatinib with or without ranitidine were listed in the table below.

	150 mg fostamatinib alone	150 mg fostamatinib + ranitidine	Mean Ratio (fostamatinib +ranitidine/fostamatinib)	90% CI
C_{max} (ng/mL)	594 (48%)	581 (52%)	0.98	0.71, 1.34
$AUC_{0\text{-}inf}$ (ng*h/mL)	6560(30%)	6400 (45%)	0.97	0.80, 1.18

(Data source: Table 14 on page 44 and table 18 on page 48 in the CSR of Study D4300C00019)

The review team agrees with the applicant that no dose modification of fostamatinib is needed when co-administering with pH-elevated drugs.

Fostamatinib as a perpetrator of DDI

R406 as an inhibitor of CYP3A

Midazolam

Study C788-018 evaluated the magnitude of the effect of multiple doses of fostamatinib on the PK of midazolam in 16 healthy subjects. A single 7.5 mg dose of midazolam hydrochloride syrup was administered on Day 1 or Day 8. Fostamatinib 100 mg was administered BID from Days 2 through 7. PK samples of midazolam were collected at pre-dose and up to 24 hours post-dose on Day 1 and Day 8. Co-administration of fostamatinib increased mean midazolam C_{max} by 9% and mean $AUC_{0\text{-}inf}$ by 25%. The mean PK parameters (±SD) of midazolam on Day 1 and on Day 8 following multiple doses of fostamatinib were listed in the table below.

	Day 1 Midazolam alone	Day 8 Midazolam + fostamatinib	Mean Ratio (Day 8/Day 1)	90% CI
C_{max} (ng/mL)	39 (± 11)	45 (± 14)	1.09	0.95, 1.25
$AUC_{0\text{-}inf}$ (ng*h/mL)	110 (± 38)	145 (± 59)	1.25	1.12, 1.38

(Data source: Table 11.4.7.1-1 on page 47 and table 11.4.7.1-2 on page 48 in the CSR of Study C-935788-018)

Simvastatin

Study D4300-0039 evaluated the magnitude of effect of multiple doses of fostamatinib on the PK of simvastatin in 21 healthy subjects. A single 40 mg oral dose of simvastatin was administered on Day 1 or Day 6. Fostamatinib 100 mg was administered BID from Days 1 through 7. PK samples of simvastatin and its metabolite, simvastatin acid, were collected at pre-dose and up to 48 hours post-dose on Day 1 and Day 6. Co-administration of fostamatinib increased mean C_{max} of simvastatin and simvastatin acid by113% and 83%, respectively. The mean $AUC_{0\text{-}inf}$ was increased by 64% and 66% for simvastatin and simvastatin acid, respectively. The mean PK parameters (CV%) of simvastatin and simvastatin acid on Day 1 and on Day 6 following multiple doses of fostamatinib were listed in the table below.

		Day 1 Simvastatin alone	Day 6 Simvastatin + fostamatinib	Mean Ratio (Day 6/Day 1)	90% CI
Simvastatin	C_{max} (ng/mL)	6.5 (67%)	14 (71%)	2.13	1.65, 2.74
	$AUC_{0\text{-}inf}$ (ng*h/mL)	28 (52%)	46 (68%)	1.64	1.33, 2.02
Simvastatin	C_{max}	1.4 (58%)	2.7 (76%)	1.83	1.57, 2.13

Acid	(ng/mL)				
	$AUC_{0\text{-}inf}$ (ng*h/mL)	19 (63%)	30 (77%)	1.66	1.46, 1.90

(Data source: Table 13 on page 52, Table 14 on page 54, and table 17 on page 59-60 in the CSR of Study D4300C00039)

All together, the review team agrees with the applicant that monitor for toxicities that may require dosage reduction of certain sensitive CYP3A4 substrates (such as, simvastatin) but no dose modification of midazolam is needed when co-administering with fostamatinib.

R406 as an inducer of CYP2C8

Pioglitazone

Study D4300-0014 evaluated the magnitude of the effect of multiple doses of fostamatinib on the PK of pioglitazone in 15 healthy subjects. A single 30 mg oral dose of pioglitazone was administered on Day 1 or Day 7. Fostamatinib 100 mg was administered BID from Day 1 through Day 8. PK samples of pioglitazone and its active metabolite, hydroxyl-pioglitazone were collected at pre-dose and up to 48 hours post-dose on Day 1 and Day 7. Co-administration of fostamatinib decreased mean C_{max} of pioglitazone and hydroxyl-pioglitazone by 17% and 9%, respectively. The mean AUC was increased by 18% and decreased by 10% for pioglitazone and hydroxyl-pioglitazone, respectively. The mean PK parameters (CV%) of pioglitazone and hydroxyl-pioglitazone on Day 1 and on Day 7 following multiple doses of fostamatinib were listed in the table below.

		Day 1 Pioglitazone alone	Day 7 Pioglitazone + fostamatinib	Mean Ratio (Day 7/Day 1)	90% CI
Pioglitazone	C_{max} (ng/mL)	899 (29%)	752 (42%)	0.83	0.64, 1.07
	$AUC_{0\text{-}inf}$ (ng*h/mL)	9970 (31%)	12400 (27%)	1.18	1.08, 1.28
Hydroxyl-pioglitazone	C_{max} (ng/mL)	380 (58%)	345 (76%)	0.91	0.79, 1.05
	$AUC_{0\text{-}48hr}$ (ng*h/mL)	14200 (20%)	12700 (27%)	0.90	0.79, 1.02

(Data source: Table 9 on page 33-34 and table 10 on page 36 in the CSR of Study D4300C00014)

The results did not demonstrate the *in vivo* induction potential of fostamatinib, such as, decreased exposure of pioglitazone, increased exposure of hydroxyl-pioglitazone, or increased ratio of hydroxyl-pioglitazone vs. pioglitazone exposure although R406 produced induction of CYP2C8 activity that was approximately 70% of that observed for rifampicin, a positive control in the *in vitro* study. The lack of *in vivo* induction may be attributable to the relatively low R406 plasma exposures achieved at clinical doses compared to the high *in vitro* exposure at which the effect was observed. Therefore, the review team agrees with the applicant that no dose modification of fostamatinib is needed when co-administering with CYP2C8 substrates.

Fostamatinib and R406 as inhibitors of BCRP

Rosuvastatin

Study D4300-0039 also evaluated the magnitude of effect of multiple doses of fostamatinib on the PK of rosuvastatin in 21 healthy subjects. A single 20 mg oral dose of rosuvastatin was administered on Day 1 or Day 6. Fostamatinib 100 mg was administered BID from Day 1 through Day 9. PK samples of rosuvastatin were collected at pre-dose and up to 96 hours post-dose on Day 1 and Day 6. Co-administration of fostamatinib increased mean rosuvastatin C_{max} by 88% and mean $AUC_{0\text{-}inf}$ by 96%. The mean PK parameters (CV%) of rosuvastatin on Day 1 and on Day 6 following multiple doses of fostamatinib were listed

in the table below.

	Day 1 rosuvastatin alone	Day 6 fostamatinib + rosuvastatin	Mean Ratio (Day 6/Day 1)	90% CI
C_{max} (ng/mL)	5.3 (39%)	10.0 (37%)	1.88	1.69, 2.10
$AUC_{0\text{-}inf}$ (ng*h/mL)	47(36%)	92 (35%)	1.96	1.78, 2.15

(Data source: Table 11 on page 47-48 and table 16 on page 58 in the CSR of Study D4300C00039)

The review team agrees with the applicant that monitor for toxicities that may require dosage reduction of BCRP substrates (such as, rosuvastatin) when co-administering with fostamatinib.

Fostamatinib as an inhibitor of P-gp

Digoxin

Study D4300-0026 evaluated the magnitude of the effect of multiple doses of fostamatinib on the PK of digoxin at steady state in 21 healthy subjects. Digoxin was administered as a loading dose of 0.25 mg BID on Day 1 and 0.25 mg once daily on Day 2 to Day 15. Fostamatinib 100 mg tablet was administered BID on Day 9 to Day 15. PK samples of digoxin were collected at pre-dose and up to 18 hours post-dose on Day 8 and Day 15. Co-administration of fostamatinib increased mean digoxin $C_{max,ss}$ by 70% and mean AUC_{ss} by 37%. The mean PK parameters (CV%) of digoxin on Day 8 and on Day 15 following multiple doses of fostamatinib were listed in the table below.

	Day 8 Digoxin alone	Day 15 fostamatinib + Digoxin	Mean Ratio (Day 15/Day 8)	90% CI
$C_{max,ss}$ (ng/mL)	1.3 (27%)	2.2 (27%)	1.70	1.46, 1.98
AUC_{ss} (ng*h/mL)	13(23%)	18 (19%)	1.37	1.30, 1.46

(Data source: Table 6 on page 31 and table 8 on page 33 in the CSR of Study D4300C00026)

The review team agrees with the applicant that monitor for toxicities that may require dosage reduction of P-gp substrates (such as, digoxin) when co-administering with fostamatinib.

Narrow Therapeutic Index Drugs

Warfarin

Study D4300-0013 evaluated the magnitude of the effect of multiple doses of fostamatinib on the PK of warfarin in 15 healthy subjects. A single 25 mg oral dose of warfarin was administered on Day 1 or Day 14. Fostamatinib 100 mg was administered BID on Day 8 to Day 20. PK samples of warfarin were collected at pre-dose and up to 168 hours post-dose on Day 1 and Day 14. Co-administration of fostamatinib increased mean AUC of R-warfarin and S-warfarin by 18% and 13%, respectively, while the mean C_{max} was similar with or without fostamatinib. The mean PK parameters (CV%) of R-warfarin and S-warfarin on Day 8 and on Day 14 following multiple doses of fostamatinib were listed in the table below.

		Day 1 warfarin alone	Day 14 Warfarin + fostamatinib	Mean Ratio (Day 14/Day 1)	90% CI
R-warfarin	C_{max} (ng/mL)	1210 (16%)	1200 (18%)	1.02	0.97, 1.08
	$AUC_{0\text{-}inf}$ (ng*h/mL)	69800 (23%)	79800 (21%)	1.18	1.13, 1.23
S-	C_{max}	1200 (18%)	1170 (21%)	0.99	0.92, 1.06

	warfarin	(ng/mL)				
		$AUC_{0\text{-}inf}$ (ng*h/mL)	40900 (28%)	45500 (31%)	1.13	1.07, 1.19

(Data source: Table 7 on page 39 and table 8 on page 41 in the CSR of Study D4300C00013)

The review team agrees with the applicant that no clinical relevant drug interactions were observed when warfarinwas co-administered with fostamatinib.

Oral Contraceptives

Ethinyl estradiol and levonorgestrel

Study D4300-0012 evaluated the magnitude of the effect of multiple doses of fostamatinib on the PK of oral contraceptive Microgynon in 33 healthy subjects. Microgynon was administered once daily with placebo BID for 21 days in Treatment A. Fostamatinib 100 mg was administered BID with Microgynon once daily for 21 days in Treatment B. PK samples of ethinyl estradiol and levonorgestrel were collected at pre-dose and up to 24 hours post-dose on Day 21 in both treatment groups. Co-administration of fostamatinib increased mean AUC_{ss} of ethinyl estradiol by 28% and mean $C_{max,ss}$ by 34 %, while the mean AUC and C_{max} of levonorgestrel at steady state were similar with or without fostamatinib. The mean PK parameters (CV%) of ethinyl estradiol and levonorgestrel on Treatment A and on Treatment B following multiple doses of fostamatinib were listed in the table below.

		Treatment A Day 21 Microgynon alone	Treatment B Day 21 Microgynon + fostamatinib	Mean Ratio (Treatment B/Treatment A)	90% CI
Ethinyl estradiol	$C_{max,ss}$ (pg/mL)	86 (29%)	116 (37%)	1.34	1.26, 1.43
	AUC_{ss} (pg*h/mL)	828 (30%)	1060 (38%)	1.28	1.21, 1.36
levonorgestrel	$C_{max,ss}$ (pg/mL)	6650 (27%)	6440 (32%)	0.97	0.90, 1.04
	AUC_{ss} (pg*h/mL)	76000 (46%)	79800 (54%)	1.05	0.98, 1.13

(Data source: Table 6 on page 41, Table 7 on page 42 and Table 8 on page 43 in the CSR of Study D4300C00012)

The review team agrees with the applicant that no clinical relevant drug interactions were observed when Microgynon (ethinyl estradiol and levonorgestrel) was co-administered with fostamatinib.

Of note (1) although different fostamatinib formulation were used in the DDI studies (Table 109 in appendix) to investigate the drug interaction, the interpretation of the PK results either fostamatinib acting as a perpetrator or victim in the DDI studies leading to potential dose modification applies to the commercial tablets; (2) the PK results of 100 mg BID applies to 150 mg BID as the PK is linear up to 200 mg BID.

Is the commercial tablet formulation bioequivalent to the tablet formulation used in the Phase 3 ITP studies?

Yes, the commercial 150 mg fostamatinib orange film coated (OFC) tablets manufactured by Patheon are bioequivalent to the 150 mg fostamatinib OFC-I tablets manufactured by AZ used in efficacy and safety Studies C788-047 and C788-048. In addition, the 150 mg fostamatinib OFC-I tablets manufactured by (b) (4) used in clinical Study C788-049 are bioequivalent to the AZ tablets.

The bioequivalence between the 150 mg fostamatinib OFC-I tablets manufactured by AZ and 150 mg fostamatinib OFC tablets by Patheon was conducted in Study C788-054 because the commercial product will be manufactured at Patheon with different tablet film coating. It was an open label, single center, randomized, partial replicate, 3-way crossover study in 42 healthy subjects. The treatment reference is two replicates of a single dose of 150 mg OFC-I tablet manufactured by AZ (Replicate 1 [R1] and Replicate 2 [R2]). The same dose strength tablet manufactured by Patheon is used as treatment Test (T). The treatment sequences included R1TR2, R1R2T and TR1R2. Serial blood PK samples of R406 were collected up to 96 hours following dosing in each treatment period. Table 18 showed that the geometric mean ratio of 99.11% for R406 $AUC_{0\text{-}inf}$ and 94.27% for R406 C_{max} and the 90% CIs fell within the acceptable equivalence interval for $AUC_{0\text{-}inf}$ (91.42, 107.45) and C_{max}(82.23, 108.08) indicating that the bioequivalence was established between the 150 mg OFC-I tablet manufactured by Patheon and the OFC ones manufactured by AZ.

Table 18: Comparison of AUC and C_{max} between To-be-marketed Fostamatinib Tablets and the Tablets used in Phase 3 Studies

	Study C788-052		Study C788-054	
	150 mg, OFC-I tablet by AZ (R)	150 mg, OFC-I tablet by (b) (4) (T)	150 mg, OFC-I tablet by AZ (R)	150 mg, OFC tablet by Patheon (T)
Geometric Mean $AUC_{0\text{-}inf}$ (ng*hr/mL)	6996	6628	7212	7148
AUC T/R Ratio	94.75%		99.11%	
AUC Ratio 90% CI	87.20-102.95		91.42-107.45	
Geometric Mean C_{max} (ng/mL)	566.8	544.5	592.2	558.3
C_{max} T/R Ratio	96.08%		94.27%	
C_{max} Ratio 90% CI	82.71-111.61		82.23-108.08	

(Data Source: Table 9 on page 38 in the CSR of Study C-935788-052 and Table 8 on page 50 in the CSR of Study C-935788-054)

BE studies C788-052 was conducted between the 150 mg fostamatinib OFC-I tablets manufactured by AZ and those by (b) (4) due to the different manufacture place. The study design is similar to Study C788-054. One single dose of 150 mg fostamatinib OFC-I tablet manufactured

by AZ was used as reference and replicated (R1 and R2). The 150 mg fostamatinib OFC-I tablet manufactured by (b) (4) was found to be bioequivalent to those manufactured by AZ in 42 healthy subjects with a geometric mean ratio (90% CI) of 94.75% (87.20, 102.95) for R406 $AUC_{0\text{-}inf}$ and 96.08% (82.71, 111.61) for R406 C_{max} (Table 18).

X X

Primary Reviewer

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7 Statistical and Clinical and Evaluation

7.1. Sources of Clinical Data and Review Strategy

7.1.1. Table of Clinical Studies

The clinical trials that are pertinent to the review of efficacy and safety included in this NDA are summarized in the table below.

Table 19 Listing of Clinical Trials for Efficacy and Safety Relevant to NDA 209299

Trial ID	Design	Regimen	Primary Endpoint	Patients enrolled	No. of Centers and Countries/Status
Controlled Studies to Support Efficacy and Safety					
C788-047 (C-935788-047)	Phase 3, randomized (2:1), double-blind, placebo-controlled, parallel group study	Fostamatinib: 100 mg bid for 4 weeks then 150 mg bid for remainder of study Placebo: bid	Stable platelet response by Week 24, defined as having a platelet count of at least 50,000/mcL on at least 4 of the 6 visits over Weeks 14-24.	76 patients (fostamatinib: 51, placebo: 25)	35 sites in 8 countries (US, Canada, Europe and Australia)/ completed
C788-048 (C-935788-048)	Phase 3, randomized (2:1), double-blind, placebo-controlled, parallel group study	Fostamatinib: 100 mg bid for 4 weeks then 150 mg bid for remainder of study Placebo: bid	Stable platelet response by Week 24, defined as having a platelet count of at least 50,000/mcL on at least 4 of the 6 visits over Weeks 14-24.	74 patients (fostamatinib: 50, placebo: 24)	23 sites in 8 countries in Europe/ completed
Other studies pertinent to the review of efficacy or safety					
C788-049 (C-935788 - 049)	Phase 3, open-label extension study	Fostamatinib (Responder: same dose group as main study. Fostamatinib Non-responder: 100 mg bid for 4 weeks then 150 mg bid for remainder of	-Stable platelet count of at least 50,000/mcL within 12 weeks of beginning active treatment. - Sustained stable platelet response, defined as no two visits at least 4 weeks apart, with a	123 patients (previously enrolled in study 047 or 048)	53 sites in 15 countries (US, Canada, Europe, Australia)/ ongoing

		study)	platelet count < 50,000/ mcL, within a period of 12 months following initial achievement of the target platelet count.		
D4300-022	Phase 2, open-label, ascending dose, pilot study to assess efficacy and safety of fostamatinib in adult refractory ITP.	Fostamatinib 75 to 175 mg bid (majority received 150 mg bid)		18 adult patients with refractory ITP	2 sites in US/ongoing

[Source: FDA compilation from Sponsor's submission]

7.1.3. Review Strategy

The clinical review was primarily based on three clinical trials (C788-047, C788-048 and C788-049) to support efficacy and safety of the proposed indication and included the following:

- Electronic submission of the clinical study reports and other relevant portions of the NDA (EDR link to submission: \\CDSESUB1\EVSPROD\NDA209299\209299.enx.)
- Efficacy and safety data were audited or reproduced using ADaM and STDM;
- Regulatory history;
- Applicant's responses to FDA information requests;
- Relevant published literature; and
- The 120-day safety update.

The C788-047 (C-935788-047), C788-048 (C-935788-048) and C788-049 (C-935788-049) trials will also be referred interchangeably in this review as 047, 048 and 049 trials, respectively.

All tables and figures in this review are those of the reviewers unless noted otherwise.

Data and Analysis Quality

The data were submitted in SDTM and ADaM formats and were reasonable to review. The quality and integrity of the submitted data appeared adequate. It was possible to reproduce the applicant's analyses and results.

7.2. Review of Relevant Individual Trials Used to Support Efficacy

Studies C788-047 and C788-048

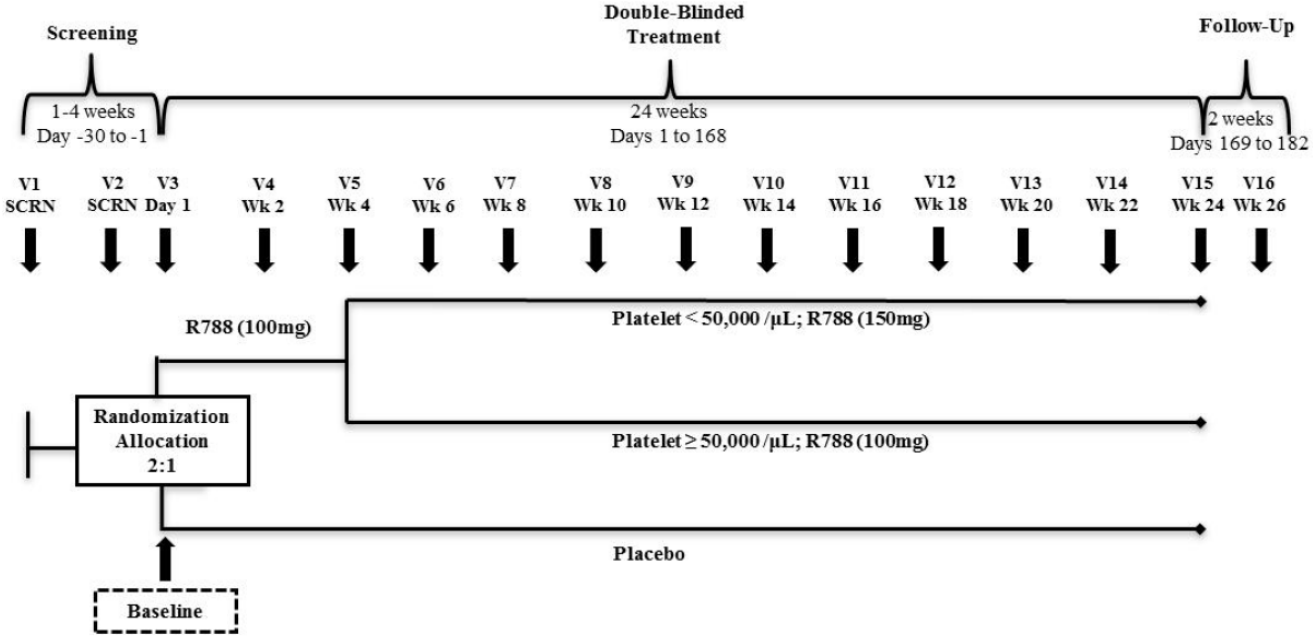
Trial Design and Endpoints

Trial ID and Title:
The C788-047 (C-935788-047) and C788-048 (C-935788-048) trials were identical in design and had identical titles, "A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Study of Fostamatinib Disodium in the Treatment of Persistent/Chronic Immune Thrombocytopenic Purpura."

Trial Design

Both trials were phase 3, randomized, double-blind, placebo-controlled, multi-center, parallel group trials to assess the efficacy of 24 weeks of treatment with fostamatinib versus placebo in achieving a stable platelet count in patients with ITP who have received at least one prior systemic treatment. A total of approximately 75 patients was to be randomized (2:1) to receive fostamatinib or placebo for 24 weeks. Randomization was to be stratified by splenectomy (yes or no) and severity of thrombocytopenia (platelets < or ≥ 15,000/mcL). Randomization was to occur using an Interactive Web Response System (IWRS). The trial consisted of 16 visits over a 26-week period.

Figure 3 C788-047 and C788-048: Trial Design



[Source: C788-047 and C788-048 protocols]

The protocols required patients to have a history consistent with "persistent/chronic ITP" in accordance with the American Society of Hematology (ASH), 2011 Practice Guidelines.

Review comment: According to the ASH 2011 practice guideline for ITP, the International Working Group (IWG) consensus panel defines "ITP as newly diagnosed (diagnosis to 3 months), persistent (3 to 12 months from diagnosis), or chronic (lasting for more than 12 months)." However, these definitions have not been formally validated and may not apply to patients with secondary ITP. To be eligible for the applicant's phase 3 trials, subject had to have no known etiology for thrombocytopenia.

Fostamatinib (or matching placebo) was to be administered at an initial dose of 100 mg PO BID and starting at Week 4 could be increased to 150 mg PO BID if the platelet count remained <50,000/mcL and the study drug had been well tolerated. Patients with platelet counts ≥50,000/mcL stayed on fostamatinib 100 mg BID. The dose could be reduced as low as 100 mg PO once daily at any time if dose limiting adverse events were observed.

Table 20 C788-047 and C788-048: Dose Adjustment

Dose	Dose Level -1	Dose Level -2	Dose Level -3[a]	Dose Level -4[a]
100 mg PO *bid*	150 mg PO *qd*	100 mg PO *qd*	discontinue	----
150 mg PO *bid*	100 mg PO *bid*	150 mg PO *qd*	100 mg PO *qd*	discontinue

[Source: C788-047 and C788-048 protocols]

Patients were allowed to continue to receive specific concurrent ITP therapies at trial entry throughout their participation in the study [glucocorticoids (< 20 mg prednisone equivalent per day), azathioprine or danazol]. This was in consideration of the patients with low platelet counts randomized to the placebo arm. Doses and regimens of allowed therapies at entry could not be changed during the 24-week treatment period of the study, even with platelet response.

Prior to the randomization to double-blind treatment (Day 1), all therapeutic agents, other than those allowed as concomitant ITP therapy (glucocorticoids, < 20 mg prednisone/day equivalent or azathioprine or danazol) were to be discontinued in accordance with the washout period as described in the table below. The duration of the washout period was defined by the half-life of the therapeutic agent.

Table 21 C788-047 and C788-048: Washout Requirements

Drug	Prohibited Period (from last dose of agent)
IVIg or anti-D IgG	7 days
Cyclosporine, mycophenolate mofetil	14 days
Eltrombopag	14 days
Romiplostim	21 days
Rituximab or other anti-CD20 monoclonal antibody	6 weeks
Alkylating agents (eg, cytoxan)	8 weeks
Investigational agent	30 days or 5 half-lives, whichever is greater

[Source: C788-047 and C788-048 protocols]

Starting at Week 12, patients with a platelet count < 50,000/mcL or those who failed to achieve an increase of at least 20,000/mcL (if baseline platelet count < 15,000/mcL) were to be considered non-responders and were allowed to discontinue from the trial. Non-responders could proceed to receive open-label fostamatinib in the long-term follow-up extension study (C788-049), provided they had received 150 mg PO bid for at least 4 weeks (unless this higher dose was not well tolerated). In addition, patients who successfully completed the scheduled 24-week treatment period could also continue to receive open-label fostamatinib therapy in the extension study (C788-049).

Patients were to self-administer the study drug in the morning and evening with or without food throughout the 24-week treatment period. An independent Safety Review Committee (SRC) was to monitor safety throughout the study. Platelet counts were to be performed by local laboratories and a central laboratory for testing other hematology, serum chemistry, urinalysis, International Normalized Ratio/Activated Partial Thromboplastin (INR/aPTT), and serum pregnancy.

Bleeding symptoms were to be assessed using both the ITP Bleeding Scale (IBLS) and the WHO bleeding scale. The IBLS included assessment of bleeding at nine anatomical sites (skin, oral, epistasis, gastrointestinal, urinary, gynecological, pulmonary, intracranial hemorrhage and subconjunctival hemorrhage), graded from 0 (none) to 2 (marked bleeding). Assessment of bleeding at two sites, skin and oral, was also to be performed during the physical examination. The WHO bleeding scale was to be used throughout the study to assess and record the severity of bleeding (using a 5-point scale ranging from 0, no bleeding, to 4, debilitating blood loss).

Reviewer Comment: As stated above, both IBLS and WHO bleeding scales are subjective assessments and are not formally validated. Potential limitations to the WHO bleeding scale

include dependence on clinician interpretation of patient recall, inability to distinguish among bleeding events occurring at different anatomical sites, and an inherent assumption of linear increases in severity of bleeding across the response categories.

Trial Objectives:
The primary objective was to evaluate the efficacy of fostamatinib compared with placebo in achieving a stable platelet response in patients with ITP.

Secondary objectives included comparison of the incidence of bleeding complications and the overall safety and tolerability in patients receiving fostamatinib versus placebo.

Eligibility Criteria:

Key Inclusion Criteria:

1. Willing and able to provide written informed consent.
2. Diagnosis of ITP for at least 3 months and no known etiology for thrombocytopenia.
3. Average platelet count < 30,000/mcL (and none > 35,000 unless as a result of rescue therapy) from at least 3 qualifying counts within the preceding 3 months. At least 2 of the qualifying counts must have been taken during the screening period.
4. Previously received at least 1 typical regimen for the treatment of ITP. The typical regimen can include such approved agents as:
    - a thrombopoietin (romiplostim, eltrombopag), unless contraindicated
    - corticosteroids with or without splenectomy
    - intravenous immunoglobulin.
5. Male or female at least 18 years of age.
6. Performance status on Karnofsky performance status scale (KPS) ≥ 70
7. Concurrent treatment for ITP may consist of either glucocorticoids (< 20 mg prednisone equivalent per day), or azathioprine or danazol. The dose of the concurrent medication must have been stable for 14 days prior to baseline and must be expected to remain stable throughout the study. No other concurrent medications for ITP are permitted.
8. Other therapeutic agents for ITP had to have been discontinued in accordance with the washout periods.
9. Female subject must be either post-menopausal for at least 1 year or surgically sterile; or if female of child-bearing potential, must not be pregnant or lactating and must agree to use an acceptable method of birth control throughout the duration of the trial and for 30 days following the last dose.

Key Exclusion Criteria:

1. ITP associated with lymphoma, chronic lymphocytic leukemia, viral infection, autoimmune disorders, thyroid disease, human immunodeficiency virus, or hepatitis or induced or alloimmune thrombocytopenia, or thrombocytopenia associated with myeloid dysplasia.
2. Subject with autoimmune hemolytic anemia.

3. History of or active, clinically significant, respiratory, gastrointestinal (pancreatitis), renal, hepatic, neurological, psychiatric, musculoskeletal, genitourinary, dermatological, or other disorders that could affect the conduct of the study or the absorption, metabolism or excretion of the study drug.
4. Had any major cardiovascular event within the 6 months prior to randomization, including but not limited to; myocardial infarction, unstable angina, cerebrovascular accident, pulmonary embolism, or New York Heart Association Class III or IV heart failure.
5. Uncontrolled or poorly controlled hypertension, defined as systolic blood pressure ≥ 140 mmHg, or diastolic blood pressure ≥ 90 mmHg, whether or not the subject is receiving anti-hypertensive treatment. Patients may be rescreened if the blood pressure is successfully and promptly controlled (within 30 days) using conventional anti-hypertensive therapy to achieve optimal blood pressure control (< 140/90 mmHg).
6. History of coagulopathy including prothrombotic conditions such as Factor V Leiden, APC resistance, AT-III deficiency and lupus anticoagulant, or arterial or deep venous thrombosis within 6 months prior to randomization.
7. In patients with deep venous thrombosis greater than 6 months prior to randomization, anticoagulants must have been discontinued for at least 30 days and subsequent D-dimer must be within normal limits for the site's local laboratory.
8. Bleeding assessment score of Grade 2 at any site by the ITP Bleeding Scale (IBLS).
9. Has 1 or more of the following laboratory abnormalities: leukocyte count < 2,500/mcL, neutrophil count of < 1,500/mcL, lymphocyte count < 750/mcL, Hgb < 10 g/dL without ongoing transfusion support, or transaminase levels (ALT, AST) > 1.5x ULN, total bilirubin > 2.0 mg/dL, or estimated glomerular filtration rate (eGFR) < 30 mL/min at the time of screening.
10. Significant infection, or an acute infection such as influenza, or is known to have an active inflammatory process at the time of screening and/or baseline (Day 1).
11. Acute gastrointestinal symptoms at the time of screening and/or baseline (e.g., nausea, vomiting, diarrhea, abdominal pain).
12. Subject has increased the dose of, or added, prescription drugs within the 2 weeks prior to Day 1, unless agent is agreed to be not clinically relevant.
13. Had positive results for HIV, HBV, or HCV by standard serologic tests.
14. Received any blood or blood products within the 2 weeks prior to randomization. IVIg or anti-rho (D) immunoglobulin (anti-D IgG) is allowed if used for rescue therapy, unless platelet count is > 30,000/mcL at the time of randomization.
15. Currently enrolled in an investigational drug or device study or has used an investigational drug/device within 30 days or 5 half-lives (whichever is longer) of Day 1.
16. History of alcohol or substance abuse that may impair or risk the subject's participation in the study.
17. Known allergy and/or sensitivity to the test article or its components.
18. Had major surgery within 28 days prior to randomization or has a surgical wound that is not fully healed.

Schedule of Events:

Table 22 C788-047 and C788-048: Schedule of Study Procedures

	Screening Day -30 to Day -1		Baseline	Treatment Period						Follow-up
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6-8	Visit 9-11	Visit 12-14	Visit 15[a]	Visit 16
Study Procedure	Scrn A	Scrn B[b]	Day 1	Week 2 ±3 days	Week 4 ±3 days	Weeks 6, 8, 10 ±3 days	Weeks 12, 14, 16 ±3 days	Weeks 18, 20, 22 ±3 days	Week 24 ±3 days	Week 26 ± 7 days
Informed Consent	X									
Inclusion/Exclusion	X	X								
Medical History	X		X							
Physical Exam and KPS[c]	X		X		X	Week 8	Weeks, 12, 16	Week 20	X	X
Concomitant Meds	X		X	X	X	X	X	X	X	X
Vital Signs[d]	X	X	X	X	X	X	X	X	X	
Bleeding Assessment[e]	X		X	X	X	X	X	X	X	X
ECG	X								X[l]	
CBC/Diff/Retic Count	X		X	X	X	Week 8	Weeks 12, 16	Week 20	X	X
Platelet Count[f]	X	X	X	X	X	X	X	X	X	X
Serum Chemistry	X		X		X	Week 8	Weeks 12, 16	Week 20	X	X[m]
LFTs[g]				X		Weeks 6, 10	Week 14	Weeks 18, 22		
INR/aPTT	X		X							
Immunoglobulin levels	X		X						X	
Urinalysis	X		X		X	Week 8	Weeks 12, 16	Week 20	X	
Pregnancy Test[h]	X		X		X	Week 8	Weeks 12, 16	Week 20	X	
D-dimer[i]	X									
SF-36[j]			X		X		Week 12		X	
Study Drug Dispensed			X	X	X	X	X	X		
Study Drug Accountability				X	X	X	X	X	X	
PK[k]				X		Week 6			X	
Adverse Events				X	X	X	X	X	X	X
Dose Adjustment					X	X	X	X		

a. Visit 15: Patients who withdraw early from the study will have a withdrawal visit equivalent to the Visit 15 study assessments.
b. Screening B is to confirm the platelet count is < 30,000/mcL.
c. Physical exam will include KPS at all visits and height and weight at baseline only.
d. Vital Signs include blood pressure, pulse and temperature.
e. Bleeding Assessment includes IBLS and WHO Bleeding Scale.
f. Platelet counts will be performed at the local lab.
g. LFTs include ALT, AST, ALP, LDH, and Bilirubin (total, direct, and indirect).
h. Pregnancy Test: For women of childbearing potential, regardless of birth control methodology. Serum test at screening and baseline (central lab) and urine tests at baseline and all other selected visits (performed at the site). The subject may begin treatment once the baseline urine pregnancy test is known to be negative (need not wait for serum pregnancy test).
i. D-dimer: D-dimer test will be performed at the local (site) laboratory at screening for any subject with a history of deep venous thrombosis (more than 6 months prior to randomization) who has not previously had the D-dimer tested. All anticoagulants must have been discontinued for 30 days prior to any D-dimer testing.
j. SF-36: At visits where the SF-36 is evaluated, the SF-36 must be the first assessment performed.
k. PK: an additional PK sample will be collected from patients whose dose is escalated at the next visit following dose escalation.
l. ECG: ECG at Visit 15 is only required for patients who enroll in the follow-up extension study.
m. Serum Chemistry: Serum chemistry analysis at the follow-up visit is only required if LFTs results were abnormal

at the Week 24 Visit.
[Source: C788-047 and C788-048 protocols]

Patients who fail to meet eligibility criteria could be re-screened once if there is an expectation that the subject would be eligible after the repeat screen (for example successful treatment of hypertension). Before a subject could be re-screened, approval was to be obtained from the Medical Monitor.

Platelet count:
During Screening Visit A (Visit 1), platelet count (performed at local lab) was to be obtained at least 4 days prior to Day 1 to allow for a second platelet count. Patients were to return for Screening Visit B (Visit 2) for an additional screening visit to assess the platelet count and vital signs. Screening Visits A and B were to be separated by at least 3 full days. The average platelet count from the 3 qualifying counts (Visits 1 and 2 and one count within 3 months of baseline) was to be < 30,000/mcL. In addition, the individual platelet count at any visit could not exceed 35,000/mcL, unless as a result of rescue therapy.

Medical history included documentation of ITP diagnosis and the following test results (if performed) to rule out secondary ITP:

- Helicobacter pylori
- Active viral infection including HIV, Hepatitis A, B, and C.
- Thyroid disease including negative test for antithyroglobulin antibodies and/or TSH level.
- Presence of autoimmune hemolytic anemia, direct antiglobulin test (DAT) and reticulocyte count.
- Tests for antinuclear antibodies (ANA), antiphospholipid antibodies (APLA) including anticardiolipin and lupus anticoagulant, anti-double stranded DNA, rheumatoid factor, and complement (C3 and C4).
- Bone marrow aspirate and biopsy.

<u>Treatment Modification Plan:</u>
For excessive increase in platelet count, no changes in the dose/regimen of allowed concomitant therapeutic agents (azathioprine, glucocorticoids, danazol) were to be made and the following guidelines were to be followed:

- For platelet counts > 250,000/mcL:
  - Reduce the dose of study drug to dose level -1.
  - Monitor the platelet count every 72 hours until platelet count falls to <200,000/mcL.
- For platelet counts > 150,000/mcL and ≤ 250,000/mcL:
  - Continue study drug at full dose.
  - Monitor the platelet count every 72 hours until stable to assure it does not exceed 250,000/mcL.

Rescue therapy was allowed for patients in the following circumstances:

- Platelet count < 50,000/mcL and at immediate risk of bleeding or with clinically significant bleeding or wet purpura.
- Platelet count < 50,000/mcL and requires urgent or emergent surgery (elective surgeries must be postponed until study completion).

Allowed rescue therapy included the following:

- IVIg: up to 1 g/kg x 1-3 days, or
- IV anti-D: up to 50-75 mcg/kg x 1-2 days, or
- IV methylprednisolone up to 1 g/day x 1-3 days or oral dexamethasone up to 40 mg/day x 1-2 days or oral prednisone up to 1 mg/kg/day x 1-3 days.

Patients could be withdrawn from the study in the following circumstances:

- Lack of platelet response (defined as platelet count < 50,000/mcL or increase of < 20,000/mcL over baseline [if baseline is < 15,000/mcL]) after 12 weeks of therapy, of which 4 weeks must have been at 150 mg PO BID (unless this higher dose was not well tolerated). Patients who were withdrawn could proceed to receive fostamatinib in the open-label follow-up extension study (C788-049).
- Requirement for rescue therapy after Week 10 (non-responders).

In addition, treatment with the study drug administration could be modified for adverse events that included the following circumstances:

- Increases in ALT, AST, or bilirubin
- ANC < 1000/mm^3 or 1.0 x 10^9/L
- Severe diarrhea
- Increase in BP to > 140/90 mmHg
- Other severe or life-threatening adverse events considered related to study drug administration.

Following resolution of the AE that resulted in dose reduction, dose re-escalation could be considered. If a subject experienced additional dose limiting adverse events, the dose could be further reduced to as low as 100 mg once daily (in the morning).

For non-diarrhea gastrointestinal toxicities, symptomatic treatment (e.g., omeprazole or ranitidine) was to be initiated. In the event of significant upper abdominal pain/distress, the possibility of pancreatitis was to be considered and serum amylase and lipase monitored.

Dose adjustments for increased LFT, management of neutropenia, diarrhea and increased blood pressure were as follows:

Dose Modification for Possible Drug-Induced Liver Injury (DILI):

Fostamatinib can inhibit UGT1A1 (enzyme responsible for the glucuronidation of bilirubin); occasionally an isolated increase in total and unconjugated (indirect) bilirubin may be observed. Study drug was not to be interrupted for an isolated increase in total and unconjugated (indirect) bilirubin.
-If AST or ALT ≥ 3x ULN and total bilirubin (TBL)> 2x ULN, with ALP < 2x ULN (Hy's law criteria), treatment with the study drug was to be discontinued immediately.
-If AST or ALT ≥ 3x ULN or TBL > 2x ULN with symptoms (nausea, vomiting, abdominal pain):

- Study drug administration was to be interrupted immediately.
- LFTs, including bilirubin and alkaline phosphatase were to be repeated every 72 hours until ALT/AST or TBL returned to < 1.5x ULN.
- When the ALT/AST or TBL returned to < 1.5x ULN study drug could be restarted at dose level -1.

-If AST or ALT ≥ 3x ULN or TBL > 2x ULN and subject is asymptomatic:

- LFTs (including bilirubin and ALP) were to be repeated within 72 hours.
- If repeat testing showed an increase in ALT/AST or TBL and the ALT/AST>5x ULN, study drug administration was to interrupted immediately.
- LFTs, including bilirubin and alkaline phosphatase were to be repeated every 72 hours until ALT/AST was decreasing, and to be followed until transaminase returned to < 1.5x ULN.
- Upon return of ALT/AST or TBL to < 1.5x ULN, study drug could be restarted at dose level -1.

Management of neutropenia:
-If decrease in absolute neutrophil count (ANC) to < 1,000/mcL:

- ANC testing was to be repeated within 72 hours.
- If repeat testing confirmed that ANC is < 1,000/mcL, study drug administration was to be interrupted immediately and ANC testing repeated at 72 hour intervals.
- When ANC recovered to > 1,500/mcL, study drug administration was to be restarted at dose level -1.

-If second event of ANC < 1,000/mcL occurred:

- ANC testing was to be confirmed as above.
- If confirmed, study drug was to be interrupted immediately until ANC > 1,500/mcL.
- And study drug was to be restarted at dose level -2.

Management of diarrhea:
Monitoring and early aggressive treatment of diarrhea was recommended to avoid severe complications such as dehydration.
-For Grade 1 or 2 diarrhea

- Study drug could be continued.
- All laxatives were to be discontinued.
- Patients were to be instructed to drink 8-10 glasses of water or clear fluids per day.
- Patients were to be encouraged to make dietary changes including elimination of dairy

products and eating smaller but more frequent meals.
- Microbiologic evaluation of stool sample and antibiotics initiation were to be considered if subject was neutropenic.
- For Grade 1, initiating treatment with loperamide was to be considered and for Grade 2, treatment with loperamide was to be initiated.
- Patients with persistent diarrhea (> 48 hours) were to be monitored for dehydration and electrolyte imbalance.

- For Grade 3 or 4 diarrhea:
- Treatment with study drug was to be interrupted immediately.
- Aggressive fluid replacement was to be initiated to treat potential dehydration.
- Microbiologic evaluation of stool sample and antibiotics initiation were to be considered if subject was neutropenic.
- Treatment with loperamide was to be initiated and continued until the diarrhea had been resolved.
- When diarrhea improved to ≤ Grade 1, study drug was to be restarted at dose level -1.

-Management of Second Event of Grade 3 and 4 Diarrhea
- Treatment with study drug was to be interrupted immediately.
- Aggressive fluid replacement was to be initiated to treat potential dehydration.
- Microbiologic evaluation of stool sample and antibiotics initiation were to be considered if subject was neutropenic.
- Treatment with loperamide was to be initiated and continued until the diarrhea had been resolved.
- When diarrhea improved to ≤ Grade 1, study drug was to be restarted at dose level -2.

Management of hypertension:
Blood pressure was to be kept below 140/90 mmHg. For patients with increased cardiovascular risk, diabetes or renal insufficiency, maintaining the blood pressure below 130/80 mmHg was considered. If aggressive and appropriate anti-hypertensive therapy did not control BP (<140/90), it was recommended to reduce the dose of study drug. The following events required discontinuation of the study drug:
- The subject becomes symptomatic due to blood pressure elevation.
- The blood pressure cannot be brought under control despite best efforts at blood pressure management.

- If BP ≥ 180/110 mmHg at any time after randomization:
- Study drug administration was to be interrupted immediately.
- Anti-hypertensive medication was to be initiated or increased.
- BP reassessed twice weekly.
- If repeat BP ≥ 180/110 mmHg despite anti-hypertensive treatment, study drug was to be discontinued.
- Anti-hypertensive medications were to be increased until controlled.
- Study drug was to be restarted when blood pressure < 140/90 mm Hg.

- If the BP was 160-179 systolic or 100-109 diastolic at any visit after randomization:

- Study drug was to be continued at assigned dose level.
- Anti-hypertensive therapy was to be initiated or increased immediately.
- Reassessed BP twice weekly.
- If, after 1 week, the BP remained ≥ 160-179 systolic or ≥ 100-109 diastolic despite aggressive antihypertensive therapy, study drug administration was to be interrupted.
- Anti-hypertensive medications were to be increased until controlled.
- Study drug was to be restarted when blood pressure < 140/90 mm Hg.

- If BP is ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic but below 160 systolic or 100 diastolic at any visit after randomization:

- Study drug was to be continued at assigned dose level and blood pressure assessment repeated within 1 week.
- If blood pressure remained above ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic after 1 week, antihypertensive therapy was to be initiated or increased immediately.
- Monitoring BP weekly was to be continued until controlled.
- If BP remained ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic for more than 8 weeks, despite aggressive antihypertensive therapy, dose of study drug was to be reduced to dose level -1.

Study Endpoints

The primary efficacy endpoint was achievement of a stable platelet response by Week 24, defined as having a platelet count of at least 50,000/mcL on at least 4 of the last 6 scheduled visits between Weeks 14-24. Patients who discontinue treatment prior to Week 24 due to lack of efficacy or to due an AE, or who receive rescue treatment after 10 weeks, were to be considered non-responders. The null and alternative hypotheses for the comparison of fostamatinib vs. placebo were as follows: H_0: $p_F = p_P$ vs. H_1: $p_F \neq p_P$ (p_F and p_P: true proportions of achieving a stable platelet response by 24 weeks for fostamatinib and placebo, respectively.) The null hypothesis was to be tested using a 2-sided Fisher's Exact Test conducted with a significance level of 0.05.

Secondary efficacy endpoints were as follows:

1. Platelet response (a platelet count of at least 50,000/mcL) at Week 12.
2. Platelet response (a platelet count of at least 50,000/mcL) at Week 24.
3. Among patients with a baseline platelet count < 15,000/mcL, achievement of a count ≥ 30,000/mcL, and at least 20,000/mcL above baseline, at Week 12.
4. Among patients with a baseline platelet count < 15,000/mcL, achievement of a count ≥ 30,000/mcL, and at least 20,000/mcL above baseline, at Week 24.
5. Frequency and severity of bleeding according to the ITP Bleeding Score (IBLS) over the 24-week study period.
6. Frequency and severity of bleeding according to the World Health Organization (WHO) bleeding scale over the 24-week study period.

The secondary efficacy endpoints were to be analyzed using the fixed sequence testing procedure with the endpoints order as shown above. Testing for a given endpoint was to be performed only if the null hypothesis was rejected for all previously tested endpoints. A significance level of 0.05 was to be used for all tests.

Statistical Analysis Plan

The first edition of the Statistical Analysis Plan (SAP) for Study 047 was dated June 27, 2014. The second edition was dated August 14, 2016; there were no major changes to the efficacy analyses in the second edition.

The first edition of the SAP for Trial 048 was dated July 29, 2015. This edition included a sensitivity analysis based on multiple imputation methods for the primary efficacy endpoint. The second edition of the SAP was dated October 3, 2016; there were no major changes to efficacy analyses specified in the first edition.

Efficacy analysis:
All efficacy analyses were to be performed using the intent-to-treat (ITT) population defined as all randomized patients. The efficacy analyses based on the ITT population were considered the primary efficacy analyses. Patients were to be analyzed according to their randomized treatment assignment.

All efficacy endpoints were also to be analyzed based on the Per-Protocol (PP) population. The PP population was to include all patients in the ITT population who had no major protocol violations. Major protocol violations included patients:

- Not receiving any study treatment
- Not receiving the correct study treatment
- Failing to meet eligibility criteria
- Other major protocol violations, as determined by a blinded review of the data.

Baseline measurements were defined as the last measurement for the corresponding variable before the first randomized dose at Visit 3 (Day 1). For all variables, change from baseline was defined as the post-baseline measurement minus the baseline measurement.

Safety analysis:
The Safety Population was to include all randomized patients who received any amount of randomized study drug and patients were to be analyzed according to the actual treatment received.

Sample size:
The sample size of 75 patients (fostamatinib: 50, placebo: 25) in each trial was determined based on a two-sided, Fisher's Exact Test with an alpha level of 0.05, 90% power for the primary efficacy endpoint of achieving a stable platelet response and a 2:1 (fostamatinib:placebo) allocation, assuming a true proportion for fostamatinib of 0.40 and a true proportion for

placebo of 0.05.

Reviewers Notes: In the SAP, the sponsor proposed using exact (Clopper-Pearson) confidence intervals for the response rate in each arm. The sponsor however presented interval estimates based on the Normal approximation. This approximation yields intervals with poor coverage if the response rate and/or the sample is small. Consequently, confidence interval of a difference in response rates based on Normal approximations are inaccurate. In the primary efficacy analysis, the sponsor presented interval estimates for the difference in the response using a Normal approximation. We communicated to the sponsor our concerns following the mid-cycle meeting. In their response dated October 17, 2017, the sponsor presented further analysis using the Miettinen-Nurminen and Newcombe methods. These intervals are based on asymptotic Normality and have the same problems as the Normal approximation. In this review, we present more conservative interval estimates for the difference in response rate; these are based on the Exact unconditional interval estimation method.

Missing data for the primary and secondary efficacy endpoints were to be imputed using the last observation carried forward (LOCF) method. For the primary efficacy endpoint, for example, if a platelet count was missing for Weeks 14 and 18, the last platelet count prior to Week 14 was to be imputed for Week 14 and the last platelet count prior to Week 18 was to be imputed for Week 18. The value of the primary efficacy endpoint was then to be determined by whether the subject's platelet count was ≥ 50,000/mcL for at least 4 of the last 6 scheduled visits over Weeks 14-24, including those visits with imputed values. No imputation was to be performed for missing data other than for the primary and secondary efficacy endpoints.

Review comment: The LOCF method is problematic as the last platelet count value may not always reflect the true platelet count for the missing data. In the March 26, 2014 advice letter, the FDA commented that the Agency did not agree with applying the LOCF method for missing data imputation for the primary efficacy endpoint analysis. This position is consistent with the missing data imputation method for the primary efficacy analysis for Nplate (romiplostim) which was approved in 2008. It was defined that if no platelet measurements were available on the weekly scheduled dose day, then that week was considered to have no platelet response. Patients who discontinued early from the study were considered not to have had a weekly platelet response after study discontinuation.

Protocol Amendments

The clinical trial landmarks and protocol amendments are summarized below.

Table 23 C788-047 and C788-048: Landmarks and Key Protocol Amendments

Date	Landmarks
December 16, 2013	C788-047 and C788-048: Initial protocol (version 1) No patients were enrolled under version 1.
April 8, 2014	C788-047 and C788-048: Version 2

	- Revised the inclusion criteria to require that a subject must have had a diagnosis of ITP for at least 3 months prior to being randomized. - Revised the eligibility criteria to exclude only patients at significant risk of DVT. The timeframe has been shortened to thrombosis within the 6 months prior to randomization and, for patients who have a more distant history of DVT, results of a D-dimer test must be within the normal range as a measure of low risk for DVT recurrence. - Revised the exclusion criteria to specify that the IBLS score cannot be greater than 2 at any of the sites evaluated. - Added D-dimer testing to Screening Visit A and the footnotes to the table were updated to specify that the D-dimer test should be performed at the local lab and is only required for patients who have a history of deep vein thrombosis greater than 6 months prior to randomization. -An ECG has been added to the Visit 15 assessment for patients going onto the extension study to assure that a recent ECG is available, prior to treatment, for those patients who roll-over into the extension study, particularly those patients previously randomized to placebo. - Allowed for additional flexibility in study drug dose for patients in whom clinical benefit is shown, the text was modified that patients who have a dose reduction to due adverse events may be allowed to have their dose re-escalated after the adverse event has resolved.
July 14, 2014	C788-047: Study initiation date (first subject first dose of study drug)
November 21, 2014	C788-047: Version 3 - Revised the inclusion criteria to clarify what constitutes a typical treatment regimen for ITP. - Added exclusion of patients who have had major surgery within 28 days prior to randomization. - Revised the washout requirements to clarify that patients must discontinue all therapeutic agents, other than those allowed as ITP concomitant therapy. - Added a footnote to the Double-Blind Treatment table in each section to clarify that patients may continue the specific concurrent therapies for ITP that are allowed at study entry.
December 9, 2014	C788-048: Version 3 (same revisions as for C788-047)
January 9, 2015	C788-048: Study initiation date (first subject first dose of study drug)
April 21, 2016	C788-047: Study completion date (last subject completion)
August 31, 2016	C788-048: Study completion date (last subject completion)

[Source: FDA compilation]

Data Quality and Integrity: Sponsor's Assurance

For both 047 and 048 trials, a clinical contract research organization (CRO) was delegated to perform study activities (team training, site monitoring and management, data management,

randomization code assignment, and some aspects of pharmacovigilance). A safety CRO performed safety database set-up, data entry and maintenance, coding of serious adverse event (SAE) data and SAE case processing. Original data and any changes were recorded using the electronic data capture system, with changes tracked and recorded in an electronic audit trail. According to the applicant, the handling of data, including data quality assurance, complied with the protocol and all applicable regulatory requirements and guidelines (e.g., ICH and GCP).

The applicant provided signed certification by Anne-Marie Duliege, MD (the executive vice president and chief medical officer) that the contents of the study reports for C788-047 and C788-048 accurately describe the conduct and results of the studies.

7.2.2. Study Results

Compliance with Good Clinical Practices

Both 047 and 048 trials were reviewed and approved by the Independent Ethics Committees or Institutional Review Boards and conducted in accordance with Good Clinical Practice (GCP) and the Declaration of Helsinki. Written informed consent was obtained from each subject prior to performance of study-specific procedures.

Financial Disclosure

The applicant provided FDA financial certification form 3454 signed by Ryan Maynard, the executive vice president and chief financial officer for Rigel Pharmaceuticals, dated April 6, 2017. The applicant certified to the following statement:

"As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

The submission contained a list of clinical investigators that participated in the C788-047 (189 principal/sub-investigators) and C788-048 (81 principal/sub-investigators) trials.

In both trials, none of the investigators were full or part time sponsor employees.

Patient Disposition

C788-047:
Trial 047 randomized a total of 76 patients (fostamatinib: 51, placebo: 25) from 35 sites in 8 countries. All patients were enrolled from North American, European (mostly Western European) or Australian sites (see table 25). The PP population was to be comprised of patients in the ITT population who had no major protocol violations.

Review comment: According to the applicant's assessment, the PP population was the same as the ITT population (fostamatinib: 51 patients, placebo: 25 patients). However, based on the provided datasets, patients with major protocol violations were identified in both arms (fostamatinib: 19 patients [37%), placebo: 8 patients [32%]). See table 29 below. No justification of the discrepancy was provided by the applicant. Additional statistical evaluation will be performed in efficacy evaluation section based on the PP population excluding patients who had major protocol violation.

C788-048:
A total of 74 patients (fostamatinib: 50, placebo: 24) were randomized from 23 sites in 8 European countries (mostly Eastern European [86%]) in the 048 trial (see table 25).

Review comment: Per applicant's analysis, the PP population was comprised of a total of 72 patients (fostamitib: 49, placebo: 23). One patient ((b) (6)) randomized to the placebo arm was provided the wrong treatment kit by mistake, and was treated with fostamatinib for 2 weeks. Therefore, this patient was excluded from the PP population. Another patient ((b) (6)) randomized to the fostamatinib arm was excluded from the PP population because within two weeks following randomization, it was determined that the patient's thrombocytopenia was not due to ITP but related to bone marrow infiltration with plasma cells due to multiple myeloma. Both patients did not achieve a stable platelet response as defined by the primary efficacy analysis.

In addition to these two patients, additional patients with major protocol violations were identified in both arms. According to the datasets, 18% and 33% of patients in the fostamatinib and placebo arm, respectively had major protocol violations (see table 30) in the 048 trial.

The table below summarizes the analysis population of the 047 and 048 trials as specified per applicant.

Table 24 C788-047 and C788-048: Analysis Populations

	C788-047			C788-048		
	Fostamatinib (n=51)	**Placebo (n=25)**	**Total (n=76)**	**Fostamatinib (n=50)**	**Placebo (n=24)**	**Total (n=74)**
ITT population	51	25	76	50	24	74
PP population	51	25	76	49	23	72

Safety population	51	25	76	51*	23*	74

* One patient randomized to the placebo arm was assigned to the wrong treatment by mistake, and was treated with fostamatinib for 2 weeks. This patient's efficacy data were analyzed with the placebo arm, but the safety data were analyzed with the fostamatinib arm.
[Source: ADSL.xpt]

Table 25 C788-047 and C788-048: Patient Enrollment by Country (ITT Population)

	C788-047			C788-048		
	Fostamatinib (n=51)	Placebo (n=25)	Total (n=76)	Fostamatinib (n=50)	Placebo (n=24)	Total (n=74)
United Kingdom	18 (35%)	7 (28%)	25 (33%)	-	-	-
USA	12 (24%)	8 (32%)	20 (26%)	-	-	-
Australia	9 (18%)	4 (16%)	13 (17%)	-	-	-
Italy	4 (8%)	3 (12%)	7 (9%)	-	-	-
Canada	5 (10%)	0	5 (7%)	-	-	-
Hungary	1 (2%)	2 (8%)	3 (4%)	-	-	-
Denmark	2 (4%)	0	2 (3%)	-	-	-
Netherlands	0	1 (4%)	1 (1%)	-	-	-
Poland	-	-	-	24 (48%)	14 (58%)	38 (51%)
Bulgaria	-	-	-	9 (18%)	4 (17%)	13 (18%)
Czech Republic	-	-	-	9 (18%)	2 (8%)	11 (15%)
Spain	-	-	-	3 (6%)	1 (4%)	4 (5%)
Norway	-	-	-	2 (4%)	1 (4%)	3 (4%)
Austria	-	-	-	1 (2%)	1 (4%)	2 (3%)
Romania	-	-	-	1 (2%)	1 (4%)	2 (3%)
Germany	-	-	-	1 (2%)	0	1 (1%)

[Source: ADSL.xpt]

In both the 047 and 048 trials, a higher proportion of patients in the fostamatinib arm completed the 24-week study period (047 [fostatinib: 24%, placebo: 4%], 048 [fostamatinib: 26%, placebo: 8%]). Reasons for discontinuing the study for patients randomized to the fostamatinib arm were consistent in both trials, which were mostly due to lack of response at Week 12 or later (047: 55%, 048: 66%) and AEs (047: 16%, 048: 4%).

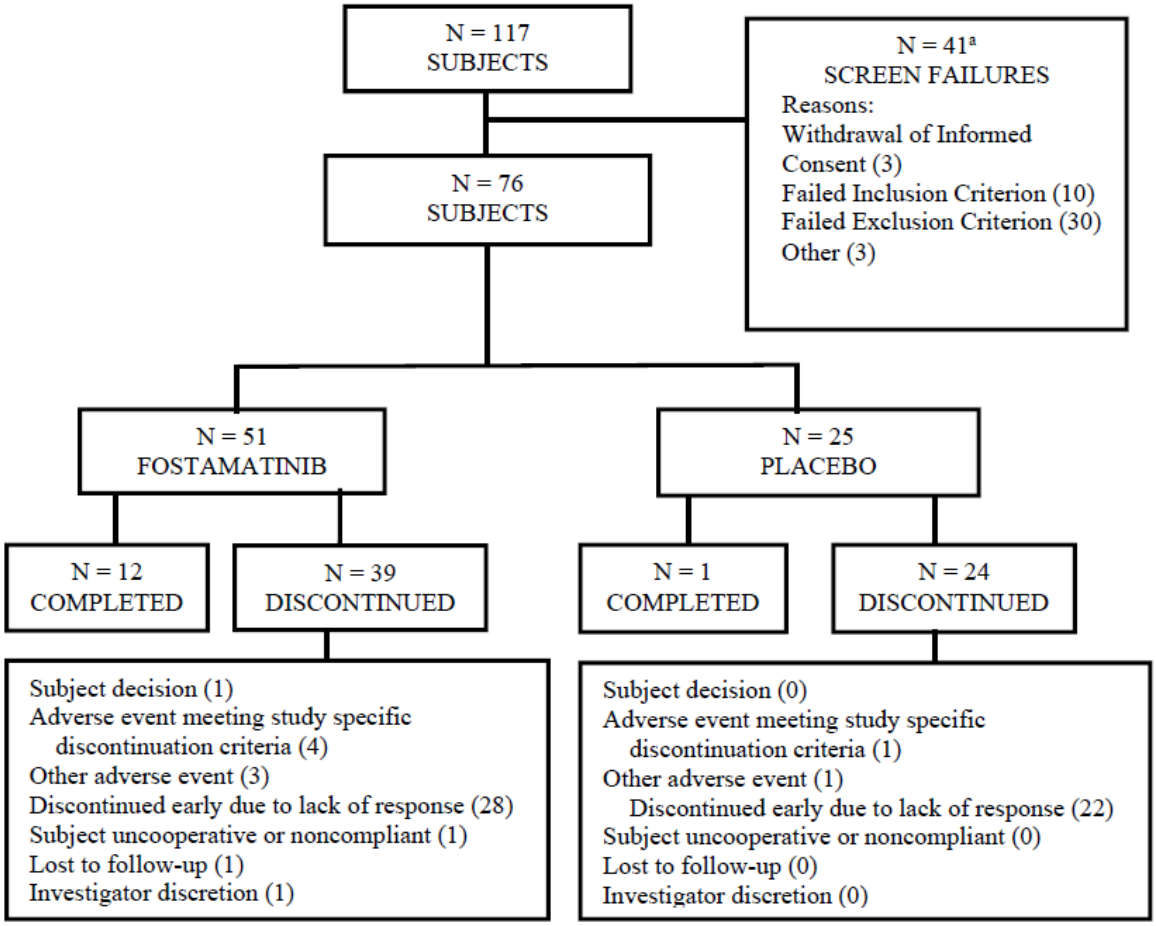
Overall, a total of 59 patients (78%) (fostamatinib: 36 patients [71%], placebo: 23 patients [92%]) from the 047 trial and 64 patients (87%) (fostamatinib: 43 patients [86%], placebo: 21 patients 88%]) from the 048 trial continued on fostamatinib treatment in the extension study. In both trials, among the patients in the fostamatinib arm that continued in the extension study, most patients transitioned after early discontinuation due to lack of response (047: 51%, 048: 64%). The table and figures below summarize patient withdrawal and disposition in both trials.

Table 26 C788-047 and C788-048: Patient Withdrawal (ITT Population)

	C788-047			C788-048		
	Fostamatinib (n=51)	**Placebo (n=25)**	**Total (n=76)**	**Fostamatinib (n=50)**	**Placebo (n=24)**	**Total (n=74)**
Patients who completed the study	12 (24%)	1 (4%)	13 (17%)	13 (26%)	2 (8%)	15 (20%)
Discontinued from the study early	39 (77%)	24 (96%)	63 (83%)	37 (74%)	22 (92%)	59 (80%)
Reason for discontinuation						
Discontinued early due to lack of response (at Week 12 or later)	28 (55%)	22 (88%)	50 (66%)	33 (66%)	19 (79%)	52 (70%)
AE meeting study specific discontinuation criteria	4 (8%)	1 (4%)	5 (7%)	0	2 (8%)	2 (3%)
Other AE	4 (8%)	1 (4%)	4 (5%)	2 (4%)	0	2 (3%)
Patient decision	1 (2%)	0	1 (1%)	1 (2%)	1 (4%)	2 (3%)
Patient uncooperative or noncompliant	1 (2%)	0	1 (1%)	0	0	0
Lost to follow-up	0	0	1 (1%)	0	0	0
Investigator discretion	1 (2%)	0	1 (1%)	1 (2%)	0	1 (1%)
Did patient continue in the extension study?						
No	15 (29%)	2 (8%)	17 (22%)	7 (14%)	3 (13%)	10 (14%)
Yes	36 (71%)	23 (92%)	59 (78%)	43 (86%)	21 (88%)	64 (87%)
Transitioned after early discontinuation due to lack of response	26 (51%)	22 (88%)	48 (63%)	32 (64%)	19 (79%)	51 (69%)
Transitioned after completion of the 24wk study period	10 (20%)	1 (4%)	11 (15%)	11 (22%)	2 (8%)	13 (18%)

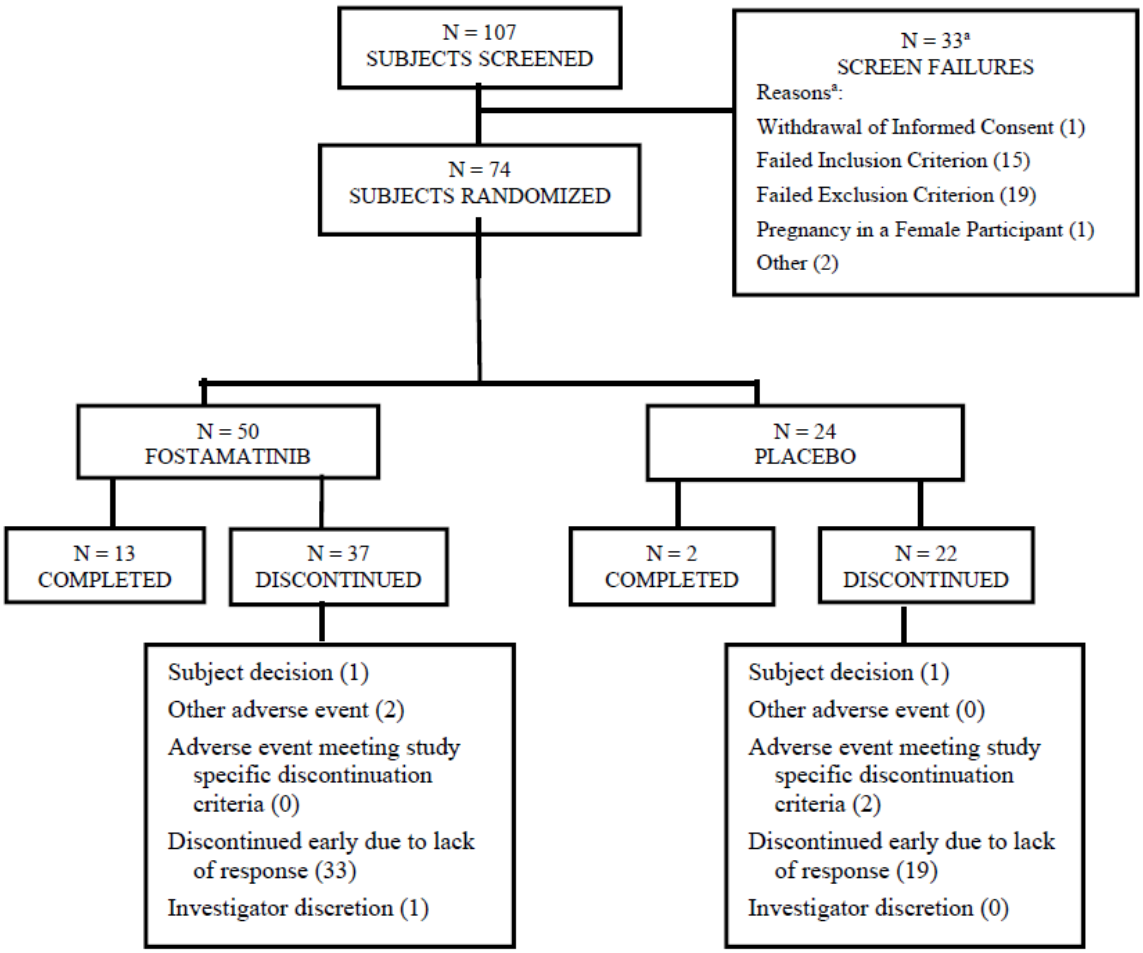
[Source: ADSL.xpt]

Figure 4 C788-047: Patient Disposition



[Source: C788-047 CSR]

Figure 5 C788-048: Patient Disposition



[a] A subject may have had more than one reason for screen failure.
[Source: C788-048 CSR]

Protocol Violations/Deviations

Overall, the reported proportion of patients that had a protocol violation was quite high in both trials (047: 90%, 048: 77%). Table 27 summarizes the protocol violations as reported by the applicant. However, the datasets also contained exemptions which were not included in the applicant's analysis. Table 28 summarizes the protocol violations including exemptions allowed by the principal investigator.

Table 27 C788-047 and C788-048: Protocol Violations (ITT Population)

	C788-047			C788-048		
	Fostamatinib (n=51)	Placebo (n=25)	Total (n=76)	Fostamatinib (n=50)	Placebo (n=24)	Total (n=74)
All patients*	47 (92%)	21 (84%)	68 (90%)	38 (76%)	19 (79%)	57 (77%)
Visit/procedure requirement	38 (75%)	17 (68%)	55 (72%)	26 (52%)	15 (63%)	41 (55%)

Laboratory	14 (28%)	4 (16%)	18 (24%)	3 (6%)	1 (4%)	4 (5%)
Visit schedule	9 (18%)	6 (24%)	15 (20%)	10 (20%)	6 (25%)	16 (22%)
Non-compliance	8 (16%)	3 (12%)	11 (14%)	0	0	0
Regulatory	0	0	0	8 (16%)	3 (13%)	11 (15%)
Eligibility criteria	6 (12%)	2 (8%)	8 (11%)	7 (14%)	4 (17%)	11 (15%)
Concomitant medication	5 (10%)	3 (12%)	8 (11%)	1 (2%)	1 (4%)	2 (3%)
Other	6 (12%)	1 (4%)	7 (9%)	4 (8%)	0	4 (5%)
Dosing deviation	1 (2%)	0	1 (1%)	4 (8%)	4 (17%)	8 (11%)

*Based on number of patients. A patient can appear in more than one category.
[Source: ADDV.xpt]

When including the exemptions, 93% and 82% of patients in the 047 and 048 trial, respectively, had protocol violations. Most of the violations were related to visit/procedure requirement, eligibility criteria, laboratory procedures and visit schedules. Most of the protocol violations in the "regulatory" and "other" categories were related to informed consent document (failure to re-sign consent with re-screening or signing an incomplete informed consent).

Although the overall proportions of patients that had protocol violations were quite high in both trials, the proportions of protocol violations in each category were similar between the treatment arms in both trials.

Table 28 C788-047 and C788-048: Protocol Violations Including Exemptions Allowed by the PI (ITT Population)

	C788-047			C788-048		
	Fostamatinib (n=51)	**Placebo (n=25)**	**Total (n=76)**	**Fostamatinib (n=50)**	**Placebo (n=24)**	**Total (n=74)**
All patients*	48 (94%)	23 (92%)	71 (93%)	40 (80%)	21 (88%)	61 (82%)
Visit/procedure requirement	40 (78%)	18 (72%)	58 (76%)	26 (52%)	15 (63%)	41 (55%)
Laboratory	16 (31%)	6 (24%)	22 (29%)	3 (6%)	1 (4%)	4 (5%)
Visit schedule	12 (24%)	6 (24%)	18 (24%)	10 (20%)	6 (25%)	16 (22%)
Non-compliance	8 (16%)	3 (12%)	11 (15%)	0	0	0
Regulatory	0	0	0	8 (16%)	3 (13%)	11 (15%)
Eligibility criteria	17 (33%)	6 (24%)	23 (30%)	10 (20%)	7 (29%)	17 (23%)
Other	6 (12%)	2 (8%)	8 (11%)	4 (8%)	0	4 (5%)
Concomitant medication	6 (12%)	4 (16%)	10 (13%)	1 (2%)	1 (4%)	2 (3%)
Dosing deviation	1 (2%)	0	1 (1%)	5 (10%)	4 (17%)	9 (12%)
Exemptions (other)	14 (28%)	6 (24%)	20 (26%)	5 (10%)	4 (17%)	9 (12%)

*Based on number of patients. A patient can appear in more than one category.
[Source: ADSL.xpt]

Tables 29 and 30 summarize major protocol violations with regard to eligibility criteria, concomitant therapy or wrong study treatment. In 047 and 048 trials, 27 patients (36%) (fostamatinib: 19 patients [37%], placebo: 8 patients [32%]) and 17 patients (23%) (fostamatinib: 9 patients [18%], placebo: 8 patients [33%]), respectively, had major protocol violations. In the 047 and 48 trials, a total of 4 patients (5%) (fostamatinib: 3 patients [6%], placebo: 1 patient [4%]) and 3 patients (4%) (fostamatinib: 1 patient [2%], placebo: 2 patients [8%]), respectively, did not meet the baseline platelet count requirement. In the 048 trial, a total 3 patients (6%) in the fostamatinib arm had not received at least one prior systemic treatment for ITP. A total of 6 patients (8%) (fostamatinib: 3 patients [6%], placebo: 3 patients [12%]) in the 047 trial and 1 patient (1%) (fostamatinib: 0 patient, placebo: 1 patients [4%]) in the 048 trial received prohibited treatment or wrong study treatment during the trial.

Table 29 C788-047: Major Protocol Violations (ITT Population)

	Fostamatinib (n=51)	**Placebo (n=25)**
Major protocol violations	19 (37%)	8 (32%)
Eligibility criteria	17 (33%)	6 (24%)
Did not use central lab for hematology levels	5 (10%)	1 (4%)
Patient was on 20mg of prednisone vs 10mg.	1 (2%)	0
Positive HBV	1 (2%)	0
Did not meet baseline platelet count requirement	3 (6%)	1 (4%)
Did not meet the Hgb or lymphocyte count requirement	4 (8%)	3 (12%)
Patient was a screen failure couple months ago	1 (2%)	0
Received new prescription drug within 2 weeks of Day 1	1 (2%)	0
Had IBLS score of Grade 2	1 (2%)	0
Did not meet blood pressure requirement	1 (2%)	1 (4%)
Patient was taking 2 meds for ITP (methylprednisolone and azathioprine)	0	1 (4%)
Shorter washout duration	0	1 (4%)
Had history of SLE	0	1 (4%)
Concomitant therapy	3 (6%)	3 (12%)
Had transfusion as rescue therapy[1]	1 (2%)	0
Dose increase or initiation of steroids[2]	1 (2%)	2 (8%)
Received Nplate[3]	0	1 (4%)
Reduction of concurrent ITP medication (danazol) from 400 mg to 200 mg due to elevated ALT values	1 (2%)	0

Based on number of patients. A patient can appear in more than one category.
1. Patient (b) (6) randomized to the fostamatinib arm received transfusion as rescue therapy due to bleeding.
2. Patient (b) (6) randomized to the fostamatinib arm was prescribed dexamethasone 40 mg, patients (b) (6) and (b) (6) randomized to the placebo arm increased dose of prednisone during the trial.
3. Patient (b) (6) randomized to the placebo arm was given Nplate for the overseas trip.
[Source: ADDV.xpt]

Table 30 C788-048: Major Protocol Violations (ITT Population)

	Fostamatinib (n=50)	Placebo (n=24)
Major protocol violations	9 (18%)	8 (33%)
Eligibility criteria	9 (18%)	7 (29%)
Did not receive previous treatment for ITP[1]	3 (6%)	0
Did not use central lab used hematology levels	0	1 (4%)
Patient is taking prednisone 15 mg	0	1 (4%)
Had thyroid disease	3 (6%)	
Did not meet baseline platelet count requirement	1 (2%)	2 (8%)
Did not meet Hgb, lymphocyte count requirement	1 (2%)	2 (8%)
Did not meet requirement for liver enzymes	0	1 (4%)
Received prescription drug within 2 wks of day 1	1 (2%)	
Had IBLS score of Grade 2	1 (2%)	1 (4%)
Did not meet blood pressure requirement	1 (2%)	0
Shorter washout duration	0	1 (4%)
D-dimer not in normal range/had DVT < 6 mos	2 (4%)	0
Received wrong study treatment	0	1 (4%)
Received the kit (study med) for different arm[2]	0	1 (4%)

Based on number of patients. A patient can appear in more than one category.
1. Patients (b) (6) randomized to fostamatinib arm did not receive prior treatment for ITP. However, none of these patients were responders as defined in the primary endpoint.
2. Patient (b) (6) randomized to the placebo arm received the wrong kit (study treatment) for the different arm by the system.
[Source: ADDV.xpt]

Review comment: In both 047 and 048 trials, patients who had achieved a stable platelet response (as defined by the primary endpoint) mostly met the requirement for the platelet count (see table 38; two responders had baseline average platelet count of ≥30,000/mcL [patient (b) (6) had average platelet count of 30 x 10^9/L and patient (b) (6) average platelet count was 35 x 10^9/L]), met the requirement for prior systemic therapy and did not receive prohibited treatment or wrong study treatment during the trial. Other major protocol violations among the responders included dose reduction of concurrent ITP medication (danazol) from 400 mg to 200 mg due to elevated ALT values, use of local hemoglobin values for screening, higher average blood pressure than permitted and history of thyroid disease which are unlikely to affect the primary endpoint results.

Therefore, it is unlikely that these major protocol violations affected the results of the primary endpoint.

Table of Demographic Characteristics

Patient demographics were largely balanced between the treatment arms in both trials. Approximately 60% of patients were females in both trials, the median age was 57 years (range 20-88) in study 047 vs. 49.5 years (range 20-82) in study 048. The proportions of patients who

were younger than 65 years and whose race was White were larger in the 048 trial (age <65 years [047: 66%, 048: 82%], White [047: 86%, 048: 100%]).

Table 31 C788-047 and C788-048: Patient Demographics (ITT Population)

	C788-047			C788-048		
	Fostamatinib (n=51)	**Placebo (n=25)**	**Total (n=76)**	**Fostamatinib (n=50)**	**Placebo (n=24)**	**Total (n=74)**
Gender						
Female	30 (59%)	17 (68%)	47 (62%)	31 (62%)	13 (54%)	44 (60%)
Male	21 (41%)	8 (32%)	29 (38%)	19 (38%)	11 (46%)	30 (41%)
Age (years)						
Median	57	57	57	49.5	49.5	49.5
Range	20-88	26-77	20-88	21-82	20-78	20-82
Age (by category, years)						
< 65	32 (63%)	18 (72%)	50 (66%)	41 (82%)	20 (83%)	61 (82%)
≥ 65	19 (38%)	7 (28%)	26 (34%)	9 (18%)	4 (17%)	13 (18%)
Race						
White	44 (86%)	21 (84%)	65 (86%)	50 (100%)	24 (100%)	74 (100%)
Asian	3 (6%)	2 (8%)	5 (7%)	0	0	0
Black/African American	2 (4%)	2 (8%)	4 (5%)	0	0	0
Other	2 (4%)	0	2 (3%)	0	0	0

[Source: ADSL.xpt]

When pooling the patient demographics from the 047 and 048 trials, the median age was 54 years old (range 20-88). Most of the patients enrolled in both trials were White (93%) and 61% of patients were female.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline ITP history and previous treatment for ITP were also broadly balanced between the treatment arms in both 047 and 048 trials. Majority of patients in both trials had chronic ITP (047: 92%, 048: 95%). To be eligible, average platelet count had to be < 30,000/mcL (and none > 35,000 unless a result of rescue therapy) from at least 3 qualifying counts within the preceding 3 months. The baseline median platelet count (defined as the last platelet count prior to the first dose of study drug which was mostly on Day 1) was under 20 $x10^9$/L in both trials (047: 15 $x10^9$/L, 048: 16 $x10^9$/L). The eligibility requirement for both trials restricted IBLS score to less than 2. The IBLS rating included assessment of bleeding at nine anatomical sites over the past week from 0 (none) to 2 (marked bleeding). The WHO bleeding scale is a five-point scale (from 0 [no bleeding] to 4 [debilitating blood loss]) and was assessed by the investigator. The baseline median IBLS scores showed that patients had no or slight bleeding (047: 0.11 [range 0-0.4], 048: 0 [range 0-1.0]). The baseline median WHO bleeding scores showed similar findings (047: 1.0 [range 0-2], 048: 0 [range 0-1]).

The median number of prior therapies (counting different corticosteroids as one therapy and different IVIGs as one therapy) was 3 (range 1-9) in study 047 and 2 (1-10) in study 048.
In the C788-048 trial, however, no previous ITP systemic therapy was provided in the datasets for 3 patients randomized to the fostamatinib arm (patients (b) (6)), suggesting that these patients were treatment naïve. All 3 patients had discontinued from the trial early due to lack of response. Majority of the patients had received prior corticosteroids in both trials (047: 93%, 048: 80%) and 54% and 41% of patients in studies 047 and 048, respectively, had received TPO receptor agonist (eltrombopag and/or romiplostim). A total of 30 patients (40%) and 23 patients (31%) in studies 047 and 048, respectively, had undergone splenectomy. At baseline, a total of 34 patients (45%) and 36 patients (49%) in studies 047 and 048, respectively, were receiving ITP therapy.

Table 32 C788-047 and C788-048: Baseline ITP History and Previous ITP Therapy (ITT Population)

	C788-047			C788-048		
	Fostamatinib (n=51)	Placebo (n=25)	Total (n=76)	Fostamatinib (n=50)	Placebo (n=24)	Total (n=74)
Persistent or chronic ITP						
Persistent	3 (6%)	3 (12%)	6 (8%)	3 (6%)	1 (4%)	4 (5%)
Chronic	48 (94%)	22 (88%)	70 (92%)	47 (94%)	23 (96%)	70 (95%)
Duration of ITP (years)						
Median	7.50	5.50	6.75	8.80	10.80	9.55
Range	0.6-53.0	0.4-45.0	0.4-53.0	0.3-50.2	0.9-29.1	0.3-50.2
Most recent platelet count ($x10^9$/L)						
Median	17	17	17	13.5	21	14.5
Range	0-34	2-35	0-35	0-34	1-35	0-35
Baseline platelet count[1] ($x10^9$/L)						
Median	15	16	15	16	21	16
Range	1-51	1-48	1-51[1]	1-33	1-156	1-156[1]
Baseline platelet count <15 x 10^9/L						
Yes	25 (49%)	12 (48%)	37 (49%)	22 (44%)	9 (38%)	31 (42%)
No	26 (51%)	13 (52%)	39 (51%)	28 (56%)	15 (62%)	43 (58%)
IBLS scores across 9 anatomical sites						
Median	0.13	0.11	0.11	0	0	0
Range	0-0.4	0-0.4	0-0.4	0-1.0	0-0.3	0-1.0
WHO bleeding scale scores						

Median	1.0	0	1.0	0	0	0
Range	0-2	0-2	0-2	0-1	0-1	0-1
Prior therapies						
Median (range)	3 (1-9)	5 (1-10)	3 (1-10)	3 (1-13)	3 (1-10)	3 (1-13)
1-2	14 (28%)	6 (24%)	20 (26%)	21 (42%)	11 (46%)	32 (43%)
≥ 3	37 (73%)	19 (76%)	56 (74%)	26 (52%)	13 (54%)	39 (53%)
Prior therapies[2]						
Median (range)	3 (1-9)	4 (1-8)	3 (1-9)	2 (1-10)	2 (1-8)	2 (1-10)
1-2	16 (31%)	7 (28%)	23 (30%)	24 (48%)	14 (58%)	38 (51%)
≥ 3	35 (69%)	18 (72%)	53 (70%)	23 (46%)	10 (42%)	33 (45%)
Currently on ITP therapy						
Yes	23 (45%)	11 (44%)	34 (45%)	26 (52%)	10 (42%)	36 (49%)
Prior ITP procedure /therapy						
Splenectomy						
Yes	20 (39%)	10 (40%)	30 (40%)	14 (28%)	9 (38%)	23 (31%)
No	31 (61%)	15 (60%)	46 (60%)	36 (72%)	15 (63%)	51 (69%)
Corticosteroids[3]	46 (90%)	25 (100%)	71 (93%)	39 (78%)	20 (83%)	59 (80%)
Rituximab	26 (51%)	11 (44%)	37 (49%)	8 (16%)	3 (13%)	11 (15%)
TPO medication	26 (51%)	15 (60%)	41 (54%)	20 (40%)	10 (42%)	30 (41%)
Avatrombopag	0	0	0	1 (2%)	0	1 (1%)
Eltrombopag (olamine)	19 (37%)	14 (56%)	33 (43%)	16 (32%)	7 (29%)	23 (31%)
Romiplostim	18 (35%)	11 (44%)	29 (38%)	13 (26%)	6 (25%)	19 (26%)
Danazol	7 (14%)	4 (16%)	11 (15%)	12 (24%)	5 (21%)	17 (23%)
Dapsone	10 (20%)	3 (12%)	13 (17%)	0	0	0
Imunoglobulins[4]	32 (63%)	17 (68%)	49 (65%)	19 (38%)	9 (38%)	28 (38%)
Immuno-Suppressant[5]	22 (43%)	12 (48%)	34 (45%)	18 (36%)	10 (42%)	28 (38%)
Cyclophosphamide	3 (6%)	2 (8%)	5 (7%)	5 (10%)	4 (17%)	9 (12%)

1. There were a total of 5 patients that had a baseline platelet count of >35 x 10^9/L in the 047 and 048 trials (047 [fostamatinib: 3, placebo: 1], 048 [fostamatinib: 0, placebo: 1]). In the 048 trial, patient (b) (6) in the placebo arm had screening platelet counts of 4 x10^9/L and 35 x10^9/L, however, at Day 1 the platelet count was 156 x10^9/L because the patient was randomized before the wash out for the rescue treatment was ended.
2. Counting different corticosteroids as one therapy; immunoglobulin, immunoglobulin G human and immunoglobulin human normal as one therapy; and eltrombopag and eltrombopag olamine as one therapy.
3. Includes dexamethasone, glucocorticoids, hydrocortisone, methylprednisolone, prednisolone and prednisone.
4. Includes anti-D immunoglobulin, immunoglobulin G human, immunoglobulin human normal.
5. Includes azathioprine, cyclosporin, mycophenolate mofetil and sirolimus.
[Source: ADSL.xpt, ADQS.xpt and ADCM.xpt]

Pooled analysis of studies 047 and 048:
A total of 140 patients (93%) enrolled in studies 047 and 048 had chronic ITP. The median duration of ITP diagnosis was 8.5 years. The median baseline platelet count of the 150 patients

was 16 x 10^9/L and 70 patients (47%) were on ITP therapy at trial entry. A total of 53 patients (35%) had undergone splenectomy.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment Compliance:
Treatment compliance was defined as the actual number of doses (tablets) the patient took during the period divided by the total number of tablets expected to be taken, multiplied by 100. In the 047 trial, the overall median treatment compliance was 97.2% and 99.5% in the fostamatinib and placebo arm, respectively, throughout the 24-week treatment period. In the 048 trial, the overall median treatment compliance was reported as 100% in both fostamatinib and placebo arms throughout the 24-week treatment period.

Concomitant ITP Medications:
In the 047 trial, the use of concomitant ITP medications was balanced between the treatment arms except corticosteroids. A higher proportion of patients in the placebo arm received corticosteroids compared with the fostaminib arm (fostamatinib: 37%, placebo: 56%). A total of 3 patients received platelet transfusion during the study (fostamatinib: 2 patients (b) (6), (b) (6)], placebo: 1 patient [(b) (6)]). None of these three patients were responders.

In the 048 trial, overall a higher proportion of patients in the placebo arm received concomitant ITP medications (fostamatinib: 60%, placebo: 75%), including corticosteroids and immunoglobulins. One patient randomized to the placebo arm ((b) (6)) received platelet concentrate during the study. This patient was a non-responder.

Table 33 C788-047 and C788-048: Concomitant ITP Medications (ITT Population)

	C788-047			C788-048		
	Fostamatinib (n=51)	**Placebo (n=25)**	**Total (n=76)**	**Fostamatinib (n=50)**	**Placebo (n=24)**	**Total (n=74)**
All patients	35 (69%)	18 (72%)	53 (70%)	30 (60%)	18 (75%)	48 (65%)
Corticosteroids	19 (37%)	14 (56%)	34 (43%)	22 (44%)	15 (63%)	37 (50%)
Immunoglobulins	15 (29%)	7 (28%)	22 (29%)	8 (16%)	6 (25%)	14 (19%)
Immunosuppressants (azathioprine)	2 (4%)	1 (4%)	3 (4%)	4 (8%)	0	4 (5%)
Platelets*	2 (4%)	1 (4%)	3 (4%)	0	1 (4%)	1 (1%)
Anabolic steroids (danazol)	1 (2%)	0	1 (1%)	1 (2%)	0	1 (1%)

Based on number of patients. A patient can appear in more than one category.
* None of the patients that received platelets were responders.
[Source: ADCM.xpt]

Rescue medication use:
In the 047 and 048 trials, patients who used rescue therapy after Week 10 were counted as non-responders for the primary efficacy endpoint. The proportion of patients that received rescue therapy was smaller in the fostamatinib arm compared to the placebo arm in both trials

prior to Week 10 (047 [fostamatinib: 31%, placebo: 44%], 048 [fostamatinib: 18%, placebo: 29%]) and after Week 10 (047 [fostamatinib: 14%, placebo: 28%], 048 [fostamatinib: 2%, placebo: 21%]). The median number of rescue therapy administrations among patients who received rescue therapy was the same between the two arms in both trials prior to Week 10 (047 [both fostamatinib and placebo arms: 2], 048 [both fostamatinib and placebo arms: 1]) and after Week 10 (047 [both fostamatinib and placebo arms: 1], 048 [both fostamatinib and placebo arms: 1]).

Table 34 C788-047 and C788-048: Use of Rescue Therapy (ITT Population)

	C788-047		C788-048	
	Fostamatinib (n=51)	**Placebo (n=25)**	**Fostamatinib (n=50)**	**Placebo (n=24)**
Prior to Week 10				
No	35 (69%)	14 (56%)	41 (82%)	17 (71%)
Yes	16 (31%)	11 (44%)	9 (18%)	7 (29%)
Median (per patient)	2	2	1	1
Range (per patient)	1-6	1-3	1-3	1-6
After Week 10				
No	44 (86%)	18 (72%)	49 (98%)	19 (79%)
Yes	7 (14%)	7 (28%)	1 (2%)	5 (21%)
Median (per patient)	1	1	1	1
Range (per patient)	1-5	1-2	1-1	1-3

[Source: ADCM.xpt]

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was achievement of a stable platelet response by Week 24, defined as achieving a platelet count of at least 50,000/mcL on at least 4 of the last 6 scheduled visits between Weeks 14-24. Patients who discontinued treatment prior to Week 24 due to lack of efficacy or to an AE, or who received rescue treatment after Week 10, were to be considered non-responders. For patients that withdrew from the trial for reasons other than lack of efficacy or due to an AE (and did not receive rescue treatment after Week 10), missing data for the primary and secondary efficacy endpoints were to be imputed using the last observation carried forward (LOCF) method. See the above comment in the Statistical Analysis Plan section regarding the Agency's view on the LOCF analysis method.

C788-047:
In the 047 trial, a total of 9 patients (17.6%) in the fostamatinib arm and no patient in the placebo arm had achieved stable platelet response. The difference of response between the arms was 17.6% and 95% CI was (-6.1%, 40.3%) using the exact confidence interval and (7.2%, 28.1%) using the normal approximation. P-value was 0.026 using the Fisher exact test.

Review comment: A total of 3 patients (all fostamatinib arm; (b) (6))

withdrew early from the study for reasons other than lack of efficacy or AE (i.e., lost to follow-up, noncompliance, physician decision, or withdrawal by patient) and therefore had missing platelet counts during the efficacy evaluation period. The applicant applied the LOCF method to assess the response status for these 3 patients. However, it was determined that these 3 patients were non-responders. Thus, regardless of applying LOCF, these patients were non-responders and would not have biased the results in favor of fostamatinib.

C788-048:
In the 048 trial, a total of 3 patients (fostamitinib: 2 patients, placebo: 1 patient) withdrew early from the study for reasons other than lack of efficacy or AE, did not take rescue medication after Week 10 and had missing platelet counts during the efficacy evaluation period (see table 37). Using the LOCF method, one patient in each arm was determined to be a non-responder. When not applying the LOCF, these two patients would also be non-responders.

The remaining one patient ([redacted] (b) (6)) in the fostamatinib arm was a 22 year old male who withdrew (patient decision) from the study on Day 113 (after Week 16) due to relocation to another country for work/study. This patient had received rescue medication (IVIg) during the Screening B visit. The last platelet count at Week 16 was 101 x 10^9/L. The applicant included this patient as a responder applying the LOCF method for the remaining weeks of the 24-week study period (i.e., Weeks 18, 20, 22 and 24) (see table 38).

In addition, one patient ([redacted] (b) (6)) randomized to the placebo arm in the 048 trial achieved the primary endpoint for stable response. The post-baseline platelet counts ranged from 420,000/mcL (at Week 2) to 16,000/mcL (at Week 16) with no rescue therapy. The narrative for this patient was not provided. The FDA requested more information for this patient on October 26, 2017. The applicant provided the following information on October 31, 2017:

> Subject [redacted] (b) (6) met the criteria for the primary endpoint of stable response while being randomized to the placebo group in Study 048. When this study was unblinded, Rigel investigated whether the subject had any unusual characteristics.
>
> The subject is a 78-year-old male who was diagnosed with ITP in [redacted] (b) (6) with a platelet count of 2,000/mcL, petechiae, and a bone marrow biopsy consistent with the clinical diagnosis of immune thrombocytopenia. He was then treated with oral steroids. The response was very variable with platelet counts ranging from 240,000 to 6,000/mcL between [redacted] (b) (6) At the same time, the subject developed hypertension as a complication of steroid therapy; thus, the steroid doses were tapered and stopped a few times, which further contributed to variability in platelet counts. Prior to study entry, the investigator questioned whether the subject met the criteria of idiopathic cyclic thrombocytopenia but concluded that this case did not meet those criteria.
>
> For Study 048, the subject was screened twice, in [redacted] (b) (6). The last dose of steroid therapy was administered on [redacted] (b) (6), and the subject did not

receive any further rescue medication. He was enrolled and randomized to the placebo arm on (b) (6). The subject continued to have highly variable platelet counts on placebo. While he did meet the primary endpoint criteria per se, his platelet counts continued to be highly variable, ranging from 19,000 to 420,000/mcL sometimes within a 2-week period. This variability is in contrast to the platelet counts observed with responder subjects on fostamatinib. This subject never received rescue medication on study. He completed Study 048. In (b) (6), he received fostamatinib in the extension Study 049 starting at the dose of 150 mg bid. The platelet variability was reduced (range: 52,000 – 307,000/mcL) in Study 049. The figure below summarizes the platelet count changes for this patient.

Figure 6 Patient (b) (6): Platelet Counts

(b) (6)

Using the LOCF method, a total of 9 patients (18%) in the fostamatinib arm and 1 patient (4.2%) in the placebo arm achieved stable platelet response. The difference of the response between the arms was 13.8% and 95% CI was (-11.0%, 37.6%) using the exact confidence intervals and (0.5%, 27.2%) using the normal approximation. P-value was 0.152 using the Fisher exact test.

However, as it is uncertain whether this patient ((b) (6)) would have maintained a platelet count of at least 50,000/mcL in at least two of the visits between Weeks 18 and 24, it would be more conservative to count this patient as a non-responder. When counting this patient as a non-responder, the stable platelet response is 16.0% and 4.2% in the fostamatinib and placebo arms, respectively. The difference between the arms is 11.8% and 95% CI, (-12.9%, 35.7%) using the exact confidence intervals and (-1.1%, 24.8%) using the normal approximation. P-value is 0.256 using the Fisher exact test.

Table 35 C788-047 and C788-048: Primary Efficacy Endpoint Using the LOCF Method (ITT Population)

	C788-047		C788-048	
	Fostamatinib (n=51)	**Placebo (n=25)**	**Fostamatinib (n=50)**	**Placebo (n=24)**
Stable platelet response				
Yes	9 (17.6%)	0	9 (18.0%)	1 (4.2%)
No	42 (82.4%)	25 (100.0%)	41 (82.0%)	23 (95.8%)
Difference of response	17.6%		13.8%	

(fostamatinib-placebo)		
95% CI[a]	(-6.06%, 40.26%)	(-10.95%, 37.55%)
95% CI[b]	(7.18%, 28.11%)	(0.52%, 27.15%)
p-value[c]	0.0261	0.1519

a. Confidence interval based on exact confidence intervals.
b. Confidence interval based on normal approximation.
c. P-value from the Fisher exact test.
[Source: ADEFF.xpt]

Table 36 C788-048: Primary Efficacy Endpoint Not Using the LOCF Method (ITT Population)

	C788-047		C788-048	
	Fostamatinib (n=51)	**Placebo (n=25)**	**Fostamatinib (n=50)**	**Placebo (n=24)**
Stable platelet response				
Yes	9 (17.6%)	0	8 (16.0%)	1 (4.2%)
No	42 (82.4%)	25 (100.0%)	42 (84.0%)	23 (95.8%)
Difference of response (fostamatinib-placebo)	17.6%		11.8%	
95% CI[a]	(-6.06%, 40.26%)		(-12.94%, 35.69%)	
95% CI[b]	(7.18%, 28.11%)		(-1.1%, 24.8%)	
p-value[c]	0.0261		0.2559	

a. Confidence interval based on exact confidence intervals.
b. Confidence interval based on normal approximation.
c. P-value from the Fisher exact test.
[Source: ADEFF.xpt]

The table below summarizes the analysis of the primary efficacy endpoint response for the 047 and 048 trials using LOCF.

Table 37 C788-047 and C788-048: Primary Efficacy Endpoint Responder/Non-Responder using the LOCF Method (ITT Population)

		C788-047		C788-048	
		Fostamatinib (n=51)	**Placebo (n=25)**	**Fostamatinib (n=50)**	**Placebo (n=24)**
Responder	Completed study and did not receive rescue med after Week 10	9 (18%)	0	8 (16%)	1 (4%)
	Discontinued not due to efficacy/ AE, and did not receive rescue med after Week 10 (however, there were missing data and LOCF imputation method was used)	0	0	1* (2%)	0
Non-	Completed study and did not	2 (4%)	0	4 (8%)	1 (4%)

responder	receive rescue med after week 10				
	Discontinued for lack of efficacy/ AE or received rescue med after Week 10	37 (73%)	25 (100%)	36 (72%)	21 (88%)
	Discontinued not due to efficacy/ AE, and did not receive rescue med after Week 10 (however, there were missing data and LOCF imputation method was used)	3*(6%)	0	1* (2%)	1* (4%)

* Patients with missing data. LOCF imputation method was used.
[Source: ADEFF.xpt and ADCM.xpt]

The table below shows the platelet count changes over time for the responders in the 047 and 048 trials.

Table 38 C788-047 and C788-048: Platelet Count for Responders

Patient ID	Platelet count (x 10^9/L) at scheduled visits															
	Prior to primary endpoint evaluation										Primary endpoint evaluation period					
		Screen		Day	Study week											
	H	A	B	1	2	4	6	8	10	12	14	16	18	20	22	24
C788-047																
Fostamatinib arm																
(b) (6)	4	3	3	3	3	4	12	54	63	40	88	96	84	103	116	110
	26	19	25	25	127	58	93	102	162	139	142	106	100	83	204	105
	31	19	16	16	67	127	26	222	47	175	181	45	66	153	36	131
	0	55	19.5	6.3	45.5	146	65.1	70.9	79.6	8.5	8.8	38	131	77	115	92
	3	4	3	3	32	20	48	20	70	56	89	90	27	154	67	46
	13	23	24	13	12	21	17	46	101	99	138	136	69	101	117	100
	17	24	15	19	29	40	51	40	51	66	61	71	104	87	106	123
	24	20	23	23	78	38	121	38	66	99	77	110	132	96	119	91
	33	22	25	25	185	17	162	46	151	130	139	142	196	141	181	189
C788-048																
Fostamatinib arm																
(b) (6)	13	5	1	5	33	21	35	57	80	84	99	101	101	101	101	101
	8	4	14	30	50	9	118	29	104	81	166	89	168	130	113	22
	10	22	32	18	113	117	118	108	165	126	130	159	181	141	138	135
	26	30	34	26	254	166	191	234	186	246	255	289	291	314	337	367
	10	8	8	23	169	115	94	121	124	142	159	168	166	196	201	191
	32	21	17	16	79	26	59	47	36	112	39	82	67	36	57	70
	20	35	24	24	111	67	79	74	79	68	73	76	74	69	62	83
	34	32	22	22	67	37	40	60	78	97	102	160	141	107	138	78
	26	68/ 26	12	12	131	69	125	74	99	103	105	87	80	61	80	81
Placebo arm																

(b) (6)	27	13	4	19	420	32	162	203	115	188	62	16	213	167	133	82

To be eligible for the trial, the average platelet count had to be < 30,000/mcL (and none > 35,000 unless as a result of rescue therapy) from at least 3 qualifying counts within the preceding 3 months. At least 2 of the qualifying counts must have been taken during the screening period.
a. Patient (b) (6): Had platelet count of 54.5 x 10^9/L at screening A visit. The patient had received rescue medication (prednisone) during the visit.
b. Patient (b) (6): Withdrew from the trial on Day 113 by patient decision. Used LOCF method for platelet counts for Weeks 18, 20, 22 and 24.
c. Patient (b) (6): Had baseline average platelet count of 30,000/mcL.
d. Patient (b) (6): Had platelet count tests on two Screening A Visits (on (b) (6), the platelet count was 68 x 10^9/L, and on (b) (6) it was 26 x 10^9/L). This patient had received IVIg as rescue med on the same day as randomization.

Blue shades: Platelet count ≥ 50,000/mcL during the primary endpoint evaluation period.
Orange shades: Platelet count assessment using LOCF method.
[Source: ADEFF.xpt and ADCM.xpt]

None of the responders started on new ITP therapy, received platelet transfusion, or had the dose increased of allowed ITP therapy at baseline (< 20 mg prednisone equivalent per day, azathioprine or danazol) during the 047 or 048 trial. Rescue therapies (IVIg, anti-D or corticosteroid treatment) if received by responders were all given during the screening period and during the first month of treatment (none was given after Week 10). One responder ((b) (6)), however, continued to the open-label 049 extension trial. Three months after enrolling in study 049, the patient received blood transfusions during an event of GI hemorrhage. This patient was a non-responder in study 049. The table below summarizes the rescue therapy received by responders during the 047 and 048 trials.

Table 39 10 C788-047 and C788-048: Rescue Therapy Received by Responders

C788-047		
Patient	**Visit**	**Rescue therapy**
(b) (6)	Day 7	IVIg and dexamethasone
	Weeks 2 and 4	IVIg and prednisone
	Day 25	IVIg and dexamethasone
	Screening A	IVIg
	Screening A	Prednisone
	Days 3 and 4	Methylprednisolone
C788-048		
Patient	**Visit**	**Rescue therapy**
(b) (6)	Screening B	IVIg
	Day 1	IVIg

*Patient (b) (6) continued on the open-label 049 extension trial. Three months after enrolling in study 049, the patient received blood transfusions during an event of GI hemorrhage. This patient was a non-responder in study 049.
[Source: ADEFF.xpt and ADCM.xpt]

Efficacy Results – Secondary and other relevant endpoints

As stated, the analyses of the secondary efficacy endpoints were to be performed in the following order using the fixed sequence testing procedure:

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

Each of the first four secondary efficacy endpoints was to be analyzed in the same manner as the primary efficacy endpoint (i.e., patients who discontinue treatment prior to Week 12 or 24, as appropriate, due to lack of efficacy or to an AE or who receive rescue treatment after Week 10 but prior to Week 12 or 24, as appropriate, were to be considered non-responders).

Reviewer's comments: The primary efficacy analysis for Study 048 did not achieve statistical significance. The secondary efficacy analyses for Study 048 do not have any Type I error left for comparative analysis, p-values derived from formal testing of secondary endpoints are not meaningful.

<u>Platelet counts at Week 12 and 24:</u>

C788-047:
At Week 12, 21.6% and 0% of patients in the fostamatinib and placebo arm, respectively, had a platelet count of ≥ 50,000/mcL. The difference was 21.6%. The 95% CI was (-2.0%, 44.0%) using the exact confidence intervals and (10.0%, 33.0%) using the normal approximation, p-value=0.0127 (Fisher exact test). When excluding patient (b) (6) (without LOCF), 19.6% in the fostamatinib arm achieved a platelet count of ≥50,000/mcL at Week 12. The difference was 19.6% (95% exact CI: -4.1%, 42.1%), p-value 0.025.

At Week 24, 15.7% and 0% of patients in the fostamatinib and placebo arm, respectively, had a platelet count of ≥ 50,000/mcL. The difference was 15.7%. The 95% CI was (-8.0%, 38.4%) using the exact confidence intervals and (5.7%, 25.7%) using the normal approximation, p-value= 0.0471 (Fisher exact test).

C788-048:
At Week 12, 24.0% and 12.5% of patients in the fostamatinib and placebo arm, respectively, had a platelet count of ≥ 50,000/mcL. The difference was 11.5%. The 95% CI was (-13.0%, 35.0%) using the exact confidence intervals and (-6.0%, 29.0%) using the normal approximation.

At Week 24, using the LOCF, 16.0% and 4.2% of patients in the fostamatinib and placebo arm, respectively, had a platelet count of ≥ 50,000/mcL. The difference was 11.8%. The 95% CI was (--12.9%, 35.7%) using the exact confidence intervals and (-1.1%, 24.8%) using the normal approximation. When excluding the patient with missing data at Week 24, 14% of patients in the fostamatinib arm and 4.2% of patients in the placebo arm had achieved a platelet count of at least 50,000/mcL at Week 24. The difference was 9.8% (95% exact CI: -14.9%, 33.8%).

Table 40 C788-047 and C788-048: Secondary Efficacy Endpoints – Platelet Count ≥ 50,000/mcL at Week 12 and 24 (ITT Population, With LOCF)

	C788-047		C788-048	
	Fostamatinib (n=51)	**Placebo (n=25)**	**Fostamatinib (n=50)**	**Placebo (n=24)**
Platelet count ≥ 50,000/mcL at Week 12				
Yes	11* (21.6%)	0	12 (24.0%)	3 (12.5%)
No	40* (78.4%)	25 (100%)	38 (76.0%)	21 (87.5%)
Difference of response (fostamatinib-placebo)	21.6%		11.5%	
95% CI[a]	-2.0%, 44.0%		-13.0%, 35.0%	
95% CI[b]	10.0%, 33.0%		-6.0%, 29.0%	
p-value[c]	0.0127			
Platelet count ≥ 50,000/mcL at Week 24				
Yes	8 (15.7%)	0	8 (16.0%)**	1 (4.2%)
No	43 (84.3%)	25 (100%)	42 (84.0%)**	23 (95.8%)
Difference of response (fostamatinib-placebo)	15.7%		11.8%	
95% CI[a]	-8.0%, 38.4%		-12.9%, 35.7%	
95% CI[b]	5.7%, 25.7%		-1.1%, 24.8%	
p-value[c]	0.0471			

a. Confidence interval based on exact confidence intervals.
b. Confidence interval based on normal approximation.
c. P-value from the Fisher exact test. P-values for the 048 trial are not presented here since the primary endpoint was not met.

*Applying the LOCF method. When excluding patient (b) (6) (without LOCF), 19.6% in the fostamatinib arm achieved a platelet count of ≥50,000/mcL at Week 12. The difference was 19.6% (95% exact CI: -4.1%, 42.1%), p-value 0.025.
**Applying the LOCF method. When excluding patient (b) (6) (without LOCF), 14% of patients in the fostatmatinib arm achieved a platelet count of ≥50,000/mcL at Week 24. The difference was 9.8% (95% exact CI: -14.9%, 33.8%).
[Source: ADEFF.xpt]

Reviewer's comments: Following a sequential procedure for alpha allocation, platelet response

at Week 12 and Week 24 for Study 047 was significant (p-value < 0.05) even when the LOCF response was treated as a non-response. Statistical significance of response at Week 24 should be interpreted with caution, there were no patients in the placebo arm with documented platelet counts while only 11 patients in the fostamatinib arm had platelet counts.

Platelet count of ≥ 30,000/mcL, and at least 20,000/mcL above baseline, at Week 12 and 24 (for patients with a baseline platelet count < 15,000/mcL):

C788-047:
In the 047 trial, a total of 37 patients (fostamatinib: 25 patients, placebo: 12 patients) had a baseline platelet count < 15,000/mcL. Among these patients, 16% of patients in the fostamatinib arm and 0 patient in the placebo arm had achieved a platelet count of ≥ 30,000/mcL and ≥ 20,000/mcL above baseline at both Week 12 and Week 24. The difference of proportions between the arms was 16%. The 95% CI was (-17.8%, 47.8%) using the exact confidence intervals and (1.6%, 30.4%%) using the normal approximation.

C788-048:
A total of 31 patients (fostamatinib: 22 patients, placebo: 9 patients) had a baseline platelet count < 15,000/mcL in the 048 trial. According to the applicant's analysis, 27% of patients in the fostamatinib arm and 11% of patients in the placebo arm had achieved a platelet count of ≥ 30,000/mcL and ≥ 20,000/mcL above baseline at Week 12 with a difference of 16.2%. The 95% CI was (-23.1%, 52.0%) using the exact confidence intervals and (-11.6%, 43.9%) using the normal approximation.

At Week 24, the results were 13.6% and 0% of patients in the fostamatinib and placebo arm, respectively, with a difference of 13.6%. The 95% CI was (-25.2%, 49.9%) using the exact confidence intervals and (-0.7%, 28.0%) using the normal approximation.

However, for the Week 12 analysis, the applicant included one patient ([redacted] (b) (6)) in the fostamatinib arm that discontinued the study at Day 37 (Week 5) due to investigator discretion and all subsequent platelet counts were assessed using LOCF. The latest platelet count assessed 19 days after the last exposure (Week 8) was 31,000/ mcL. Excluding this patient from the analysis, at Week 12, 23% and 11% of patients in the fostamatinib and placebo arm, respectively, had achieved a platelet count of ≥ 30,000/mcL and ≥ 20,000/mcL above baseline with a difference of 11.6%. The 95% CI was (-27.4%, 48.3%) using the exact confidence intervals and (-15.4%, 38.6%) using the normal approximation.

At Week 24, the applicant's analysis included two patients in the fostamatinib arm, patient [redacted] (b) (6) (same patient as above) and patient [redacted] (b) (6), that discontinued the study on Day 37 (Week 5) and Day 113 (Week 16), respectively. The LOCF method was applied for these patients. When excluding these two patients, 4.6% and 0% of patients in the fostamatinib and placebo arm, respectively, achieved this endpoint at Week 24. The difference between the arms is 4.6%. The 95% CI was (-33.6%, 41.9%) using the exact confidence intervals and (-4.2%, 13.3%) using the

normal approximation. Table 42 summarizes the results without LOCF.

Table 41 C788-047 and C788-048: Secondary Efficacy Endpoints – Platelet Count ≥ 30,000/mcL and ≥ 20,000/mcL above Baseline at Week 12 and 24 (ITT Population with Baseline Platelet Count < 15,000/mcL)

	C788-047		C788-048*	
	Fostamatinib (n=25)	Placebo (n=12)	Fostamatinib (n=22)	Placebo (n=9)
Platelet count ≥ 30,000/mcL and ≥ 20,000/mcL above baseline (for patients with baseline platelet count < 15,000/mcL) at:				
Week 12				
Yes	4 (16.0%)	0	6 (27.3%)	1 (11.1%)
No	21 (84.0%)	12 (100%)	16 (72.7%)	8 (88.9%)
Difference of response (fostamatinib-placebo)	16.0%		16.2%	
95% CI[a]	-17.8%, 47.8%		-23.1%, 52.0%	
95% CI[b]	1.6%, 30.4%		-11.6%, 43.9%	
Week 24				
Yes	4 (16.0%)	0	3 (13.6%)	0
No	21 (84.0%)	12 (100%)	19 (86.4%)	9 (100%)
Difference of response (fostamatinib-placebo)	16.0%		13.6%	
95% CI[a]	-17.8%, 47.8%		-25.2%, 49.9%	
95% CI[b]	1.6%, 30.4%		-0.7%, 28.0%	

a. Confidence interval based on exact confidence intervals.
b. Confidence interval based on normal approximation.
* Applicant's analysis
[Source: ADEFF.xpt]

Reviewer's comment: For Study 047, p-values for the Fisher exact test are not presented in the table above, as the achievement of a platelet count ≥ 30,000/mcL and ≥ 20,000/mcL above baseline at Week 12, was not significant (Fisher Exact Test p-value of 0.28).

The table below summarizes the results of platelet count ≥ 30,000/mcL and ≥ 20,000/mcL above baseline at Week 12 and 24 (among patients with a baseline platelet count of <15,000/mcL) of the 048 trial not applying the LOCF method.

Table 42 C788-048: Secondary Efficacy Endpoints – Platelet Count ≥ 30,000/mcL and ≥ 20,000/mcL above Baseline at Week 12 and 24 (Not Applying LOCF, ITT Population with Baseline Platelet Count < 15,000/mcL)

	C788-048	
	Fostamatinib (n=22)	**Placebo (n=9)**
Platelet count ≥ 30,000/mcL and ≥ 20,000/mcL above baseline (for patients with baseline platelet count < 15,000/mcL) at:		
Week 12		
Yes	5 (22.7%)	1 (11.1%)
No	17 (77.3%)	8 (88.9%)
Difference of response (fostamatinib-placebo)	11.6%	
95% CI[a]	(-27.4%, 48.3%)	
95% CI[b]	(-15.4%, 38.6%)	
Week 24		
Yes	1 (4.6%)	0
No	21 (95.4%)	9 (100%)
Difference of response (fostamatinib-placebo)	4.6%	
95% CI[a]	(-33.6%, 41.9%)	
95% CI[b]	(-4.2%, 13.3%)	

a. Confidence interval based on exact confidence intervals.
b. Confidence interval based on normal approximation.
[Source: ADEFF.xpt]

<u>Frequency and severity of bleeding according to the IBLS and WHO bleeding scale over the 24-week study period:</u>

The IBLS and WHO bleeding scales were assessed at each visit for each patient. For the IBLS score, the mean across nine anatomical sites was calculated at each visit for each patient and the average was then obtained for each patient across the 24-week visits. For the WHO bleeding scale, the mean was also obtained for each patient across the 24-week visits. Of note, patients who had an IBLS bleeding scale score of Grade 2 at any site were excluded from the 047 and 048 trials.

The mean IBLS bleeding scores over the 24-week study period were similar between the arms in both trials (047 [fostamatinib: 0.13, placebo: 0.14], 048 [fostamatinib: 0.04, placebo: 0.06]). The mean WHO bleeding scores over the 24-week study period were also similar between the arms in both trials (047 [fostamatinib: 0.61, placebo: 0.46], 048 [fostamatinib: 0.26, placebo: 0.38]).

Review comment: It should be noted that the 95% CIs for the difference in response are not accurate due to the small number of patients and the positively skewed distribution of the bleeding score. The interval estimates are based on the assumption of approximate Normality; however, the skewed distribution of the data invalidates this assumption.

Table 43 C788-047 and C788-048: Secondary Efficacy Endpoints – IBLS and WHO Bleeding Score During the 24-Week Treatment Period (ITT Population)

	C788-047		C788-048	
	Fostamatinib (n=51)	**Placebo (n=25)**	**Fostamatinib (n=50)**	**Placebo (n=24)**
IBLS score across nine anatomical sites across visits				
Median	0.09	0.12	0.01	0.02
Mean	0.13	0.14	0.04	0.06
Range	0-0.5	0-0.3	0-0.4	0-0.2
Difference in means (fostamatinib-placebo) and 95% CI	-0.01 (-0.07, 0.04)		-0.01 (-0.05, 0.02)	
WHO bleeding scale across visits				
Median	0.33	0.17	0	0.13
Mean	0.61	0.46	0.26	0.38
Range	0-2.8	0-2.0	0-1.1	0-1.7
Difference in means (fostamatinib-placebo) and 95% CI	0.15 (-0.16, 0.45)		-0.12 (-0.32, 0.09)	

[Source: ADQS.xpt]

Additional Analyses Conducted on the Individual Trial

Sensitivity Analysis:

Multiple imputation:
For the C788-048 trial, the applicant performed multiple imputation (MI) methods (10,000 iterations) for the missing platelet counts as sensitivity analysis. The estimated proportions of patients achieving the primary efficacy endpoint were 18.00% and 4.34% in the fostamatinib and placebo group, respectively. The estimated difference between the arms was 13.66% (95% CI: 0.16%, 27.16%).

Reviewer's Note: This reviewer had the following concerns regarding the sponsor's multiple imputation (MI) technique:

1) *The assumption of monotone missing observation in patients' visit and the assumption of Normality of the distribution of platelet counts were invalid. Platelet counts were positively skewed and some missing platelet counts were not monotone missing in at*

least one patient.

2) *The sponsor pre-specified a MI technique which includes covariates (treatment and the platelet count at visits 4 to 15). In their MI implementation they did not include any covariates.*
3) *The dataset was too small for MI, only 15 (30%) and 2 (8%) patients in the fostamatinib and placebo arm, respectively, had a minimum of 4 assessments in the Week 14-24 assessment period.*

Table 44 C788-048: Primary Efficacy Endpoint – Sensitivity Analysis (ITT Population)

	C788-048	
	Fostamatinib (n=50)	**Placebo (n=24)**
Stable platelet response		
Yes	18.0%	4.3%
No	82.0%	95.8%
Difference of response (fostamatinib-placebo) and 95% CI	13.66 (0.16, 27.16)	

Reported percentages and p-value are based on the average of 10,000 iterations.

Applicant's PP population:
Sensitivity analysis of the primary efficacy endpoint using the applicant's PP population:
Using the applicant's PP population, the stable platelet response for the 047 trial was the same as the primary efficacy result as the PP population was the same as the ITT population. For the 048 trial, when using the applicant's PP population, stable platelet response was 18.4% (9 responders out of 49 patients) and 4.3% (1 responder out of 23 patients) in the fostamatinib and placebo arm, respectively. The difference between the arms was 14.1% (95% CI: 0.3, 27.7 using normal approximation).

Excluding patients with major protocol violations:
When excluding the patients that had major protocol violations as summarized in tables 29 and 30 for the 047 and 048 trials, respectively, the PP population is comprised of a total of 49 patients in study 047 (fostamatinib: 32, placebo: 17) and 57 patients in study 048 (fostamatinib: 41, placebo: 16). For the 047 trial, stable platelet response was achieved in 15.6% and 0% of patients in the fostamatinib and placebo arm, respectively. The difference between the arms was 15.6%. The 95% CI was (-13.14%, 43.46%) using the exact confidence intervals and (3.04%, 28.21%) using the normal approximation.

For the 048 trial, the stable platelet response was 14.6% and 6.3% in the fostamatinib and placebo arm, respectively, when excluding patients with major protocol violations. The difference between the arms was 8.3%. The 95% CI was (-20.52%, 36.51%) using the exact confidence intervals and (-7.67%, 24.44%) using the normal approximation.

The table summarizes the results of the primary endpoint excluding patients with major protocol violations.

Table 45 C788-048 Sensitivity Analysis: Primary Efficacy Endpoint with LOCF (Excluding Patients with Major Protocol Violations)

	C788-047		C788-048	
	Fostamatinib (n=32)	Placebo (n=17)	Fostamatinib (n=41)	Placebo (n=16)
Stable platelet response				
Yes	5 (15.6%)	0	6 (14.6%)	1 (6.3%)
No	27 (84.4%)	17 (100.0%)	35 (85.4%)	15 (93.8%)
Difference of response (fostamatinib-placebo)	15.6%		8.3%	
95% CI[a]	-13.14%, 43.46%		-20.52%, 36.51%	
95% CI[b]	3.04%, 28.21%		-7.67%, 24.44%	

a. Confidence interval based on exact confidence intervals.
b. Confidence interval based on normal approximation.
[Source: ADDV.xpt and ADEFF.xpt]

Pooled analysis:
As a post-hoc analysis, when conducting a pooled primary efficacy analysis of the 047 and 048 trials using LOCF, the difference of response between the arms was 15.8% and 95% CI was (-1.28%, 32.3%) using the exact confidence intervals and (7.33%, 24.23%) using the normal approximation. Without the LOCF method, the difference between the arms was 14.8% and 95% CI was (-2.26%, 31.41%) using the exact confidence intervals and (6.49%, 23.09%) using the normal approximation.

Table 46 Pooled Analysis of C788-047 and C788-048: Primary Efficacy Endpoint (ITT Population)

	Using LOCF		Without LOCF	
	Fostamatinib (n=101)	Placebo (n=49)	Fostamatinib (n=101)	Placebo (n=49)
Stable platelet response				
Yes	18 (17.8%)	1 (2.0%)	17 (16.8%)	1 (2.0%)
Difference of response (fostamatinib-placebo)	15.8%		14.8%	
95% CI[a]	(-1.28%, 32.3%)		(-2.26%, 31.41%)	
95% CI[b]	(7.33%, 24.23%)		(6.49%, 23.09%)	

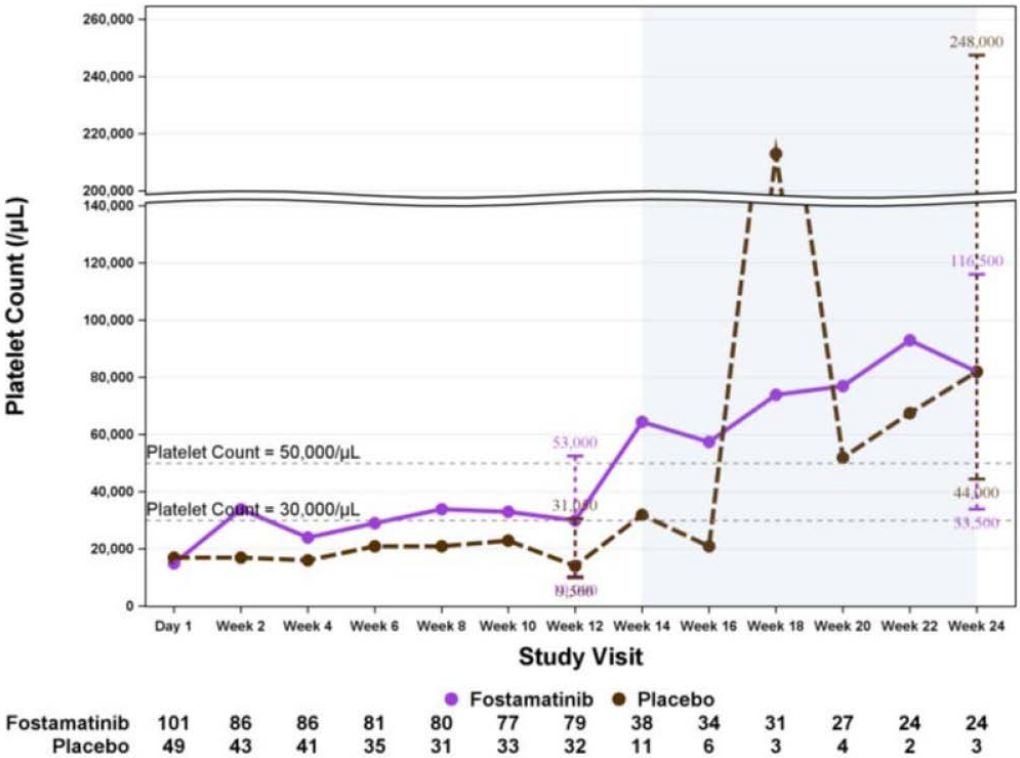
a. Confidence interval based on exact confidence intervals.
b. Confidence interval based on normal approximation.

[Source: ADEFF.xpt]

Platelet count by visit:

The applicant provided platelet count analysis over the 24-week treatment period for the 047 and 048 trials as well as a pooled analysis. Overall, from Week 2 through Week 12, the median platelet count was greater in the fostamatinib arm compared with the placebo arm in both trials. Starting at Week 12, the trials allowed patients with a platelet count < 50,000/mcL (and patients with a baseline platelet count < 15,000/mcL who had not experienced an increase in platelets of at least 20,000/mcL) to transition to the extension trial (049). Therefore, the platelet count sample sizes were lower at or after Week 12 and declined over time more substantially in the placebo group. For the pooled analysis, at Week 24, a total of 24 and 3 patients in the fostamatinib and placebo arm, respectively, remained at risk. The median platelet count for patients that remained in the 047 and 048 trials in the fostamatinib arm generally increased over time. The figure below shows the pooled median platelet count of the 047 and 048 trials over time for each arm.

Figure 7 Pooled Analysis of C788-047 and C788-048: Median Platelet Count by Study Visit for Each Arm



[Source: SCE]

In the pooled analysis for both trials, the median baseline platelet counts were similar between the arms (fostamatinib: 15 x 10^9/L, placebo: 17 x 10^9/L). The median platelet count across all post-baseline visits was 29.5 x 10^9/L (range, 2 x 10^9/L to 254.5 x 10^9/L) in the fostamatinib arm

and 17.5 x 10^9/L (range 2 x 10^9/L to 163.5 x 10^9/L) in the placebo arm.

Table 47 C788-047 and C788-048: Platelet Count (x 109/L) by Visit

	C788-047		C788-048		Pooled	
	Fos (n=51)	Placebo (n=25)	Fos (n=50)	Placebo (n=24)	Fos (n=101)	Placebo (n=49)
Baseline						
n	51	25	50	24	101	49
Median	15	16	16	21	15	17
Q1, Q3	7, 25	5.5, 23	8, 22	10, 28.5	7.5, 23.5	7, 26
Range	1, 51	1, 48	1, 33	1, 156	1, 51	1, 156
Median across all post-baseline visits*						
n	47	22	48	23	95	45
Median	29	17.8	30	17.5	29.5	17.5
Q1, Q3	10, 46	9, 31	12.5, 49	7, 33	11.5, 49	9, 32.5
Range	3, 146.5	2, 163.5	2, 25.5	2, 149	2, 254.5	2, 163.5

*All post-baseline visits include platelet counts from Weeks 2-24.
[Source: ADSL.xpt and ADEFF.xpt and ISE.itp.appendices]

Platelet count changes by fostamatinib response:

(b) (4)

The baseline median platelet count for all patients enrolled in the 047 and 048 trials was 16 x 10^9/L (range, 1 x 10^9/L to 156 x 10^9/L). Even though the comparison between the arms is based on response status of fostamatinib arm shown in the table and may be subject to bias due to the subgroup nature of the comparison, a few observations are noted: The median platelet count across all post-baseline visits for patients in the placebo arm (17.5 x 10^9/L [range, 2 x 10^9/L to 163.5 x 10^9/L]) was similar to the non-responders in the fostamatinib arm (23 x 10^9/L [range, 2 x 10^9/L to 76.5 x 10^9/L]) and lower than the responders in the fostamatinib arm (96 x 10^9/L [range, 52 x 10^9/L to 254.5 x 10^9/L]). The median post-baseline platelet counts remained similar when applying LOCF in the fostamatinib arm.

Table 48 C788-047 and C788-048 Combined: Platelet Count (x 10^9/L) by Fostamatinib Response (ITT Population)

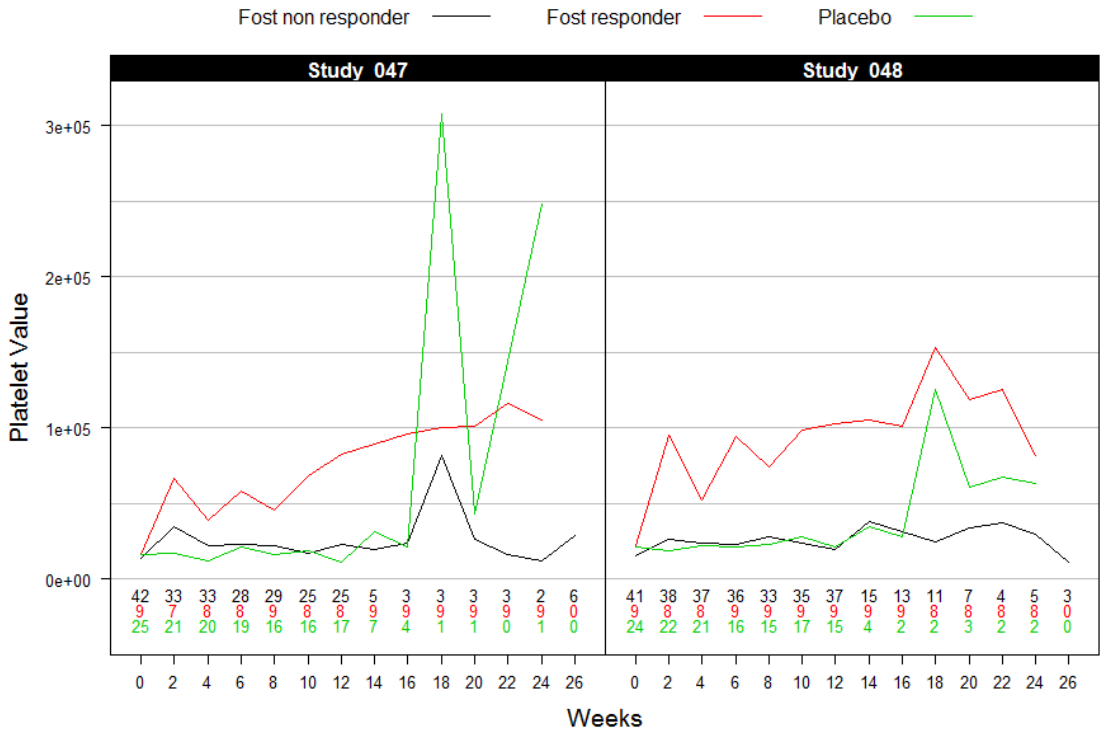
Summary Statistics	Placebo (n=49)	Fosamatinib				
		Stable response (n=18)	Stable response (n=17)[1]	No response (n=83)	No response (n=84)[1]	Total (n=101)
Baseline						
n	49	18	17	83	84	101
Median	17	18.5	19	15	14.5	15
Q1, Q3	7, 26	11, 24	12.5, 24.5	7, 22	7, 22	7.5, 23.5
Range	1, 156	3, 30	3, 30	1, 51	1, 51	1, 51
Median across all post-baseline visits*						

n	45	18	17	77	78	95
Median	17.5	95	96.5	23.1	23	29.5
Q1, Q3	9, 32.5	74, 105.5	44, 119.5	10, 34	10, 35	11.5, 49
Range	2, 163.5	52, 254.5	52, 254.5	2, 76.5	2, 76.5	2, 254.5

*All post-baseline visits include platelet counts from Weeks 2-24.
1. When counting patient (b) (6) as non-responder.
[Source: ADSL.xpt and ADEFF. xpt and Fostamatinib prescribing information]

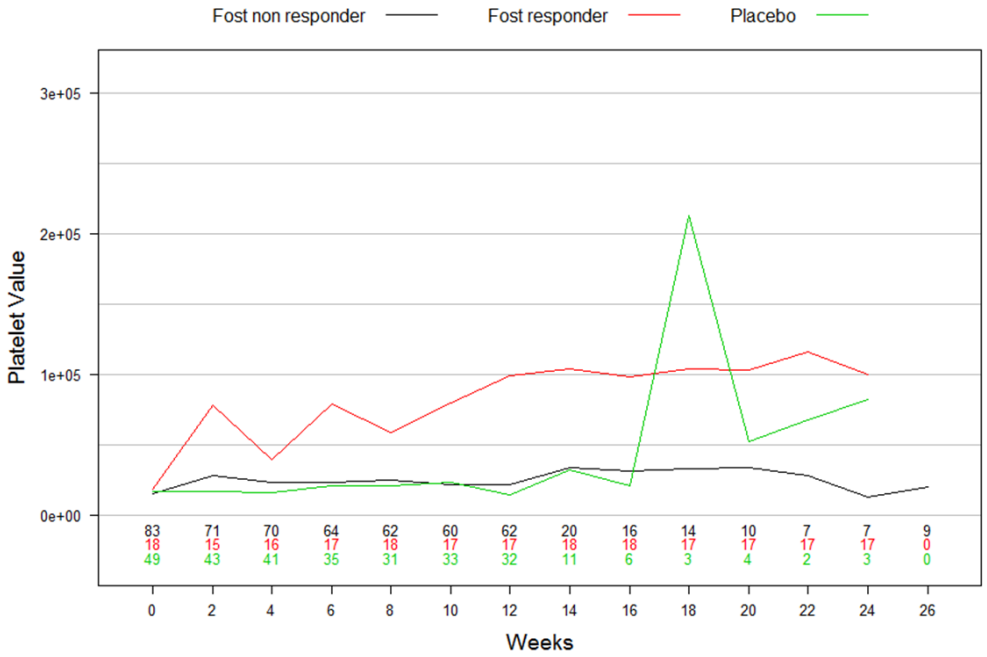
The figures below show the median platelet count changes over time by treatment arm (and by fostamatinib response) for each trial and as pooled.

Figure 8 C788-047 and C788-048: Median Platelet Count by Study Visit and Response (includes LOCF counts)



By Stella Karuri, Statistical Reviewer

Figure 9 Pooled Analysis of C788-047 and C788-048: Median Platelet Count by Study Visit and Response (includes LOCF counts)



By Stella Karuri, Statistical Reviewer

Reviewers Note: The curves in the above plots should be interpreted with caution. A large number of patients discontinued from the trials by Week 14 due to lack of platelet response. The large variation in platelet counts in the placebo after Week 18 is due to the fact that the placebo arm has very few patients: only one patient in Study 047 and 2-3 patients in Study 048).

<u>Subgroup analysis for primary efficacy endpoint:</u>
For both trials 047 and 048, the applicant estimated the difference in response in key subgroups as shown in Table 49 and Table 50. These results used the applicants LOCF imputations for platelet count. No multiple testing procedure was pre-specified for subgroup analyses. Higher responses were observed in the fostamatinib arm.

Reviewers Note: These analyses are considered exploratory. The results in these analyses should be interpreted with caution due to the use of imputation and the low number of responses, and in some cases, low patient numbers in the subgroups.

Table 49 C788-047: Subgroup Analyses of the Primary Efficacy Endpoint with LOCF (ITT Population)

Sub-group		Arm	Yes	# Pts	%Yes	Diff% (Fos-placebo)	95% CI*	95% CI**
Age	<65	Fos	6	32	18.8	18.8	5.2, 32.3	-10.3, 46.0
		Placebo	0	18	0.0			
	≥65	Fos	3	19	15.8	15.8	-0.6, 32.2	-27.0, 57.8
		Placebo	0	7	0.0			
Baseline Platelet	<15x10^9/L	Fos	4	25	16.0	16.0	1.6, 30.4	-17.8, 47.8
		Placebo	0	12	0.0			
	≥15x10^9/L	Fos	5	26	19.2	19.2	4.1, 34.4	-15.9, 51.4
		Placebo	0	13	0.0			
	<20x10^9/L	Fos	6	35	17.1	17.1	4.7, 29.6	-12.7, 44.8
		Placebo	0	16	0.0			
	≥20x10^9/L	Fos	3	16	18.8	18.8	-0.3, 37.9	-21.2, 55.5
		Placebo	0	9	0.0			
Gender	Female	Fos	5	30	16.7	16.7	3.3, 30.0	-13.0, 44.5
		Placebo	0	17	0.0			
	Male	Fos	4	21	19.0	19.0	2.3, 35.8	-22.0, 56.8
		Placebo	0	8	0.0			
Previous TPO medication	N	Fos	5	25	20.0	20.0	4.3, 35.7	-17.6, 55.6
		Placebo	0	10	0.0			
	Y	Fos	4	26	15.4	15.4	1.5, 29.3	-16.5, 45.0
		Placebo	0	15	0.0			
Prior splenectomy	N	Fos	6	31	19.4	19.4	5.4, 33.3	-11.0, 47.8
		Placebo	0	15	0.0			
	Y	Fos	3	20	15.0	15.0	-0.6, 30.6	-25.0, 52.0
		Placebo	0	10	0.0			
Race	Non-White	Fos	2	7	28.6	28.6	-4.9, 62.0	-35.3, 80.6
		Placebo	0	4	0.0			
	White	Fos	7	44	15.9	15.9	5.1, 26.7	-10.6, 41.0
		Placebo	0	21	0.0			

Fos=fostamatinib, diff=Difference (Fostamatinib – Placebo)
* Interval based on Normal approximation, ** Exact interval
[Source: ADEFF.xpt]

Table 50 C788-048: Subgroup Analyses of the Primary Efficacy Endpoint with LOCF (ITT Population)

Sub-group		Arm	Yes	# Pts	%Yes	Diff% (Fos-placebo)	95% CI*	95% CI**
Age	<65	Fos	8	41	19.5	19.5	7.4, 31.6	-6.9, 44.4
		Placebo	0	20	0.0			
	≥65	Fos	1	9	11.1	-13.9	-61.0, 33.3	-68.7, 43.4
		Placebo	1	4	25.0			
Baseline Platelet	<15x10^9/L	Fos	2	22	9.1	9.1	-2.9, 21.1	-29.4, 45.9
		Placebo	0	9	0.0			
	≥15x10^9/L	Fos	7	28	25.0	18.3	-2.1, 38.7	-12.8, 47.9
		Placebo	1	15	6.7			
	<20x10^9/L	Fos	4	30	13.3	4.2	-16.7, 25.1	-29.8, 38.0
		Placebo	1	11	9.1			
	≥20x10^9/L	Fos	5	20	25.0	25.0	-6.0, 44.0	-9.6, 55.9
		Placebo	0	13	0			
Gender	Female	Fos	5	31	16.1	16.1	3.2, 29.1	-16.6, 46.8
		Placebo	0	13	0.0			
	Male	Fos	4	19	21.1	12.0	-13.0, 37.0	-25.0, 46.5
		Placebo	1	11	9.1			
Previous TPO medication	N	Fos	6	30	20.0	12.9	-6.8, 32.5	-19.2, 43.6
		Placebo	1	14	7.1			
	Y	Fos	3	20	15.0	15.0	-0.6, 30.6	-25.0, 52.0
		Placebo	0	10	0.0			
Prior splenectomy	N	Fos	6	36	16.7	10.0	-7.5, 27.5	-20.4, 39.0
		Placebo	1	15	6.7			
	Y	Fos	3	14	21.4	21.4	-0.1, 42.9	-19.8, 58.2
		Placebo	0	9	0.0			
Race	W	Fos	9	50	18.0	13.8	0.5, 27.1	-10.9, 37.5
		Placebo	1	24	4.2			

Fos=fostamatinib, diff=Difference (Fostamatinib – Placebo), NW=Non-white, W=White,
* Interval based on Normal approximation, ** Exact interval
[Source: ADEFF.xpt]

According to the applicant's submission on July 10, 2017, among patients in the fostamatinib arm who received prior TPO receptor agonist therapy, there were a total of 8 patients who had a response as defined in the primary endpoint (study 047: (b) (6), (b) (6), study 048: (b) (6)). The datasets were not provided. The response rates in this subgroup were 19% (5 out of 26 patients) and 15% (3 out of 20 patients) in the 047 and 048 trial, respectively. The reason for prior TPO receptor agonist discontinuation in these eight responders was due to loss of response. In addition, two responders also did not tolerate other therapies.

Table 51 C788-047 and C788-048: Summary of Reasons for TPO Receptor Agonist Discontinuation for Fostamatinib Responders as Defined in the Primary Endpoint

Study	Patient	Reasons for TPO receptor agonist discontinuation
C788-047	(b) (6)	This patient (previously splenectomized) was on romiplostim from (b) (6) The patient totally lost the response (and to IVIg as well), which "precipitated" the need to enter the study. The patient had also failed at least 5 other therapies.
		This patient was on eltrombopag from (b) (6) and (b) (6) The treatment was discontinued both times due to loss of response. The second treatment was also discontinued based on bone marrow findings.
		This patient (previously splenectomized) was on eltrombopag from (b) (6) and on romiplostim from (b) (6) to (b) (6) and (b) (6) All treatments were discontinued due to loss of response. The patient joined the study because all other therapies had failed.
		This patient was on eltrombopag olamine from (b) (6) to (b) (6). Treatment was discontinued due to lack of response. The patient joined the study to avoid taking steroids.
		This patient was on eltrombopag olamine from (b) (6) to (b) (6). Treatment was discontinued due to loss of response. The patient had other treatment options but was interested in participating in a clinical study.
C788-048		This patient was on eltrombopag from (b) (6) This patient had an initial response, followed by a loss of response.
		This patient was on eltrombopag from (b) (6) and on romiplostim from (b) (6) Treatments were discontinued because the patient "was in a patient named program" and loss of response, respectively. The patient did not tolerate other therapies.
		This patient was on romiplostim from (b) (6) and (b) (6) and on eltrombopag olamine from (b) (6) to (b) (6) Treatments were stopped because of large variations in platelet count and no response, respectively. The patient did not tolerate other therapies.

[Source: Applicant's response to information request]

Patient Reported Outcome (SF-36 assessments):

For both 047 and 048 trials, SF-36 assessments (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, mental health, physical component score, and mental component score) were collected at baseline, Weeks 4, 12 and 24.

Reviewer's Note: Comparison between the arms at and after Week 14 should be interpreted with caution due to high study discontinuation from lack of platelet response. In addition, there was no type I error allocation to compare PRO assessments between the two arms.

In the 047 trial, descriptive statistics summarizing mean scores and changes from baseline for the SF-36 did not demonstrate differences between the two arms.

In the 048 trial, with the exception at Week 4 favoring the fostamatinib arm of certain items (bodily pain, general health, and physical health summary), descriptive statistics did not demonstrate differences between the two arms.

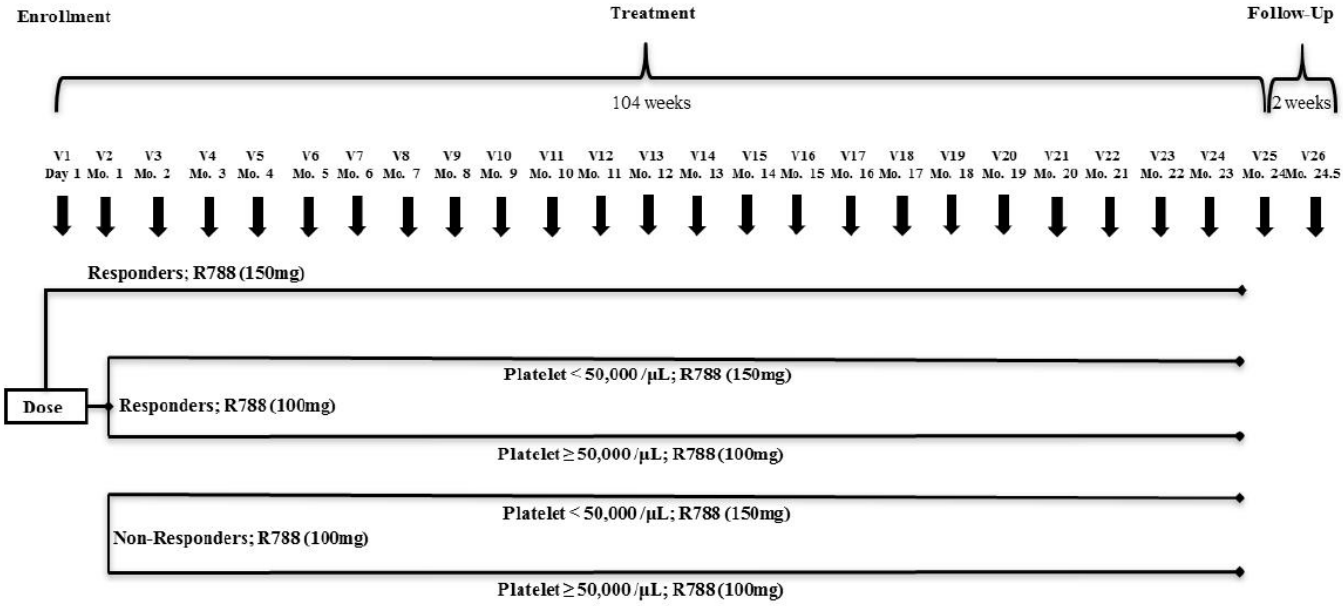
7.2.3. Study C788-049

Trial ID and Title:
C788-049 (C-935788-049): Phase 3 Open Label Extension Study of Fostamatinib Disodium in the Treatment of Persistent/Chronic Immune Thrombocytopenic Purpura.

Trial Design

This is a phase 3, multi-center, open-label, extension trial to study the long-term safety and efficacy of fostamatinib in achieving and maintaining a stable platelet response in patients with ITP over a 2-year period. The safety and efficacy results were based on interim analyses.

Figure 10 C788-049: Trial Design

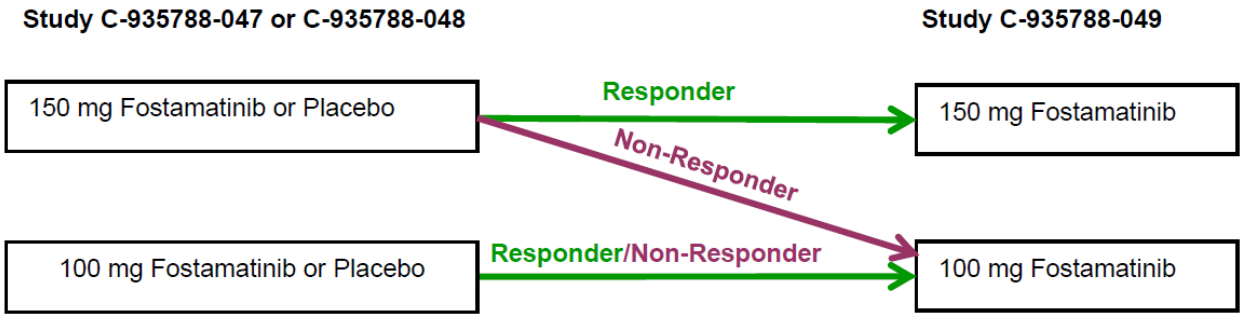


[Source: Protocol C788-049]

Eligible patients included patients from the C788-047 or C788-048 trial who had completed the Week 24 evaluation or who discontinued early (starting at Week 12) due to lack of response. All

patients were to receive open-label fostamatinib. Patients designated as responders (defined as platelet count ≥ 50,000/mcL) at the time of roll over were to continue in the extension study at their current C788-047 or C788-048 trial dose and regimen. Patients who enter the extension study as non-responders (defined as platelet count < 50,000/mcL) were to be allocated to fostamatinib 100 mg PO BID regardless of their dose and regimen in the prior trial.

Figure 11 C788-049: Initial Treatment Allocation



[Source: Protocol C788-049]

Patients were to remain blinded to their treatment assignment from C788-047 or C788-048 trials. Patients could continue to receive the concomitant medications for ITP that were allowed in the prior trial (i.e., glucocorticoids at dose < equivalent of 20 mg prednisone daily, azathioprine or danazol). Patients in whom the platelet count was stable at ≥ 50,000/mcL could have the dose of concomitant medications for ITP gradually reduced according to standard practice. At Month 1, patients receiving fostamatinib 100 mg PO BID were to have the dose escalated to 150 mg PO BID if platelet count was < 50,000/mcL and the study drug was well tolerated. Conversely, the dose could be reduced at any time to a dose of fostamatinib 100 mg PO once daily if dose limiting AEs were observed.

Patients whose platelet count was consistently < 50,000/mcL following 3 months (12 weeks) of treatment, and at least 4 weeks at a dose of 150 mg PO BID (unless this higher dose was not tolerated), were to be discontinued from the trial, unless there was a clinical benefit. Examples of clinical benefit included the following:

- Credible increase in platelet count (e.g., increase in platelet count of at least 20,000/mcL over initial baseline to a count ≥ 30,000/mcL).
- Reduction in bleeding.
- Reduction in the need for rescue therapy.

An independent SRC was to monitor safety. Platelet count testing was to be performed by local laboratories and a central laboratory was to be used for testing hematology, serum chemistry, urinalysis, INR/aPTT, serum pregnancy and biospecimen.

Trial Objectives:
The primary objective was to assess the long term safety of fostamatinib in patients with ITP.

Secondary objectives were to evaluate the long-term efficacy of fostamatinib in achieving and maintaining a stable platelet count in patients who completed the treatment phase of the C788-047 or C788-048 trials, and to assess the pharmacokinetic (PK) profile of fostamatinib in patients with ITP.

Eligibility Criteria:

Key Inclusion Criteria:

1. Must have completed the Week 24 evaluation of Study C788-047 or C788-048 or have discontinued early (starting at Week 12) due to lack of response. No more than 7 days may have elapsed between the last day of treatment on Study C788-047 or C788-048 and initial dosing (Day 1) in Study C788-049.
2. Male or female at least 18 years of age.
3. Females must be either post-menopausal for at least 1 year or surgically sterile; or if female of child-bearing potential, must not be pregnant or lactating and must agree to use an acceptable method of birth control throughout the duration of the trial and for 30 days following the last dose.

Key Exclusion Criteria:

1. Any subject who discontinued participation in Study C788-047 or C788-048 prior to Week 12 for any reason other than lack of response. Exceptions could be considered on a case-by-case basis after consultation.
2. Subjects with poorly controlled hypertension during Study C788-047 or C788-048, defined as persistent or repeated systolic ≥ 140 mmHg, or diastolic ≥ 90 mmHg whether or not the subject is receiving anti-hypertensive treatment.
3. Subjects with the following laboratory abnormalities at the time of enrollment (Day 1): a leukocyte count < 2,000/mcL, a neutrophil count of < 1,000/mcL, lymphocyte count <750/mcL, Hgb < 10 g/dL, or transaminase levels (ALT, AST) > 1.5x ULN, bilirubin >1.5x ULN, or estimated glomerular filtration rate (eGFR) < 30 mL/min.
4. Significant infection, an acute infection such as influenza, or known inflammatory process.
5. Received any blood or blood products within the 2 weeks prior to enrollment (IVIg or anti-D are allowed if used for rescue therapy).

Schedule of Events:

Table 52 C788-049: Schedule of Study Procedures

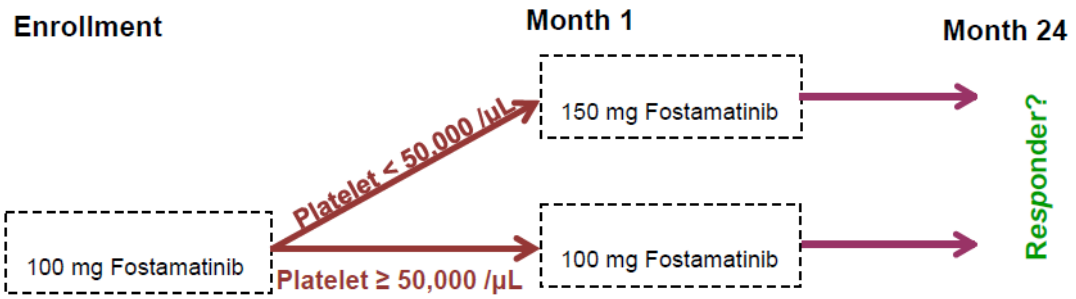
Study Procedure	Enrollment (Day 1) [a]	Treatment Period			Follow-Up[j]
		Month 1 ± 3 days	Months 2,4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24 ± 3 days	Months 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23 ±3 days	Month 24.5 ± 7 days
Informed Consent	X				
Inclusion/Exclusion	X				
Physical Exam[a] with KPS	X	X	X	X	X
Concomitant Meds	X	X	X	X	X
Vital Signs[c]	X	X	X	X	X
Bleeding Assessment[d]	X	X	X	X	X
ECG	X				
CBC/Diff/Retic Count	X		X	X	X
Platelet Count[e]	X	X	X	X	X
Serum Chemistry	X		Months 4, 8, 12, 16, 20, 24		
LFTs[f]			Months 2, 6, 10, 14, 18, 22	X	X
Immunoglobulin levels	X		Months 6, 12, 18, 24		
Urinalysis	X		Months 4, 8, 12, 16, 20, 24		X
Urine Pregnancy Test[g]	X		X		
SF-36[h]	X		Months 12, 24		
Adverse Events	X	X	X	X	X
PK[i]			Month 2		
Study Drug Dispensed	X	X	X	X	
Dose Adjustment	X	X	X	X	
Study Drug Accountability		X	X	X	

a. Enrollment (Day 1): These procedures were equivalent to Week 24 visit of Study C788-047 or C788-048; assessments performed as part of Week 24 could be used to assess subject's eligibility to roll over and did not need to be repeated specific to Study C788-049.
b. Physical exam included KPS.
c. Vital Signs included blood pressure, pulse and temperature.
d. Bleeding Assessment included IBLS and WHO Bleeding Scale.
e. Platelet counts were to be performed at the local lab.
f. LFTs included ALT, AST, ALP, LDH, and Bilirubin (total and direct).
g. Pregnancy Test: For women of childbearing potential, regardless of birth control methodology.
h. SF-36: At visits where the SF-36 was evaluated the SF-36 was the first assessment performed.
j. Follow Up visit was to be completed 2 weeks (+/- 7 days) after subject's last treatment or performed at the time of early treatment termination.
[Source: Protocol C788-049]

Treatment Modification Plan:

The initial dose was to be determined by a subject's response to treatment in the C788-047 or C788-048 trial. Beginning at Month 1, patients who initiated dosing at fostamatinib 100 mg PO BID in the extension trial and who had not previously had a dose reduction had to have their dose increased to 150 mg PO BID if the platelet count remained below 50,000/mcL and the study drug had been well tolerated.

Figure 12 C788-049: Dose Escalation - Patients Starting at 100 mg BID who Have Not Previously Had a Dose Reduction



[Source: Protocol C788-049]

In the 049 trial, treatment with the study drug administration could be modified for adverse events that include the following and was consistent with the C788-047 and C788-048 trials (see Treatment Modification Plan under section 7.2.1):

- Increases in ALT, AST, or bilirubin
- ANC < 1000/mm^3 (or 1.0 x 10^9/L)
- Severe diarrhea
- Increase in BP to > 140/90 mmHg
- Other severe or life-threatening adverse events considered related to study drug administration.

For excessive increase in platelet count as compared to the recommendations in the C788-047 or C788-048 trial, consideration was given to reduce the dose of the concomitant therapies for ITP (azathioprine, glucocorticoids, danazol). If a reduction in concurrent therapies was not effective, the following guidelines (same as C788-047 and C788-048) were to be followed:

- For platelet counts > 250,000/mcL:
  - Reduce the dose of study drug to dose level -1.
  - Monitor the platelet count every 72 hours until platelet count falls to <200,000/mcL.
- For platelet counts > 150,000/mcL and ≤ 250,000/mcL:
  - Continue study drug at full dose.
  - Monitor the platelet count every 72 hours until stable to assure it does not exceed 250,000/mcL.

Conditions in which rescue therapy could be administered and allowed therapeutic regimens were consistent with the C788-047 and C788-048 trials.

Study Endpoints

<u>Primary efficacy endpoint:</u>

The protocol contained two versions of the primary efficacy endpoint. The first version was assessing efficacy among all patients while on active treatment in one of the prior trials, in the current extension trial, or in both. The primary efficacy endpoint in this version was the achievement and maintenance of a stable platelet count defined as follows:

- Platelet count of at least 50,000/mcL within 12 weeks of beginning active treatment.
- Sustained stable platelet response; defined as no two visits, at least 4 weeks apart, with a platelet count < 50,000/mcL, without an intervening visit with a platelet count of ≥50,000/mcL unrelated to rescue therapy, within a period of 12 months following initial achievement of the target platelet count (as defined above).

Patients who discontinued treatment due to lack of efficacy or due to an AE prior to 12 months following achievement of a platelet count of at least 50,000/mcL were to be considered failures.

The second version of the primary efficacy endpoint was for the purpose of a within-subject, between-study comparison of fostamatinib and placebo among patients randomized to placebo in either of the prior trials. The primary efficacy endpoint definition in this second version was different from that in the 047/048 trials. The achievement and maintenance of a stable platelet count was defined as follows:

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

Patients who discontinued treatment due to lack of efficacy or due to an AE prior to 12 weeks following achievement of a platelet count of at least 50,000/mcL, were to be considered failures. The null and alternative hypotheses for the comparison of fostamatinib vs. placebo were:
H_0: $p_F = p_P$ vs. H_1: $p_F \neq p_P$ (where p_F and p_P are the true proportions achieving and maintaining a stable platelet count for fostamatinib and placebo, respectively). A significance level of 2-sided 0.05 was to be used.

Reviewer's Note: This study was not sized to detect a particular magnitude of an effect. No multiplicity adjustments were pre-specified and none of the two versions of the primary endpoint was pre-defined for formal statistical testing. Consequently, p-value magnitudes specified in the sponsor's results are not meaningful.

Secondary efficacy endpoints were as follows:

- The duration of any stable platelet response.

- Proportion of patients in whom a reduction in the dose of concomitant ITP therapy can be achieved while maintaining an adequate platelet count.

Duration of stable platelet response was defined as the time, following active treatment, from when the subject first achieved a platelet count of at least 50,000/mcL until the first of two visits with platelet counts < 50,000/mcL that are at least 4 weeks apart without an intervening visit with a platelet count ≥ 50,000/mcL unrelated to rescue therapy. Patients who dropped out of the trial before achieving a stable platelet response were to be assigned a value of '0' for this endpoint.

Patients who dropped out or completed the study while still maintaining a stable platelet response were to be censored as of the time of the last platelet measurement prior to dropping out or completing the trial. For patients who had achieved and maintained a stable platelet response but who discontinued treatment due to lack of efficacy or to an AE, duration of stable platelet response was to be defined as the time from first achieving a platelet count of at least 50,000/mcL until discontinuation of treatment.

Statistical Analysis Plan

There were two editions of the statistical analysis plan (SAP), dated October 22nd and March 21st, 2017. There were no major changes to the efficacy analysis in the second edition.

All efficacy endpoints were to be analyzed based on the Treated population. The efficacy analyses based on the Treated population were to be considered the primary efficacy analyses. All safety analyses were also to be performed on the Treated Population.

The Per-Protocol (PP) population was to include all patients in the Treated population who had no major protocol violations in either study. Major protocol violations included:

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

All efficacy endpoints were also to be analyzed based on the PP population. The analyses based on the PP population were to be considered secondary analyses of efficacy.

The baseline value was defined as the last measurement for the corresponding variable before the first dose of fostamatinib in study C788-047 or C788-048 (for fostamatinib patients in the previous study) or study C788-049 (for placebo patients in the previous study).

Protocol Amendments

The table below summarizes the clinical trial landmarks and key protocol amendments for the C788-049 trial.

Table 53 C788-049: Landmarks and Key Protocol Amendments

Date	Landmarks
December 18, 2013	Initial protocol (no patients enrolled under this version)
April 8, 2014	Version 2 - Added a footnote under the schedule of study procedures that if the enrollment visit occurs on the same day as Visit 15 (+ 7 days) from Study C788-047 or C788-048, assessments performed as part of Visit 15 do not need to be repeated. - Revised the dose adjustment section of the protocol to allow for flexibility in study drug dose for patients in whom clinical benefit is shown. The text was modified to indicate that patients who have a dose reduction to due adverse events may be allowed to have their dose re-escalated after the adverse event has resolved. - Revised the source data section of the protocol to more accurately reflect the requirements for source documentation and the types of source documents that will be used during the study.
October 9, 2014	Study initiation date (first subject first dose of study drug)
November 21, 2014	Version 3 - Revised the inclusion criteria to clarify the timing requirement to roll over patients from the C788-047 or C788-048 trial is starting at Week 12 rather than after Week 12. - Revised the exclusion criteria to exclude patients with hemoglobin <10 g/dL. - Revised the text that assessments (e.g., physical examination, KPS, IBLS, and WHO bleeding assessment) would be performed by the same assessor.
September 9, 2016	Cutoff date of the CSR

[Source: FDA compilation]

Data Quality and Integrity: Sponsor's Assurance

A CRO performed the study conduct activities. A biostatistics organization performed biostatistical analyses and an additional CRO prepared and maintained the electronic trial master file. A safety CRO was responsible for safety database set-up, data entry/maintenance and processing. Original data and any changes were recorded using the electronic data capture system, with changes tracked and recorded in an electronic audit trail.

The applicant provided signed certification by Anne-Marie Duliege, MD (the executive vice president and chief medical officer) that the study report accurately describes the conduct and results of the study.

7.2.4. Study Results

Compliance with Good Clinical Practices

The C788-049 trial was reviewed and approved by the Independent Ethics Committees or Institutional Review Boards and conducted in accordance with GCP and the Declaration of Helsinki. Written informed consent was obtained from each subject prior to performance of study-specific procedures.

Financial Disclosure

The submission contained FDA financial certification form 3454 signed by Ryan Maynard, the executive vice president and chief financial officer for Rigel Pharmaceuticals, dated April 6, 2017. The applicant certified that investigators that participated in the C788-049 trial did not disclose any financial interests. The submission contained a list of the 184 principal and sub-investigators who participated in the trial.

None of the investigators were full-time or part-time sponsor employees.

Patient Disposition

Out of the 150 patients that were enrolled in the C788-047 and C788-048 trials, a total of 123 patients (79 patients previously randomized to fostamatinib and 44 patients previously randomized to placebo) enrolled in the extension trial from 53 sites in 15 countries (US, Europe, Australia and Canada). As of the interim clinical data cut-off, a total of 62 patients (39 patients previously randomized to fostamatinib and 23 patients previously randomized to placebo) remained in the 049 trial. A total of 61 patients (50%) discontinued from the trial at Week 12 or later mostly (28%, 34 patients) due to lack of response. Among the 34 patients who discontinued early (at Week 12 or later) due to lack of response, 25 patients (20%) had previously been randomized to the fostamatinib arm and 9 patients (7%) to the placebo arm in the 047 or 048 trial.

The table below summarizes patient disposition of the C788-049 trial as of the interim clinical cut-off date of September 9, 2016.

Table 54 C788-049: Patient Disposition (Treated Population)

	Total (n=123)
Patients who remained in the trial	62 (50%)
Patients who discontinued from the trial early	61 (50%)

Reason for discontinuation	
Discontinued early (at Week 12 or later) due to lack of response	34 (28%)
Investigator discretion	7 (6%)
Patient decision	6 (5%)
Other AEs	6 (5%)
Study specific AE requiring Discontinuation	4 (3%)
Other	4 (3%)

[Source: ADSL.xpt]

Protocol Violations/Deviations

In the 049 trial, a total of 329 protocol violations were reported in 91 patients (74%). Most of the protocol violations were related to visit schedule (57%) and procedure requirement (41%). A total of 3 patients ((b) (6) received additional corticosteroids during study treatment and it was determined that these 3 patients were non-responders.

Table 55 C788-049: Protocol Violations (Treated Population)

	Total (n=123)
All patients*	91 (74%)
Visit schedule	70 (57%)
Visit/procedure requirement	50 (41%)
Laboratory	8 (7%)
Noncompliance	7 (6%)
Dosing	6 (5%)
Concomitant medication	3 (2%)
Regulatory	1 (<1%)

*Based on number of patients. A patient can appear in more than one category.
[Source: DV.xpt]

In addition to the 329 protocol violations in 91 patients (74%), there were a total of 26 exemptions granted to 19 patients (15%). Most of the exemptions were related to enrollment criteria and visit schedule/ procedure requirement (both 8 patients, 7%). The exemptions related to the enrollment criteria were: not meeting the requirements for lymphocyte count (5), total bilirubin (1), blood pressure (1), and receiving platelet transfusion within 2 weeks of enrollment (1, patient (b) (6)). Patient (b) (6) received platelet transfusion on Day 1 of the extension trial. This patient was a 57 year old female initially randomized to the fostamatinib arm in the 047 trial who discontinued early due to lack of response and subsequently continued on the extension trial. This patient again discontinued early from the extension trial due to lack of response and therefore was a non-responder.

Demographic and Baseline Disease Characteristics

Consistent with the 047 and 048 trials, 60% of patients that continued on the 049 trial were female, the median age was 52 years old (range, 20 to 88), and most were White (92%).

Table 56 C788-049: Patient Demographics (Treated Population)

	Total (n=123)
Gender	
Female	74 (60%)
Male	49 (40%)
Age (years)	
Median	52.0
Range	20-88
Age (by category, years)	
< 65	95 (77%)
≥ 65	28 (23%)
Race	
White	113 (92%)
Asian	4 (3%)
Black/African American	4 (3%)
Other	2 (2%)

[Source: ADSL.xpt]

Most of the patients had chronic ITP (94%), 37% of the patients had undergone splenectomy and the median baseline platelet count was 16,000/mcL (range, 1,000 to 156,000/mcL).

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Compliance:
Treatment compliance was defined as the same as the 047/148 trials (the actual number of doses [tablets] the patient took during the period divided by the total number of tablets expected to be taken, multiplied by 100). Overall, the median treatment compliance was 98.9%. Among patients with missed doses, the median number of missed doses was 3 (range, 0-138) in this trial.

Concomitant ITP Medications:
A total of 76 patients (62%) received concomitant ITP medications which mostly were corticosteroids (47%). The table below summarizes the concomitant ITP medications administered during the 049 trial.

Table 57 C788-049: Concomitant ITP Medications (Treated Population)

	Fostamatinib (n=123)
All subjects	76 (62%)
Corticosteroids	58 (47%)
Immunoglobulins	20 (16%)
Immunosuppressants[1]	6 (5%)
Vitamin K and other hemostatics (romiplostim)	3 (2%)
Platelets[2]	3 (2%)
Anabolic steroids (danazol)	2 (2%)

Based on number of patients. A patient can appear in more than one category.
1. Includes azathioprine and cyclosporine.
2. Three patients ((b) (6)), each received platelet transfusion once during the study. None of these patients was a responder.
[Source: ADCM.xpt]

Rescue medication:
In the 049 trial, a total of 37 patients (30%) received rescue therapy during the study. The median number of rescue events was 2 (range, 1-11) in patients who received rescue medication.

Among the 79 patients who received fostamatinib in the earlier trial, 19 patients (24%) received rescue therapy during the 049 trial. The median number of rescue events was also 2 (range, 1-11) in this subgroup.

Among the 44 patients who received placebo in the earlier trial, a higher proportion of patients (41%, 18 patients) received rescue therapy during the 049 trial. A total of 12 (27%) and 10 patients (23%) received rescue therapy prior and after Week 10, respectively. The table below summarizes the use of rescue therapy in this subgroup.

Table 58 C788-049: Use of Rescue Therapy Among Patients who Received Placebo in the Earlier Trial (Treated Population)

	Fostamatinib (n=44)
Subjects that received rescue therapy	18 (41%)
Prior to Week 10 (Day 73)	12 (27%)
Median (per patient)	2.0
Range (per patient)	1-11
After Week 10 (Day 73)	10 (23%)
Median (per patient)	1.5

Range (per patient)	1-9

Based on number of patients. A patient can appear in more than one category.
[Source: ADCM.xpt]

Efficacy Results - Primary Endpoint

As stated above, the protocol contained two versions of the primary efficacy endpoint assessment (i.e., assessment of all patients who received fostamatinib in 047, 048, 049 within a period of 12 months following initial achievement of the target platelet count; and within-subject, between-study comparison of fostamatinib and placebo among patients who received placebo in 047/048 and who received fostamatinib in 049 within a period of 12 weeks following initial achievement of the target platelet count).

For the current submission, no formal analysis of long term stable platelet response (first version) was conducted. The applicant plans to conduct this analysis following the completion of the 049 trial.

For the second version of the primary endpoint analysis for the purpose of a within-subject, between-study comparison of fostamatinib and placebo among patients who were randomized to placebo in studies 047 or 048, stable platelet response was defined as platelet count of at least 50,000/mcL within 12 weeks of beginning active treatment and a sustained stable platelet response defined as no two visits, at least 4 weeks apart with a platelet count < 50,000/mcL, without an intervening visit with a platelet count of ≥ 50,000/mcL unrelated to rescue therapy, within a period of 12 weeks following initial achievement of the target platelet count.

Among the 44 patients who received placebo in 047 or 048 trials, a total of 9 patients (20.5%) had achieved a stable platelet response as defined in the C788-049 protocol (second version). Patient (b) (6) who was randomized to the placebo arm in the 048 trial and assessed as a responder continued in the 049 trial. This patient was a responder in both 048 and 049 trials.

Table 59 C788-049: Platelet Count for Responders (Second Version)

Patient ID	Platelet count (x 10^9/L) at scheduled visits													
	First 12 weeks													
	Baseline	Study week												
		4	8	12	16	20	24	28	32	36	40	44	48	52
(b) (6)	11	36	46	58	54	57	53	38	64	57	28	14	77	37
	44	59	36	100	73	77	42	72	15	-	-	-	-	-
	82	230	176	307	191	133	52	52	52	80	118	112	-	-
	41	109	132	322	202	217	157	-	-	-	-	-	-	-
	31	90	72	86	98	93	93	99	108	79	-	-	-	-
	43	121	68	111	99	104	71	72	97	54	84	-	-	-
	4	81	113	107	117	95	97	49	-	86	107	146	160	191
	24	52	69	43	61	48	202	30	-	136	87	104	68	101
	40	65	112	74	66	52	-	-	-	-	-	-	-	-

1. Patient (b) (6) was randomized to the placebo arm in the 048 trial. This patient was a responder in both 048 and 049 trials.
It has been reported that two responders discontinued treatment (patient (b) (6) due to patient decision despite maintaining platelet response and patient (b) (6) due to due to hepatic enzyme elevation). Patient (b) (6) also had consecutive platelet counts below 50,000/mcL at Months 10 to 11, and Months 13 to 15 (possibly related to study drug interruption) and discontinued at Month 16.

Yellow shades: Platelet counts ≥ 50,000/mcL.
[Source: ADEFF2.xpt]

Among the patients who had a platelet response according to the second version (table 59), only 1 patient ((b) (6)) received rescue therapy during this study (oral dexamethasone 20 mg rescue therapy for 2 days on Study Days 1 and 2).

Among the 44 patients who received placebo in the previous trial and had no response in either of the blinded studies, a total of 8 patients (18.2%, 95% CI: 6.8, 29.6) achieved a response in the extension study. This analysis is slightly different from the applicant's results. The applicant used a denominator of 41 instead of 44 patients (41 of the 44 patients had ≥ 12 weeks of fostamatinib treatment after a platelet count of at least 50,000/mcL). As analyzed by the applicant, the proportion of placebo patients in Study 049 who had no response in either of the prior blinded studies but achieved a response in the extension study was 19.5% (95% CI: 7.4, 31.6). The table below shows the applicant's and FDA analysis of response among patients who had previously received placebo in the 047 or 048 trial.

Table 60 C788-049: Stable Platelet Response in Patients who had Received Placebo in Study 047 or 048.

Placebo in 047/048 study	Fostamatinib in 049 study		Total	% of 049 responders who were previously non-responders**
	Responder*	Non-responder		
Applicant's analysis				
Responder (placebo)	1 (2.4%)	0	1 (2.4%)	19.5% (95% CI: *7.4, 31.6*)
Non-responder	8 (19.5%)	32 (78.0%)	40 (97.6%)	
Total	9 (22.0%)	32 (78.0%)	41 (100%)	
FDA analysis				
Responder (placebo)	1 (2.3%)	0	1 (2.3%)	18.2% (95% CI: 6.8%, 29.6%),
Non-responder	8 (18.2%)	35 (79.5%)	43 (97.7%)	
Total	9 (20.5%)	35 (79.5%)	44 (100%)	

* Achievement of platelet count of at least 50,000/mcL within 12 weeks and a sustained stable platelet response (defined as no two visits, at least 4 weeks apart, with a platelet count < 50,000/mcL, without an intervening visit with a platelet count of ≥ 50,000/mcL unrelated to rescue therapy, within a period of 12 weeks following initial achievement of the target platelet count) among patients randomized to placebo in either study C788-047 or C788-048.

**Denominator equals to number of prior placebo patients who had ≥ 12 weeks of fostamatinib treatment after a platelet count of at least 50,000/mcL (applicant's analysis) or number of prior placebo patients (FDA analysis), confidence intervals based on exact intervals.
[Source: ADEFF.xpt and 049 CSR]

Reviewer's comment: No multiplicity adjustments were made for Study 049. The proportion in the rightmost column gives the proportion of Study 049 responders who were prior placebo patients (in Study 047 and Study 048) and experienced no response in the placebo phase. The denominator in this analysis is the total number of placebo patients in Study 049.

Efficacy Results - Secondary and other relevant endpoints

Duration of stable platelet response:

Duration of platelet response was defined as the time from when the subject first achieves a platelet count of at least 50,000/mcL until the first of two visits with platelet counts < 50,000/mcL that are at least 4 weeks apart without an intervening visit with a platelet count ≥ 50,000/mcL unrelated to rescue therapy. Patients who have achieved and are maintaining a platelet response but who discontinued because of an AE were censored at the study discontinuation date. Patients who dropped out for other reasons or completed the study or remained in the study at interim data cut while still maintaining a platelet response were censored as of the time of the last platelet measurement. In the assessment of stable platelet response, platelet counts within 28 days of rescue regimen are excluded.

Among the patients who received fostamatinib in study 047 or 048, the 17 patients who achieved a stable platelet response (without LOCF) all enrolled in study 049. The median duration of response using the Kaplan-Meier (KM) estimate for these 17 patients was not yet reached (range, 4.1 to > 20.6 months as analyzed by the applicant; and range, <1 month to >20.5 months as analyzed by the FDA).

At the time of the clinical cut-off date of the interim analysis of study 049, the KM estimated median duration of response was also not yet reached (range, 4.1 to > 14.8 months) for the 9 patients who were treated with placebo (in study 047 or 048 and continued on 049) and met the within-subject, between-study comparison of the responder endpoint.

With regard to the other secondary endpoint (reduction in the dose of concomitant ITP therapy while maintaining a platelet count >50,000/mcL), the applicant reported that the incidence of the dose reduction of concomitant ITP medication was low (11 out of 123 patients, 9%) and time on study too brief. Therefore, the analysis was not conducted for this interim report.

Reviewer's Note: There were no multiplicity adjustments for endpoints in Study 049, these analyses are considered exploratory.

Additional Analyses Conducted on the Individual Trial

Platelet count changes by fostamatinib response:
The median post-baseline platelet count based on the 9 responders was 93,000 (range, 42,000 to 171,000) in the 049 trial and was consistent with those of patients who had achieved stable response in the 047 and 048 trials. The table below summarizes the platelet count results by responders (049 separately and 047/048/049 combined) and non-responders for the period during the 049 trial only.

Table 61 C788-049: Platelet Count (x 10^9/L) by Fosamatinib Response (Version 2)

Summary Statistics	Responder in 049 (n=9)	Responder in 047/048/049[1] (n=26)	Non-responder (n=97)	Total (n=123)
Baseline				
n	9	26	97	123
Median	23	20.5	16	16
Q1, Q3	8.5, 28.5	11.5, 25	6.5, 24.5	7, 25
Range	5, 32	3, 32	1, 156	1, 156
Median across all post-baseline visits*				
n	9	25	90	115
Median	93	94	25.5	34
Q1, Q3	66, 133	74.5, 122.5	10.5, 40	14, 65.5
Range	42, 171	19, 292.5	1, 221	1, 292.5

*All post-baseline visits include platelet counts from Weeks 2-24.
1. Includes the 17 patients that achieved stable platelet response during the 047 and 048 trials and continued on the 049 trial and the 9 responders in the 049 trial. The patient that was randomized to the placebo arm and responded in the 048 trial has been included in the 9 responders in the 049 trial.
[Source: ADSL.xpt and ADEFF.xpt]

Reviewer's Note: These analyses are post-hoc analyses and are considered exploratory.

Updated efficacy results of the primary endpoint:
In the 120-day safety update, the applicant provided updated results of patients who achieved stable platelet response as defined according to the second version. With the clinical cut-off date of April 14, 2017 (with 7 months of additional follow-up), one additional patient ((b) (6)) had achieved stable platelet response. The table below summarizes the updated results.

Table 62 C788-049: Updated Platelet Count for Responders

Patient ID	Platelet count (x 10^9/L) at scheduled visits													
	First 12 weeks													
	Baseline	Study week												
		4	8	12	16	20	24	28	32	36	40	44	48	52
(b) (6)	11	36	46	58	54	57	53	38	64	57	28	14	77	37
	44	59	36	100	73	77	42	72	15	-	-	-	-	-
	82	230	176	307	191	133	52	52	52	80	118	112	-	-

(b) (6)	41	109	132	322	202	217	157	-	-	-	-	-	-	-
	31	90	72	86	98	93	93	99	108	79	-	-	-	-
	43	121	68	111	99	104	71	72	97	54	84	-	-	-
	4	81	113	107	117	95	97	49	-	86	107	146	160	191
	24	52	69	43	61	48	202	30	-	136	87	104	68	101
	40	65	112	74	66	52	-	-	-	-	-	-	-	-
	36	56	70	119	84	78	59	-	65	70	63	-	-	-

*Patient (b) (6) was added as a responder in the 120-day safety update submission.

With the update, among the 44 patients who received placebo in studies 047/048, a total of 10 patients (22.7%) now had achieved a stable platelet response including one patient who was classified as a placebo responder in the prior randomized study. Therefore, among the placebo non-responders in the prior studies, 9 patients (20.5%, 95% CI: 8.5, 32.4) had achieved a stable response in study 049 according to the second version of the primary endpoint (i.e., achievement of platelet count of at least 50,000/mcL within 12 weeks of beginning active treatment and sustained platelet response for 12 weeks following initial achievement of the target platelet count).

Table 63 C788-049: Updated Stable Platelet Response in Patients who had Received Placebo in Study 047 or 048.

Placebo in 047/048 study	Fostamatinib in 049 study		Total	% of 049 responders who were previously non-responders**
	Responder*	Non-responder		
Responder (placebo)	1 (2.3%)	0	1 (2.3%)	20.5% (95% CI: 8.5, 32.4)
Non-responder	9 (20.5%)	34 (77.3%)	43 (97.7%)	
Total	10 (22.7%)	34 (77.3%)	44 (100%)	

* Achievement of platelet count of at least 50,000/mcL within 12 weeks and a sustained stable platelet response (defined as no two visits, at least 4 weeks apart, with a platelet count < 50,000/mcL, without an intervening visit with a platelet count of ≥ 50,000/mcL unrelated to rescue therapy, within a period of 12 weeks following initial achievement of the target platelet count) among patients randomized to placebo in either study C788-047 or C788-048.
**Denominator equals to number of prior placebo patients. Confidence intervals based on exact intervals.

With the update, including the one additional responder in study 049, the KM estimated median duration of response was still not yet reached (range, 6.4 to 20.7 months) in study 049.

On February 8, 2018, the applicant provided updated datasets to support the first version of the primary endpoint (i.e., achievement a platelet count of at least 50,000/mcL within 12 weeks of beginning active treatment and sustained platelet response for 12 months following initial achievement of the target platelet count for all patients who received active treatment in one of the prior trials, in the extension trial, or in both). A total of 18 patients maintained the platelet response of at least 50,000/mcL for 12 months or longer. Of these 18 patients, 6 patients were treated with placebo in study 047/048.

7.3. Integrated Review of Effectiveness

7.3.1. Assessment of Efficacy Across Trials

Primary Endpoints

C788-047 and C788-048:
The primary endpoint of the randomized, placebo-controlled trials was achievement of a stable platelet response by Week 24, defined as reaching a platelet count of at least 50,000/mcL on at least 4 of the last 6 scheduled visits between Weeks 14-24. Patients who discontinued treatment prior to Week 24 due to lack of efficacy or to an AE, or who receive rescue treatment after 10 weeks, were to be considered non-responders. A total of 76 patients (fostamatinib: 51, placebo: 25) and 74 patients (fostamatinib: 50, placebo: 24) were randomized in the C788-047 and C788-048 trials, respectively.

In the C788-047 trial, a total of 9 patients (17.6%) in the fostamatinib arm and no patient (0%) in the placebo arm achieved this endpoint. The difference of response between the arms was 17.6% [95% CI (-6.1%, 40.3%), exact confidence interval], [95% CI (7.2%, 28.1%), normal approximation], Fisher's exact test p-value: 0.03, favoring fostamatinib.

In the C788-048 trial, this endpoint was achieved in a total of 8 patients (16.0%) in the fostamatinib arm and 1 patient (4.2%) in the placebo arm. The difference between the arms was 11.8% [95% CI (-13.0%, 35.7%), exact confidence intervals], [95% CI (-1.1%, 24.8%), normal approximation], Fisher's exact test p-value: 0.26.

The result of the FDA analysis of the C788-048 trial is different from the applicant's in that the last observation carried forward (LOCF) method was not applied for missing data imputation in the FDA analysis. When applying the LOCF method (applicant's result), a total of 9 patients (18.0%) in the fostamainib arm and 1 patient (4.2%) in the placebo arm achieved the primary endpoint. The difference of the response between the arms was 13.8% [95% CI (-11.0%, 37.6%), the exact confidence intervals], [95% CI (0.5%, 27.2%), the normal approximation], Fisher's exact test nominal p-value: 0.15. The LOCF method is problematic as the last platelet count value may not always reflect the true platelet count for the missing data. This method may bias the results toward a patient or a set of patients when the response rate is low. The other limitation of the analysis was that there were few patients who were eligible to respond due to the high study discontinuation rate prior to the assessment period. This was more of an issue in the control arm; in Trial 047 only one patient had at least 4 assessments in the Week 14 – 24 assessment period and in Trial 048 only two patients had at least 4 assessments in the Week 14 – 24 interval.

In the CSR, the applicant reported confidence intervals for the difference in response based on the Normal approximation. The Normal approximation yields intervals with poor coverage if either one of the response rates and/or the samples is small. Interval estimates based on the

Exact unconditional method are more conservative and are reported in this review.

C788-049:
The open-label, extension trial contained two versions of the primary endpoint for stable platelet response. The datasets supporting the second version was included with the original NDA submission. The second version was defined as achievement of a platelet response of at least 50,000/mcL within 12 weeks of beginning treatment with fostamatinib with no two visits, at least 4 weeks apart, with a platelet count < 50,000/mcL (without an intervening visit with a platelet count of ≥ 50,000/mcL unrelated to rescue therapy) within the period of 12 weeks following initial achievement of the target platelet count. This was for the purpose of within-subject, between-study comparison of fostamatinib and placebo among patients randomized to placebo in either of the prior trials. Among the patients randomized to the placebo arm in either of the previous trials (C788-07 or C788-048), a total of 44 patients continued on the extension trial. Of the 44 patients, a total of 10 patients (22.7%) had achieved stable response as defined according to the second version and among the placebo non-responders in the prior trials, 20.5% (95% CI: 8.5, 32.4) of patients met this endpoint.

On February 8, 2018, the applicant provided the datasets supporting the first version of the primary endpoint which was defined as achievement of platelet count of at least 50,000/mcL within 12 weeks of beginning active treatment and sustained stable platelet response defined as no two visits, at least 4 weeks apart, with a platelet count < 50,000/mcL (without an intervening visit with a platelet count of ≥50,000/mcL unrelated to rescue therapy) within a period of 12 months following initial achievement of the target platelet count. The first version was assessing efficacy among all patients while on active treatment in one of the prior randomized trials, in the extension trial or both. Among the patients who achieved platelet count of at least 50,000/mcL within 12 weeks of beginning fostamatinib treatment in study C788-047, C788-048 or C788-049, a total of 18 patients maintained the platelet count of at least 50,000/mcL for 12 months or longer.

Secondary and Other Endpoints

C788-047 and C788-048:
In the randomized, placebo-controlled trials, the secondary efficacy endpoints were to be analyzed using the fixed sequence testing and only if the results of the previously tested endpoints were statistically significant. Secondary efficacy endpoints were as follows:

1. Platelet response (a platelet count of at least 50,000/mcL) at Weeks 12 and 24.
2. Among patients with a baseline platelet count < 15,000/mcL, achievement of a count ≥ 30,000/mcL, and at least 20,000/mcL above baseline, at Weeks 12 and 24.
3. Frequency and severity of bleeding according to the ITP Bleeding Score (IBLS) and WHO over the 24-week study period.

The table below summarizes the results of the secondary endpoints without applying LOCF

method.

Table 64 C788-047 and C788-048: Results of the Secondary Endpoints (without LOCF)

	C788-047		C788-048	
	Fostamatinib (n=51)	**Placebo (n=25)**	**Fostamatinib (n=50)**	**Placebo (n=24)**
Platelet count ≥ 50,000/mcL at Week 12				
Yes	19.6%	0	24.0%	12.5%
Difference of response (fostamatinib-placebo) and 95% CI*	19.6% (-4.1%, 42.1%)		11.5% (-13.0%, 35.0%)	
p-value**	0.025			
Platelet count ≥ 50,000/mcL at Week 24				
Yes	15.7%	0	14.0%	4.2%
Difference of response (fostamatinib-placebo) and 95% CI*	15.7% (-8.0%, 38.4%)		9.8% (-14.9%, 33.8%)	
p-value**	0.0471			
Platelet count ≥ 30,000/mcL and ≥ 20,000/mcL above baseline (for patients with baseline platelet count < 15,000/mcL) at:				
Week 12				
Yes	16.0%	0	22.7%	11.1%
Difference of response (fostamatinib-placebo) and 95% CI*	16.0% (-17.8%, 47.8%)		11.6% (-27.4%, 48.3%)	
Week 24				
Yes	16.0%	0	4.6%	0
Difference of response (fostamatinib-placebo) and 95% CI*	16.0% (-17.8%, 47.8%)		4.6% (-33.6%, 41.9%)	
IBLS score across nine anatomical sites across visits				
Difference in means (fostamatinib-placebo) and 95% CI*	-0.01 (-0.07, 0.04)		-0.01 (-0.05, 0.02)	
WHO bleeding scale across visits				
Difference in means (fostamatinib-placebo)	0.15 (-0.16, 0.45)		-0.12 (-0.32, 0.09)	

and 95% CI*		

*95% CI based on exact confidence intervals.
**P-value from the Fisher exact test. P-values for the 048 trial are not presented here since the primary endpoint was not met.

Reviewer's comment: Following the sequential testing procedure, the following secondary endpoints were statistically significant in Study 047 and were supportive of the primary efficacy results: platelet response at Week 12, platelet response at Week 24. The secondary endpoint of platelet response at Week 24 however needs to interpreted with caution; at Week 24, there were no patients with platelet counts in the placebo arm and only 11 patients with platelet counts in the fostamatinib arm.

Subpopulations

In the randomized, placebo-controlled trials (C788-047 and C788-048), subgroup analyses of stable platelet response as defined by the primary endpoint was in general consistent with the ITT population.

7.3.2. Integrated Assessment of Effectiveness

The efficacy of fostamatinib was evaluated in two identical phase 3, double-blind, placebo-controlled, randomized trials (C788-047 and C78-048) and an open-label, extension trial (C788-049). The primary endpoint in the phase 3 randomized trials was stable platelet response (defined as reaching a platelet count of at least 50,000/mcL on at least 4 of the last 6 scheduled visits between Weeks 14-24). In the C788-047 trial, the difference of response between the two arms was 17.6% [95% CI (-6.1%, 40.3%), exact confidence interval], [95% CI (7.2%, 28.1%), normal approximation], Fisher's exact test p-value 0.03. In the C788-048 trial, the difference of response between the two arms was 11.8% and not statistically significant [95% CI (-13.0%, 35.7%), exact confidence intervals], [95% CI (-1.1%, 24.8%), normal approximation], Fisher's exact test p-value: 0.26. In the C788-048 trial, the primarily reason for failing to meet the primary endpoint was based on one patient in the control arm who had highly variable platelet counts, ranging from 16,000 to 420,000/mcL with no rescue therapy.

The extension trial contained two versions of the primary endpoint. The results were supportive of the results of the randomized trials:
Among all patients who achieved a platelet count of at least 50,000/mcL within 12 weeks of beginning treatment with fostamatinib in studies 047/048 or 049, a total of 18 patients maintained the platelet response of at least 50,000/mcL for 12 months or longer (version 1) and;
Among the patients who were placebo non-responders in the prior randomized trials and received fostamatinib treatment in the extension trial, the proportion of patients who maintained the platelet response of at least 50,000/mcL for 12 weeks was 20.5% (95% CI: 8.5, 32.4) (version 2).

7.4. Review of Safety

Safety Review Approach

The NDA submission included safety information of fostamatinib from 4 different populations (i.e., healthy subjects, rheumatoid arthritis, oncology, and ITP). As the dosing regimen of fostamatinib was not consistent in these populations and different background medications were used in patients with rheumatoid arthritis, oncology and ITP (i.e., methotrexate or other DMARDs [disease-modifying anti-rheumatic drugs] in rheumatoid arthritis, various chemotherapies in oncology, corticosteroids/azathioprine/danazol in ITP) and as ITP is the proposed indication in this NDA, the review of safety was primarily based on the pooled data of the two registrational placebo-controlled randomized trials and the extension trial conducted in patients with ITP (i.e., C788-047, C788-048 and C788-049) and included the following:

- Electronic submissions of the clinical study reports and other relevant portions of the NDA were reviewed;
- Safety data were audited or reproduced;
- When applicable, safety data from the phase 2 trial in ITP (D4300-022) was also analyzed;
- Safety information was also reviewed from the non-ITP populations when appropriate.;
- Applicant's responses to FDA information requests;
- Relevant published literature; and
- The 120-day safety update.

For the pooled analysis of the C788-047 and C788-048 trials, the placebo-controlled period was used which was defined as time on treatment during the 047 and 048 trials only and events that occurred after the subject enrolled in the extension trial (049) were excluded.

For the safety analysis of the extension trial (C788-049), AEs included any AEs with onset in the placebo-controlled trial (C788-047 or C788-048) that were ongoing during the C788-049 trial and AEs with onset during the C788-049 trial.

All tables and figures in this review are those of the reviewer unless noted otherwise.

7.4.2. Review of the Safety Database

Overall Exposure

A total of 4,629 patients have been reported to have received fostamatinib throughout the clinical development program in 51 trials (see table below).

Table 65 Fostamatinib Safety Database

Patient Populations	Number of Studies	Number of Patients
Immune Thrombocytopenia	4	163
Healthy volunteers	26	724
Rheumatoid Arthritis	13	3437
Oncology	4	204
Clinical Pharmacology Studies	4	101
Total	**51**	**4629**

[Source: Summary of Clinical Safety]

In the ITP trials, a total of 163 patients received at least one dose of fostamatinib including the 146 patients that received fostamatinib treatment in the 047/048 and 049 trials as shown in the following table.

Table 66 Fostamatinib Safety Database in ITP Trials

Study ID	Number of Patients	Trial Description
C788-047	51	Phase 3, randomized, double-blind, placebo-controlled, parallel group trial
C788-048	51	Phase 3, randomized, double-blind, placebo-controlled, parallel group trial
C788-049	44*	Phase 3, open-label extension trial
D4300-022	17#	Phase 2, open-label, ascending dose, pilot trial to assess efficacy and safety of fostamatinib in adult refractory ITP.
Total	**163**	

*Patients who received placebo during the placebo-controlled period and received treatment with fostamatinib in the extension trial.
#. A total of 18 patients were enrolled in the D4300-022 trial. One patient was enrolled twice.
[Source: ADSL.xpt]

In the pooled analysis of the two registrational trials (047 and 048), the median duration of study treatment was 85 days (fostamatinib: 86 days, placebo: 85 days). Seventy-seven percent of patients received study treatment for at least 12 weeks (fostamatinib: 77%, placebo: 79%).

Table 67 Pooled analysis of C788-047 and C788-048: Exposure to Study Medication (Safety Population)

	Fostaminib (n=102)	Placebo (n=48)	Total (n=150)
Duration of treatment (days)			
Median	86	85	85
Range	8-183	16-173	8-183

< 4 weeks (28 days)*	4 (4%)	3 (6%)	7 (5%)
≥ 8 weeks (56 days)*	93 (91%)	45 (94%)	138 (92%)
≥ 12 weeks (84 days)*	78 (77%)	38 (79%)	116 (77%)
≥ 24 weeks (168 days)*	20 (20%)	2 (4%)	22 (15%)

*A subject can appear in more than one category.
[Source: ADSL.xpt]

The median duration of fostamatinib exposure in the extension trial (049) only based on the 123 patients was 128 days (range, 10 to 541). The 123 patients included the 79 patients that received fostamatinib and the 44 patients that received placebo during the placebo-controlled period (i.e., during the 047 and 048 trial) and continued on the open-label extension trial (049).

Table 68 Fostamatinib Exposure (Safety Population)

	047/048 only (n=102)	**049 only (n=123)**	**047/048 & 049 (n=146)**	**047/048 & 049 (n=123)**
Exposure to fostamatinib (days)				
Median	86	128	179	204
Range	8-183	10-541	8-712	37-712

[Source: ADSL.xpt]

Based on the total of 146 patients who received at least one dose of fostamatinib throughout the placebo-controlled period (047 or 048 trial) and the extension trial (049) (see table 66 above), the median duration of fostamatinib exposure was 179 days (range, 8 to 712).

Based on the total of 123 patients who received fostamatinib during the placebo-controlled period (of the 047 or 048 trial) and patients who received placebo during the placebo-controlled period and continued with fostamatinib treatment in the extension trial, the median duration of fostamatinib exposure was 204 days (range, 37 to 712). Among these 123 patients, a total of 67 patients (55%), 30 patients (24%) and 8 patients (7%) had received fostamatinib for at least 6, 12 and 18 months, respectively.

The median average daily dose of fostamatinib per patient administered from the placebo-controlled period (047/048) throughout the extension trial (049) was 248 mg reflecting the generally administered daily dose ranges of 200 mg to 300 mg. Majority of the patients (87%) randomized to the fostamatinib arm had the dose increased from 100 mg bid to 150 mg bid.

Table 69 Mean Fostamatinib Total Daily Dose

	047/048 only (n=102)	**049 only (n=123)**	**047/048 & 049 (n=146)**
Mean total daily fostamatinib dose (mg)			
Median	260	249	248

Range	40-390	88-388	40-390

[Source: ADEX.xpt]

The median duration of follow-up of the placebo-controlled period for the pooled 047 and 048 trials was 88 days (range, 17-192) for fostamatinib and 85 days (range, 19-172) for placebo.

Relevant characteristics of the safety population:

Overall, the median age was 53.5 years (range, 20 to 88) (fostamatinib: 53.5 years [range, 20 to 88], placebo: 54.0 years [range, 20 to 78]). There were more females (61%) (fostamatinib: 60%, placebo: 63%) than males. Most of the patients were White (93%) (fostamatinib: 93%, placebo: 92%) and only a total of 4 patients (3%) were Hispanic or Latino (fostamatinib: 3%, placebo: 2%). Thirty-five percent of patients had prior splenectomy (fostamatinib: 33%, placebo: 40%).

Reviewer comment: The demographics and baseline disease characteristics of the safety population were consistent with the ITT population for studies 047 and 048 (see tables 31 and 32).

Adequacy of the safety database:

The safety data supporting this NDA is primarily based on the clinical trials conducted in patients with ITP (C788-047, C788-048, C788-049 and D4300-022) which enrolled a total of 163 patients. The approval of Promacta (eltrombopag) was based on a safety database of a total of 313 patients with ITP (including 100 patients that received eltrombopag in the randomized trial) and Nplate (romiplostim) was based on a safety database of a total of 204 patients with ITP (including 83 patients that received romiplostim in the randomized trial). Considering the size of the safety database of past approvals for the ITP indication, the safety database of fostamatinib in ITP trials falls short. However, the safety analysis of fostamatinib for ITP was based on placebo-controlled randomized trials which is adequate for safety evaluation. Also, with regard to race, most of the patients in the safety database were White (93%) in the phase 3 trials. Non-Whites (including Hispanic/Latino) were under-represented (African Americans: 2%, Asians: 3%, Hispanic/Latino: 3% received fostamatinib).

The AE datasets contained events up to 30 days after the last dose of study treatment. Even though AEs after 30 days of the last dose were not included, considering that 55% and 24% of patients had received fostamatinib for at least 6 and 12 months, respectively, the data cut-off time for safety reporting is acceptable.

7.4.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The overall quality of data appears to be adequate for safety evaluation. The submission

contains appropriate analyses and reports. No major concerns regarding data integrity were identified during the safety review.

Categorization of Adverse Events

In studies 047, 048 and 049, MedDRA terminology version 18.1 was used to categorize adverse events. In study D4300-022, MedDRA terminology version 13.0 was used. In general, severity of adverse events was classified as mild, moderate, or severe. Life-threatening or fatal AEs were included in the severe category. To describe severity of diarrhea, AEs were graded according to the National Cancer Institute Common Technology Criteria for Adverse Events (NCI-CTCAE) version 4.0 coding system. Grade Mapping of the verbatim AE terms to MedDRA Preferred Term and System Organ Class (SOC) was acceptable.

Treatment-emergent AEs were defined as AEs that started or worsened in severity on or after the first dose of study medication. For dose modification, the most severe action was taken for analysis purpose with the following order of increasing in severity: dose interruption, dose reduction and study drug withdrawal.

Routine Clinical Tests

Routine clinical assessments in the 047, 048 and 049 trials included physical examination, Karnofsky performance status, vital signs, bleeding assessment, urinalysis, platelet count tests, pregnancy tests and laboratory tests. See tables 22 and 52 of this review.

7.4.4. Safety Results

Table 70 summarizes the safety results of the pooled analysis of studies 047 and 048; and table 71 for study 049. Overall, the incidences of adverse events that occurred in the open-label extension study (049) were largely consistent with the fostamatinib arm in the phase 3 randomized studies (047 and 048).

Table 70 Pooled Analysis of C788-047 and C788-048: Overall Summary of Safety (Placebo-Controlled Period)

	Fostaminib (n=102)	Placebo (n=48)
All Deaths	1 (<1%)	1 (2%)
Patients with TEAEs	85 (83.3%)	36 (75.0%)
Average number of AEs per patient in patients with ≥ 1 AE	5	4
Mild*	33 (32.4%)	20 (41.7%)
Moderate*	37 (36.3%)	9 (18.8%)
Severe*	15 (14.7%)	7 (14.6%)
Treatment-related TEAEs	60 (58.8%)	13 (27.1%)
TESAEs	13 (12.7%)	10 (20.8%)

Treatment related SAEs	4 (3.9%)	1 (2.1%)
Serious Bleeding	4 (3.9%)	5 (10.4%)
AEs leading to any study drug withdrawal	10 (9.8%)	4 (8.3%)

* Subject is only counted once based on the most severe AE.
[Source: ADAE.xpt]

Table 71 C788-049: Overall Summary of Safety

	Fostaminib (n=123)
All Deaths	1 (<1%)
TEAEs	89 (72.4%)
Mild*	29 (23.6%)
Moderate*	42 (34.1%)
Severe*	18 (14.6%)
Treatment-related TEAEs	60 (48.8%)
TESAEs	21 (17.1%)
Treatment related SAEs	4 (3.3%)
Serious Bleeding	10 (8.1%)
AEs leading to any study drug withdrawal	12 (9.8%)

* Subject is only counted once based on the most severe AE.
[Source: ADAE.xpt]

Deaths

A total of two patients (fostamatinib: 1 patient [1%], placebo: 1 patient [2%]) died in the 047 and 048 trials.

In the 047 trial, patient (b) (6) who received the placebo treatment died due to sepsis 19 days after the last dose.

In the 048 trial, patient (b) (6) who received treatment with fostamatinib died 71 days after the last dose due to multiple myeloma. Patient (b) (6) was a 66 year-old White female with an 11-year history of ITP. Her medical history included chronic obstructive pulmonary disease and hypertension. Prior treatment for ITP included methylprednisolone, mycophenolate mofetil, prednisone, cyclosporine, dexamethasone, azathioprine, and danazol. On (b) (6) the patient started fostamatinib treatment at 100 mg bid. On (b) (6) the patient experienced epistaxis and bruising and was admitted to the hospital for rescue therapy with IVIG and was also treated with tranexamic acid, etamsylate, and prednisone. Platelet count was 4 x 10^9/L (reference range [RR] 150-400). On (b) (6) (Day 18), the patient was suspected of having multiple myeloma due to a high level of protein unrelated to the IVIG infusion. Bone marrow showed an excessive plasmacyte count of 78%. On

(b) (6) the study drug was discontinued due to multiple myeloma and the patient was withdrawn from the study with the last dose received on (b) (6) The last platelet count obtained on (b) (6) was 5 x 10^9/L. On (b) (6)(71 days after the last dose), the patient died due to multiple myeloma; an autopsy was not performed. The occurrence of multiple myeloma was assessed as unlikely related to the study drug, citing intercurrent illness as an alternative explanation.

Table 72 Pooled Analysis of C788-047 and C788-048: Summary of Deaths by Cause During the Placebo-Controlled Period (Safety Population)

Preferred Term	Fostaminib (n=102)	Placebo (n=48)
Sepsis	0	1 (2%)
Plasma cell myeloma	1 (<1%)	0

[Source: ADAE.xpt]

In the extension study (049), a total of one patient (<1%) died prior to the clinical data cut-off. The patient (b) (6)) was a 55-year-old White female with a 6-year history of ITP. Her medical history included spondylolisthesis, herpes simplex recurrent infections, bleeding, psoriasis, monoclonal gammopathy, hypertension, and otitis. Prior treatment for ITP included splenectomy, rituximab, dapsone, prednisone, eltrombopag, immunoglobulin, romiplostim, cyclosporin, cyclophosfamide, and micofenolate therapy. On (b) (6), the patient initiated fostamatinib treatment in the previous blinded study (047). On (b) (6) the patient rolled over into the open-label study (049) and initiated open-label fostamatinib at 100 mg bid. Fostamatinib was increased to 150 mg bid on (b) (6). The last dose of fostamatinib was taken on (b) (6). On (b) (6)(Day 39 of study 049), the patient developed sepsis. On (b) (6)the patient was admitted to the emergency department for septic shock, probably due to gastroenteritis. On admission, the patient was aphasic and pupillary light reflex was normal. Platelet count was 8 x 10^9/L and the patient received platelet transfusions. A nasogastric tube was inserted and meropenem was started. A CT scan of the head was normal ruling out a brain hemorrhage. On (b) (6), blood cultures revealed streptococcus pneumonia, urine culture revealed candida, and cytomegalovirus-DNA was positive (low). She had purpura and ecchymosis on trunk and limbs. The patient was treated with oxygen at 6 liters/min, and BP was low at 100/58 mmHg. The patient's hemodynamic instability rapidly worsened and noradrenaline and dopamine were started along with furosemide and continuous veno-venous hemofiltration dialysis. The patient was treated with piperacillin/ tazobactam, ciprofloxacin, fluconazole, and vancomycin. The patient developed multi-organ failure and worsened neurologically. She was sedated and intubated, and a brain CT on (b) (6) scan showed some hyperdensities in subarachnoid spaces. Her hemorrhagic syndrome worsened with conjunctival hemorrhage, and signs of ischemia on hands and nose. Due to elevation of fibrin D-dimer, an angio CT scan of thorax and abdomen was performed, which revealed no pulmonary embolism, bilateral pleural effusion, homogenous enhancement of renal parenchyma, and no lymphadenopathies. On (b) (6) , the patient had a Glasgow coma score of 3 when sedation was discontinued, without

trunk reflexes. Treatment was started with ceftazidime. An electroencephalogram showed no electrical activity and an angio CT scan of the brain showed ischemia of middle cerebral artery with absence of intracranial blood flow. The patient died on (b) (6) (19 days after the last dose) from sepsis. The investigator assessed the sepsis as severe in intensity and unlikely related to the study drug, citing intercurrent illness as an alternative explanation. The last platelet count taken on (b) (6) was 10 x 10^9/L.

An additional death (patient (b) (6)) was reported in study D4300-022. Patient (b) (6) was an 80-year-old White male with a history of ITP. His medical history included obstructive sleep apnea, hypertension, congestive heart failure, tingling in toes, joint pain, vertigo, and right lung does not open completely. The patient started treatment with fostamatinib 100 mg bid on (b) (6). On (b) (6), the patient died from anoxic encephalopathy. The immediate cause of death included on the death certificate was cardiopulmonary arrest secondary to congestive heart failure and hypertension. The event of anoxic encephalopathy was assessed as not related to the study treatment. The last dose of the study treatment was unknown.

The table below summarizes the deaths that in occurred in ITP trials among patients who took fostamatinib.

Table 73 Reported Deaths Among Patients Who Took Fostamatinib in ITP Studies

Preferred Term	Patient ID	Age/Sex	Days on Study	Day of death relative to last dose
Study C788-048				
Plasma cell myeloma	(b) (6)	66/F	18	71
Study C788-049				
Sepsis	(b) (6)	55/F	124	19
Study D4300-002				
Anoxic encephalopathy	(b) (6)	80/M	424	unknown

[Source: ADAE.xpt]

Serious Adverse Events

<u>Pooled analysis of 047 and 048 during the placebo-controlled period:</u>
Serious TEAEs occurred more frequently in the placebo arm (fostamatinib: 13%, placebo: 21%). The TESAEs that occurred in the placebo arm were mostly due to thrombocytopenia (4%) and bleeding related events (10%) (i.e., epistaxis, gastrointestinal hemorrhage, menorrhagia and petechiae). TESAEs that occurred in more than one patient in the fostamatinib arm were epistaxis and thrombocytopenia (2 patients each, 2%). The other TESAEs that occurred in the fostamatinib arm were contusion, febrile neutropenia, hypertensive crisis, pneumonia, syncope, vaginal hemorrhage, bronchitis, retinal tear, plasma cell myeloma, diarrhea, ITP flare and transient ischemic attack. All TESAEs that occurred in the fostamatinib arm were reported

as recovered or resolved except the one patient that had plasma cell myeloma and had a fatal outcome.

Table 74 Pooled analysis of C788-047 and C788-048: TESAE Reported in > 1 Patient in Any Treatment Arm During the Placebo-Controlled Period by Preferred Term (Safety Population)

Preferred Term	Fostaminib (n=102)	Placebo (n=48)
All TESAEs	13 (12.7%)	10 (20.8%)
Epistaxis	2 (2.0%)	1 (2.1%)
Thrombocytopenia[1]	2 (2.0%)	2 (4.2%)
Menorrhagia	0	2 (4.2%)

1. Thrombocytopenia includes platelet count decreased
[Source: ADAE.xpt]

Serious TEAEs assessed as treatment-related were reported in 4 patients (4%) in the fostamatinib arm (febrile neutropenia, pneumonia, diarrhea, hypertensive crisis) and 1 patient (2%) in the placebo arm (menorrhagia). The narratives for events that occurred in patients in the fostamatinib arm are summarized below:

Patient (b) (6) was a 39-year-old white male with a 6-year history of ITP. He initiated fostamatinib at 100 mg bid on (b) (6). The dose was decreased to 50 mg once daily due to diarrhea ((b) (6)). On (b) (6)(Study Day 103), the patient developed a fever of 38.4°C with diarrhea, and was hospitalized. Neutrophil count was 0.58 x 10^9/L, and platelet count was 8.5 x 10^9/L. The patient was diagnosed with severe neutropenic fever due to infection of unknown origin, possibly viral. On (b) (6), the event resolved and the patient was discharged. Study drug was interrupted and resumed on (b) (6) The investigator assessed the febrile neutropenia as severe in intensity and possibly related to the study drug.

Patient (b) (6), a 40 year-old Hispanic female with a 15-year history of ITP, initiated fostamatinib at 100 mg bid on (b) (6) On (b) (6) (Study Day 23), the patient was hospitalized for pneumonia with fever, fatigue, mild shortness of breath on exertion, pleuritic chest pain and hypoxia. Leukocyte count was 13,000, and temperature 40.0°C (104°F) rectally. Bilateral interstitial pneumonia was diagnosed. On (b) (6) the event resolved, and the patient was discharged from the hospital. Fostamatinib was discontinued due to the AE. The investigator assessed the pneumonia as severe in intensity and probably related to the study drug.

Patient (b) (6), a 76-year-old Caucasian female with a 2-year history of ITP, initiated fostamatinib at 100 mg bid on (b) (6) On (b) (6) (Study Day 54), the patient experienced frequent diarrhea (5 to 9 times per day) that subsequently became bloody with a rash appearing on the torso. On (b) (6) the diarrhea became Grade 3 (severe), and the patient was hospitalized. Stool cultures were negative. Treatment included loperamide, without relief, and a partial intravenous IgG infusion that was discontinued due to

pyrexia. The patient was discharged from the hospital on (b) (6) and the event was considered recovered. Study drug was discontinued on the day of event onset. The investigator assessed the diarrhea as moderate in intensity and possibly related to the study drug.

Patient (b) (6), a 71 year-old Caucasian female with a 10-year history of ITP and a history of treated hypertension, initiated fostamatinib at 100 mg bid on (b) (6) On (b) (6) (Study Day 21), the patient was hospitalized with hypertensive crisis, including nausea and angina pectoris for approximately 24 hours and blood pressure of 180/90 to 200/100 mm Hg, which was successfully treated. On (b) (6) the patient was discharged with blood pressure within normal range. Study drug was interrupted during hospitalization and was resumed at the same dose after hospitalization on (b) (6) The patient completed study 048, however, did not continue on the extension study. The investigator assessed the hypertensive crisis as severe in intensity and probably related to the study drug.

C788-049:
A total of 21 patients (17%) experienced a TESAE during the extension trial. TESAEs that occurred in at least 2% of patients (by SOC) were blood and lymphatic system disorders (4%), gastrointestinal disorders (4%), infections and infestations (3%), respiratory, thoracic and mediastinal disorders (2%) and skin and subcutaneous tissue disorders (2%). TESAEs reported in more than 1 patient by Preferred Term were thrombocytopenia, epistaxis, petechiae and GI hemorrhage. All TESAEs were reported as resolved except the patient that had sepsis and died and one other patient who had thrombocytopenia which was ongoing at the time of the database cut-off.

Table 75 C788-049: TESAE Reported in >1 Patients by Preferred Term

Preferred Term	Fostaminib (n=123)
All TESAEs	21 (17.1%)
Thrombocytopenia	5 (4.1%)
Epistaxis	3 (2.4%)
Petechiae	2 (1.6%)
Gastrointestinal hemorrhage	2 (1.6%)

[Source: ADAE.xpt]

TESAEs reported in 4 patients (atrial fibrillation, diarrhea, infection and increased ALT/AST) were considered treatment-related. The narratives for these patients are summarized below:

Patient (b) (6) was a 71-year-old white female with a 19-year history of ITP. This patient was randomized to the placebo group in the initial study. On (b) (6) the patient rolled over into the extension study and initiated open-label fostamatinib 100 mg bid. On (b) (6) fostamatinib was increased to 150 mg bid. The last dose of fostamatinib 150 mg bid prior to the SAE was taken on (b) (6) On (b) (6) (Study Day 150), the

patient was hospitalized with palpitations associated with chest discomfort. The patient presented with palpitations after breakfast with no shortness of breath, chest pain, or dizziness, no prior similar episode, no thyroid dysfunction, and no infective symptoms. On observation, pulse was 120 beats per minute (bpm) and irregular, BP was 191/86, and oxygen saturation was 95% on room air. Examination was unremarkable other than bilateral pedal edema. ECG showed the patient was in atrial fibrillation with a rate of 120 bpm. The atrial fibrillation was a new onset and rapid. The patient was hemodynamically stable. Chest x-ray was normal. Routine pathology was completed. The patient was treated with oral loading doses of atenolol, digoxin, and magnesium sulfate infusion. The patient was not anticoagulated, after discussion with hematology. Indapamide was stopped. The patient converted to sinus rhythm the same day. The patient was discharged from the hospital on (b) (6) and the event was considered resolved. Fostamatinib was interrupted in response to the AE. The investigator assessed the atrial fibrillation as moderate in intensity and possibly related to the study drug.

Patient (b) (6) was an 88-year-old Caucasian female with a 14-year history of ITP. On (b) (6) in the initial randomized study, the patient initiated fostamatinib at 100 mg bid. On (b) (6) the patient rolled over into the extension study and initiated open-label fostamatinib at 100 mg bid; fostamatinib was increased to 150 mg bid on (b) (6) due to platelet count < 50,000/mcL. On (b) (6) the patient had the onset of diarrhea. On (b) (6) the patient complained of dizziness and lightheadedness, which was thought to be due to dehydration caused by diarrhea. The patient was hospitalized on the same day with a platelet count of 33 x 10^9/L (reference range [RR]: 140 – 400). The patient reported an increase in diarrhea in the preceding few weeks. Study drug was initially held in response to the adverse event of diarrhea. Since the diarrhea resulted in volume depletion, hypotension, weakness and enhanced frailty, the study drug was discontinued due to the event. The last day of treatment with study drug was on (b) (6) and the patient was withdrawn from the study on (b) (6) The investigator assessed the diarrhea as moderate in intensity and probably related to the study drug.

Patients (b) (6) was a 20-year-old white female with an 11-year history of ITP. On (b) (6) in the initial blinded study, the patient initiated fostamatinib at 100 mg bid. On (b) (6) the patient rolled over into the extension study and initiated open-label fostamatinib at 100 mg bid. On (b) (6) fostamatinib was increased to 150 mg bid. The last dose of fostamatinib prior to the SAE was taken on (b) (6) On (b) (6) (Study Day 68), the patient experienced fever and chills, and was hospitalized for infection (a more specific diagnosis was not made). Laboratory results done on (b) (6) included C-reactive protein (CRP) 49.0 mg/L (RR 0.0-5.0 mg/L) and platelets 17 x 10^9/L (RR 150-400). On (b) (6) the patient was treated with Avelox (moxifloxacin). CRP on (b) (6) was 49.0 mg/L and on (b) (6) was 59.7 mg/L. On (b) (6) (b) (6) the event was considered resolved and the patient was discharged from the hospital. On (b) (6) CRP level normalized to 1.0 mg/L. No action was taken with study drug in response to the event. The patient continued in the study. The last platelet count obtained at Month 4 (before discontinuing from the study) was 67 x 10^9/L. The investigator assessed the

infection as moderate in intensity and possibly related to the study drug.

Patient (b) (6) is a 50-year-old white female with a history of ITP, diagnosed in 2013. The patient was hospitalized due to an ALT and AST greater than 10 ULN (upper limit of normal). On (b) (6) (probable recent historical value prior to study entry), AST was 15.8 u/L and ALT was 10.0 u/L. On (b) (6) at the screening visit, ALT was 9 IU/L (RR 0 – 32), AST was 12 IU/L (RR 0 – 40 IU/L), and ALP was 51 IU/L (RR 42 - 107 IU/L). The study drug was started on (b) (6) and the dose was increased to 150 mg bid on (b) (6) due to low platelets. On (b) (6) the ALT was 194 IU/L (RR 0 – 32 IU/L), AST was 90 IU/L (RR 0 - 40 IU/L, and the ALP was normal. From (b) (6) to (b) (6) the study drug was interrupted due to mild hepatotoxicity. On (b) (6) the study drug was resumed at 100 mg bid. The study drug dose was increased to 150 mg bid on (b) (6) The patient rolled over from study 048 to extension study on (b) (6) The patient initiated open-label treatment with fostamatinib at 100 mg bid. The last dose of fostamatinib 100 mg bid prior to the SAE was taken on (b) (6) On (b) (6) the patient presented to the site for her scheduled Month 1 visit. The ALT was 990.5 u/L (RR 0 – 55) and an AST was 556.4 u/L (RR 0 - 34). The patient was hospitalized due to risk of liver damage. The patient was asymptomatic, and there were no other complaints except for blood in the urine and nausea, which spontaneously resolved two days prior to admission. Skin had petechiae and suffusion. On (b) (6) LDH was 646 u/L (RR 125 - 220), platelets were 6 giga/L (RR 142 – 440), total bilirubin was 11.86 µmol/L (RR 3.4 – 20.5), GGT was 62 u/L (RR – 7.2). An ultrasound of the abdomen showed normal findings, liver was not enlarged, and was homogenous, with normal echogenic parenchyma, without focal lesions, non-dilated bile ducts and portal vessels. Intravenous methylprednisolone was given for platelet rescue therapy. On (b) (6) fostamatinib was discontinued and the patient was withdrawn from the study. On (b) (6) (b) (6) GGT peaked at 78.0 u/L (RR was not provided). The patient was diagnosed with toxic drug induced hepatitis in the course of treatment for idiopathic thrombocytopenia. On (b) (6) the patient was discharged from the hospital on a tapering dose of steroids and with an AST of 44.6 u/L (RR was not provided) and ALT 256.1 u/L (RR was not provided). At follow-up on September 14, 2016, no clinically significant lab results were detected, and the event was considered recovered. The ALT was 52.1 u/L (RR was not provided), AST was 14.5 u/L (RR was not provided), ALP was 69.4 u/L (RR was not provided), total bilirubin was 13.09 µmol/L (RR was not provided), LDH was 230 u/L (RR was not provided, C-reactive protein was 0.4 mg/L (RR was not provided), GGT was 57.8 u/L (RR was not provided), and platelets were 23 giga/L (RR was not provided). The patient remained stable. The investigator assessed the ALT and AST > 10 ULN as severe in intensity and probably related to the study drug. The investigator cited no evidence suggestive of an intercurrent issue precipitating the liver abnormalities and no apparent viral disease, alcohol or drug ingestion.

Dropouts and/or Discontinuations Due to Adverse Effects

Pooled analysis of 047 and 048 during the placebo-controlled period:
In the pooled analysis of studies 047 and 048, a slightly higher proportion of patients in the fostamatinib treatment arm experienced an AE that lead to study drug withdrawal

(fostamatinib: 10 patients [10%], placebo: 4 patients [8%]). There were no AEs that lead to study treatment withdrawal in more than 1 patient in either arm.

Table 76 Pooled analysis of C788-047 and C788-048: AE Leading to Study Drug Withdrawal During the Placebo-Controlled Period by Preferred Term (Safety Population)

Preferred Term	Fostaminib (n=102)	Placebo (n=48)
Any AE leading to study drug withdrawal	10 (9.8%)	4 (8.3%)
Abdominal discomfort	0	1 (2.1%)
Abdominal pain	1 (1.0%)	0
ALT increased	1 (1.0%)	0
Chest pain	1 (1.0%)	0
Diarrhea	1 (1.0%)	1 (2.1%)
Epistaxis	0	1 (2.1%)
Headache	1 (1.0%)	0
Hypertension	0	1 (2.1%)
Neutropenia	1 (1.0%)	0
Pneumonia	1 (1.0%)	0
Plasma cell myeloma	1 (1.0%)	0
Syncope	1 (1.0%)	0
Thrombocytopenia	1 (1.0%)	0

[Source: ADAE.xpt]

C788-049:
In the extension trial, a total of 12 patients (10%) experienced an AE that lead to discontinuation of the study treatment including one patient that had sepsis and had a fatal outcome.

Table 77 C788-049: AE Leading to Study Drug Withdrawal

Preferred Term	Fostaminib (n=123)
All TEAEs	12 (9.8%)
Diarrhea	4 (3.3%)
Transaminases increased	2 (1.6%)
Abdominal pain upper	1 (0.8%)
Blood bilirubin increased	1 (0.8%)
Neutropenia	1 (0.8%)
Rash	1 (0.8%)
Sepsis	1 (0.8%)
Tachycardia	1 (0.8%)

[Source: ADAE.xpt]

<u>Dose Interruption or Dose Reduction due to Adverse Event:</u>
Pooled analysis of the 047 and 048 trials during the placebo-controlled period:

A total of 23 patients experienced an TEAE that lead to study treatment interruption (fostamatinib: 18 patients [18%], placebo: 5 patients [10%]). TEAEs leading to study treatment interruption that occurred in > 1% of patients in the fostamatinib arm were ALT increased (5%), diarrhea (3%), hypertension (2%) and influenza like illness (2%).

Fostamatinib dose reductions due to TEAEs were generally infrequent and occurred a total of 18 times during the placebo-controlled period in the 047 and 048 trials (from 150 mg to 100 mg bid [12], from 100 mg bid to 150 mg once daily [3], from 150 mg once daily to 100 mg once daily [1] and other [2]). A total of 9 patients (9%) in the fostamatinib arm versus 1 patient (2%) in the placebo arm had an TEAE that lead to dose reduction as the worst action. Adverse events leading to dose reduction that occurred in the fostamatinib arm in more than 1 patient were diarrhea, transaminase increased and hypertension (2 patients each).

Table 78 Pooled Analysis of C788-047 and C788-048: Dose Modification of Study Treatment Due to TEAEs During the Placebo-controlled Period (Safety Population)

	Fostaminib (n=102)	Placebo (n=48)
AEs leading to dose interruption	18 (17.6%)	5 (10.4%)
AEs leading to dose reduction	9 (8.8%)	1 (2.1%)

[Source: ADAE.xpt]

Significant Adverse Events

In the pooled analysis of the 047 and 048 trials, treatment-emergent severe AEs (defined as life-threatening or fatal) occurred in a total of 22 patients (14.7%) during the placebo-controlled period and the incidence was similar between the two arms (fostamatinib: 15 patients [14.7%], placebo: 7 patients [14.6%]). Severe AEs that occurred in more than one patient in the fostamatinib arm were thrombocytopenia/platelet count decreased, blood pressure increased/hypertensive crisis and dyspnea (2 patients each, 2%). The other severe AEs that occurred in the fostamatinib arm were arthralgia, chest pain, contusion, diarrhea, dizziness, febrile neutropenia, hypoxia, neutropenia, nephrolithiasis, pain in extremity, pneumonia, syncope and toothache. The severe AEs that occurred in the placebo arm were predominantly related to bleeding (6%) (gastrointestinal hemorrhage, menorrhagia and petechiae) and thrombocytopenia (4%); other severe AEs in the placebo arm were single cases of hypertension, muscle rupture, anemia, and sepsis.

Severe AEs that were assessed as treatment related occurred in 8 patients (7.8%) in the fostamatinib arm (arthralgia, blood pressure increased, chest pain, diarrhea, dizziness, dyspnea, febrile neutropenia, hypertensive crisis, hypoxia, neutropenia, and pneumonia) and 1 patient (2.1%) in the placebo arm (hypertension).

In the 049 trial, severe AEs occurred in a total of 18 patients (15%). Severe AEs that were

reported for more than 1 patient were thrombocytopenia/platelet count decreased (7 patients, 5.7%), gastrointestinal hemorrhage and hepatic enzyme increased/transaminases increased (both 2 patients, 1.6%). Other severe AEs were gastric antral vascular ectasia, rectal hemorrhage, haematochezia, diarrhea, bile duct stone, muscle rupture, nephrolithiasis, petechiae, purpura, aortic stenosis, and sepsis.

Treatment Emergent Adverse Events and Adverse Reactions

Pooled Analysis of Studies 047 and 048 During the Placebo-Controlled Period:
Overall, a higher proportion of patients in the fostamatinib arm (83%) compared to the placebo arm (75%) had a TEAE. Most of the patients experienced mild (fostamatinib: 32%, placebo: 42%) or moderate (fostamatinib: 36%, placebo: 19%) TEAEs as the greatest severity. For severe TEAEs, see the above review under the "Significant AEs" subsection.

The most frequent TEAEs (>10%) that occurred in the fostamatinib arm and at least 5% greater incidence compared to the placebo arm by SOC were gastrointestinal disorders (48% vs. 31%), infections and infestations (28% vs. 23%), investigations (28% vs. 10%), vascular disorders (25% vs. 19%), skin and subcutaneous disorders (18% vs. 10%), general disorders and administration site conditions (17% vs. 10%) and blood and lymphatic system disorders (14% vs. 8%).

Table 79 Pooled analysis of C788-047 and C788-048: TEAE Reported in ≥ 5% of Patients in Any Treatment Arm During the Placebo-Controlled Period by System Organ Class (Safety Population)

System Organ Class	Fostaminib (n=102)	Placebo (n=48)
Gastrointestinal disorders	49 (48.0%)	15 (31.3%)
Infections and infestations	29 (28.4%)	11 (22.9%)
Investigations	28 (27.5%)	5 (10.4%)
Nervous system disorders	26 (25.5%)	13 (27.1%)
Vascular disorders	25 (24.5%)	9 (18.8%)
Respiratory, thoracic and mediastinal disorders	23 (22.5%)	10 (20.8%)
Skin and subcutaneous tissue disorders	18 (17.6%)	5 (10.4%)
General disorders and administration site conditions	17 (16.7%)	5 (10.4%)
Blood and lymphatic system disorders	14 (13.7%)	4 (8.3%)
Musculoskeletal and connective tissue disorders	10 (9.8%)	4 (8.3%)
Metabolism and nutrition disorders	7 (6.9%)	2 (4.2%)
Injury, poisoning and procedural complications	6 (5.9%)	2 (4.2%)

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

TEAEs that occurred in at least 10% of patients and greater than two-fold incidence in the fostamatinib arm compared with the placebo arm by Preferred Term were diarrhea,

hypertension, nausea, AST/ALT increased, rash, neutropenia, chest pain, fatigue and contusion.

Table 80 Pooled analysis of C788-047 and C788-048: TEAE Reported in ≥ 5% of Patients in Any Treatment Arm During the Placebo-Controlled Period by Preferred Term (Safety Population)

Preferred Term	Fostaminib (n=102)	Placebo (n=48)
All TEAEs	85 (83.3%)	36 (75.0%)
Diarrhea	32 (31.4%)	7 (14.6%)
Hypertension[1]	28 (27.5%)	6 (12.5%)
Nausea	19 (18.6%)	4 (8.3%)
Epistaxis	16 (15.7%)	5 (10.4%)
Respiratory infection[2]	11 (10.8%)	3 (6.3%)
Dizziness	11 (10.8%)	4 (8.3%)
Headache	11 (10.8%)	9 (18.8%)
ALT increased	10 (9.8%)	0
AST increased	9 (8.8%)	0
Rash[3]	9 (8.8%)	1 (2.1%)
Abdominal pain[6]	7 (6.9%)	2 (4.2%)
Neutropenia[4]	6 (5.9%)	0
Chest pain	6 (5.9%)	1 (2.1%)
Fatigue[5]	6 (5.9%)	1 (2.1%)
Contusion	6 (5.9%)	0
Petechiae	4 (3.9%)	3 (6.3%)
Dyspnea	4 (3.9%)	3 (6.3%)
Vomiting	3 (2.9%)	3 (6.3%)

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
1. Hypertension includes blood pressure increased, blood pressure diastolic increased and blood pressure systolic increased.
2. Respiratory infection includes upper respiratory infection, lower respiratory infection and viral upper respiratory infection.
3. Rash includes rash erythematous and rash macular.
4. Neutropenia includes neutrophil count decreased.
5. Fatigue includes asthenia.
6. Abdominal pain includes abdominal pain upper.
[Source: ADAE.xpt]

C788-049:

In the extension trial, 72% of patients had an TEAE. The most frequent TEAEs by SOC (>20%) were in the gastrointestinal disorders (39%); respiratory, thoracic, and mediastinal disorders (25%); skin and subcutaneous disorders (24%); and infections and infestations (22%).

Most of the patients experienced TEAEs that were mild (24%) or moderate (34%) as the

greatest severity. Severe AEs were reported in a total of 18 patients (15%).

The most frequently reported TEAEs (>10%) were diarrhea, hypertension, petechiae and epistaxis.

Table 81 C788-049: TEAE Reported in ≥ 5% of Patients by Preferred Term

Preferred Term	Fostaminib (n=123)
All TEAEs	89 (72.4%)
Diarrhea	30 (24.4%)
Hypertension[1]	21 (17.1%)
Petechiae	17 (13.8%)
Epistaxis	16 (13.0%)
Respiratory infection[2]	11 (8.9%)
Fatigue[3]	11 (8.9%)
Abdominal pain[4]	10 (8.1%)
Nausea	10 (8.1%)
Dizziness	9 (7.3%)
Headache	9 (7.3%)
Thrombocytopenia[5]	8 (6.5%)
Rash[6]	7 (5.7%)
Cough	7 (5.7%)
Vomiting	7 (5.7%)

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
1. Hypertension includes blood pressure increased, blood pressure diastolic increased and blood pressure systolic increased.
2. Respiratory infection includes upper respiratory infection and lower respiratory infection.
3. Fatigue includes asthenia.
4. Abdominal pain includes abdominal pain upper and abdominal pain lower.
5. Thrombocytopenia includes platelet count decreased.
6. Rash includes rash erythematous and rash macular.
[Source: ADAE.xpt]

Pooled analysis of 047 and 048 during the placebo-controlled period:
Treatment-related AEs considered as possibly or probably related to the study treatment occurred in 59% of patients in the fostamatinib arm compared with 27% in the placebo arm. The most frequently reported treatment-related AEs in the fostamatinib arm (>5%) were diarrhea, hypertension, nausea, ALT/AST increased, and dizziness.

Table 82 Pooled analysis of C788-047 and C788-048: Treatment-Related AEs Reported in ≥ 5% of Patients in Any Treatment Arm During the Placebo-Controlled Period by Preferred Term (Safety Population)

Preferred Term	Fostaminib (n=102)	Placebo (n=48)
All	60 (58.8%)	13 (27.1%)
Diarrhea	28 (27.5%)	6 (12.5%)
Hypertension[1]	22 (21.6%)	2 (4.2%)
Nausea	15 (14.7%)	3 (6.3%)
ALT increased	10 (9.8%)	0
Dizziness	9 (8.8%)	2 (4.2%)
AST increased	7 (6.7%)	0

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
1. Hypertension includes blood pressure increased and blood pressure systolic increased.
[Source: ADAE.xpt]

In the C788-049 trial, a total of 60 patients (49%) had an AE that was assessed as treatment-related. The most frequently reported treatment-related AEs (≥5%) were diarrhea (22%) and hypertension (11%).

Laboratory Findings

Pooled Analysis of Studies 047 and 048 During the Placebo-Controlled Period:
Post-baseline laboratory abnormalities that occurred during the placebo-controlled period are summarized in the table below. Generally, the incidences of laboratory abnormalities were higher in the fostamatinib arm, except for “hemoglobin low” and “estimated GFR low.”

For the laboratory results related to liver function test, refer to section 7.4.5.

Table 83 Pooled analysis of C788-047 and C788-048: Post-Baseline Laboratory Abnormalities During the Placebo-Controlled Period (Safety Population)

	Fostaminib (n=102)	Placebo (n=48)
Hematology tests		
Leukocyte low	17 (16.7%)	4 (8.3%)
Lymphocyte count low	14 (13.7%)	6 (12.5%)
Hemoglobin low	14 (13.7%)	14 (29.2%)
Neutrophil count low	9 (8.8%)	1 (2.1%)
Chemistry tests		
Albumin low	7 (6.9%)	2 (4.2%)
Creatinine elevated	9 (8.8%)	3 (6.3%)
Estimated GFR low	8 (7.8%)	5 (10.4%)

Potassium high	1 (<1%)	0
Potassium low	14 (13.7%)	3 (6.3%)
Sodium high	24 (23.5%)	8 (16.7%)
Sodium low	2 (2.0%)	0
Coagulation tests		
aPTT high	3 (2.9%)	0
PT high	1 (<1%)	0

[Source: ADLB.xpt]

C788-049:
During the open-label extension trial, the incidences of laboratory abnormalities were generally consistent with those in the fostamatinib arm during the placebo-controlled period.

Table 84 C788-049: Post-Baseline Laboratory Abnormalities

	Fostaminib (n=123)
Hematology tests	
Leukocyte low	18 (14.6%)
Lymphocyte count low	20 (16.3%)
Hemoglobin low	20 (16.3%)
Neutrophil count low	32 (26.0%)
Chemistry tests	
Albumin low	2 (1.6%)
Creatinine elevated	5 (4.1%)
Estimated GFR low	0
Potassium high	1 (<1%)
Potassium low	5 (4.1%)
Sodium high	8 (6.5%)
Sodium low	1 (<1%)
Coagulation tests	
aPTT high	0
PT high	0

[Source: ADLB.xpt]

Vital Signs

Refer to Section 7.4.5.

Electrocardiograms (ECGs)

In the 047, 048 and 049 trials, ECGs were performed only at screening. The ECG analyses were

not conducted during these trials.

A total of 4 patients had cardiac AEs on treatment with fostamatinib (one patient experienced atrial fibrillation and angina pectoris; and 3 patients experienced tachycardia). The atrial fibrillation was serious and all other AEs were reported as mild or moderate in severity.

QT

The applicant performed a thorough QT (TQT) study which was a double-blind, double-dummy, randomized, positive- and placebo-controlled, parallel study to evaluate the effect of fostamatinib on ventricular repolarization in healthy subjects, following administration of fostamatinib 100 mg bid and 300 mg bid. Overall summary of findings of the QT interdisciplinary review team (IRT) are as follows: "No significant QTc prolongation effect of R935788 (R788) was detected in this TQT study. The largest upper bounds of the 2-sided 90% CI for the mean difference between R788 (100 mg BID and 300 mg BID) and placebo were below 10 ms, the threshold for regulatory concern as described in ICH E14 guidelines. The largest lower bound of the two-sided 90% CI for the ΔΔQTcF for moxifloxacin was greater than 5 ms, and the moxifloxacin profile over time is adequately demonstrated, indicating that assay sensitivity was established."

Refer to the QT-IRT review dated November 29, 2017.

Immunogenicity

The application did not contain evaluation regarding immunogenicity.

7.4.5. Analysis of Submission-Specific Safety Issues

Based on non-clinical studies, literature (Robinson et al., 2010 and Arora et al., 2005) and prior clinical experience with fostamatinib, adverse events of specific interest were the following: bleeding, GI toxicities (nausea, vomiting, diarrhea and abdominal pain), infection, hypertension, neutropenia, transaminase elevation and bilirubin elevation.

<u>Pooled analysis of 047 and 048 during the placebo-controlled period:</u>
Adverse events of specific interest that occurred ≥ 10% more often in the fostamatinib arm were GI toxicities (fostamatinib: 41%, placebo: 21%), hypertension (fostamatinib: 28%, placebo: 13%) and transaminase elevation (fostamatinib: 14%, placebo: 0).

Table 85 Pooled analysis of C788-047 and C788-048: Summary of TEAEs of Specific Interest that Occurred During the Placebo-Controlled Period (Safety Population)

	Fostaminib (n=102)		Placebo (n=48)	
	All	Severe	All	Severe
Bleeding	28 (27.5%)	1 (1.0%)	17 (35.4%)	3 (6.3%)
GI toxicities*	42 (41.2%)	1 (1.0%)	10 (20.8%)	0

Nausea	19 (18.6%)	0	4 (8.3%)	0
Diarrhea*	32 (31.4%)	1 (1.0%)	7 (14.6%)	0
Abdominal pain*	7 (6.9%)	0	2 (4.2%)	0
Vomiting*	4 (3.9%)	0	3 (6.3%)	0
Infection*	31 (30.4%)	1 (1.0%)	10 (20.8%)	1 (2.1%)
Hypertension*	28 (27.5%)	2 (2.0%)	6 (12.5%)	1 (2.1%)
Neutropenia*	7 (6.9%)	2 (2.0%)	0	0
Transaminase elevation*	14 (13.7%)	0	0	0
Bilirubin elevation	2 (2.0%)	0	0	0

*Includes multiple adverse event preferred terms.
Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt] 30 (29.4%)

Table 86 Pooled analysis of C788-047 and C788-048: Treatment-Related TEAEs of Specific Interest that Occurred During the Placebo-Controlled Period (Safety Population)

	Fostaminib (n=102)	Placebo (n=48)
Bleeding	4 (3.9%)	3 (6.3%)
GI toxicities*	35 (34.3%)	8 (16.7%)
Nausea	15 (14.7%)	3 (6.3%)
Diarrhea*	28 (27.5%)	6 (12.5%)
Abdominal pain*	5 (4.9%)	2 (4.2%)
Vomiting*	2 (2.0%)	1 (2.1%)
Infection*	4 (3.9%)	0
Hypertension*	22 (21.6%)	2 (4.2%)
Neutropenia*	6 (5.9%)	0
Transaminase elevation*	11 (10.8%)	0
Bilirubin elevation	2 (2.0%)	0

*Includes multiple adverse event preferred terms.
Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

C788-049:

In general, the incidences of AE of specific interest that were reported in the extension trial were largely consistent with those in the fostamatinib arm during the placebo-controlled period except for the following: the incidences of GI toxicities (including nausea and diarrhea), infection, hypertension and transaminase elevation were greater during the placebo-controlled period while during the extension trial, greater proportion of patients had severe bleeding (5% vs. 1%) and severe transaminase elevation (2% vs. 0).

Table 87 C788-049: Summary of TEAEs of Specific Interest (Safety Population)

	Fostaminib (n=123)	
	All	**Severe**
Bleeding	39 (31.7%)	6 (4.9%)
GI toxicities*	40 (32.5%)	1 (<1%)
Nausea	10 (8.1%)	0
Diarrhea*	30 (24.4%)	1 (<1%)
Abdominal pain*	11 (8.9%)	0
Vomiting*	7 (5.7%)	0
Infection*	28 (22.8%)	1 (<1%)
Hypertension*	21 (17.1%)	0
Neutropenia*	5 (4.1%)	0
Transaminase elevation*	8 (6.5%)	2 (1.6%)
Bilirubin elevation	3 (2.4%)	0

*Includes multiple adverse event preferred terms.
Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
[Source: ADAE.xpt]

Bleeding:
Pooled analysis of 047 and 048 during the placebo-controlled period:
Overall, bleeding occurred more frequently in the placebo arm (fostamatinib: 28 patients [28%], placebo: 17 patients [35%]) as expected. Bleeding events that occurred at a greater incidence in the fostamatinib arm included epistaxis (16% vs. 10%), contusion (6% vs. 0), gingival bleeding (3% vs. 2%) and blood blister (2% vs. 0).

Moderate to severe bleeding also occurred more frequently in the placebo arm (fostamatinib: 10 patients [9.8%], placebo: 8 patients [16.7%]). The only moderate or severe bleeding AE that occurred with higher incidence in the fostamatinib arm were vaginal bleeding (1% vs. 0), contusion (2% vs. 0) and hemorrhage (1% vs. 0). Severe bleeding occurred in a total of 4 patients [fostamatinib: 1 patient (contusion), placebo: 3 patients (GI hemorrhage, menorrhagia and petechiae, in 1 patient each) and all severe events lead to hospitalization.

Table 88 Pooled analysis of C788-047 and C788-048: Bleeding Reported in >1 Patient in Fostamatinib Arm During the Placebo-Controlled Period by Preferred Term (Safety Population)

Preferred Term	Fostaminib (n=102)	Placebo (n=48)
Any bleeding	28 (27.5%)	17 (35.4%)
Mild*	18 (17.6%)	9 (18.8%)
Moderate*	9 (8.8%)	5 (10.4%)
Severe*	1 (1.0%)	3 (6.3%)

Epistaxis	16 (15.7%)	5 (10.4%)
Contusion	6 (5.9%)	0
Petechiae	4 (3.9%)	3 (6.3%)
Gingival bleeding	3 (2.9%)	1 (2.1%)
Hemorrhage	2 (2.0%)	2 (4.2%)
Blood blister	2 (2.0%)	0

* Patient is only counted once based on the most severe AE.
A patient can appear in more than 1 category as analyzed by Preferred Term.
[Source: ADAE.xpt]

A higher proportion of patients in the placebo arm also experienced serious bleeding (fostamatinib: 4%, placebo: 10%). The only serious bleeding AEs that occurred in more than 1 patient in either arm were epistaxis in the fostamatinib arm and menorrhagia in the placebo arm (2 patients each).

Table 89 Pooled analysis of C788-047 and C788-048: Serious Bleeding Reported in Patients in Any Treatment Arm During the Placebo-Controlled Period by Preferred Term (Safety Population)

Preferred Term	Fostaminib (n=102)	Placebo (n=48)
Any serious bleeding	4 (3.9%)	5 (10.4%)
Epistaxis	2 (2.0%)	1 (2.1%)
Menorrhagia	0	2 (4.2%)
Vaginal hemorrhage	1 (1.0%)	0
Contusion	1 (1.0%)	0
Petechiae	0	1 (2.1%)
Gastrointestinal hemorrhage	0	1 (2.1%)

[Source: ADAE.xpt]

C788-049:
A total of 39 patients (32%) reported bleeding in the 049 trial. Severe bleeding occurred in 5% of patients. Bleeding AEs that occurred in > 10% of patients were petechiae and epistaxis. Severe bleeding AEs were gastrointestinal hemorrhage, rectal hemorrhage, haematochezia, petechiae, and purpura and these were also considered serious bleeding.

Table 90 C788-049: Bleeding Reported in >1 Patient

Preferred Term	Fostaminib (n=123)
Any bleeding	39 (31.7%)
Mild*	19 (15.4%)
Moderate*	14 (11.4%)
Severe*	6 (4.9%)
Petechiae	17 (13.8%)
Epistaxis	16 (13.0%)

Contusion	4 (3.2%)
Gastrointestinal hemorrhage	3 (2.4%)
Gingival bleeding	3 (2.4%)
Rectal hemorrhage	2 (1.6%)
Haematochezia	2 (1.6%)
Hematoma	2 (1.6%)
Hemorrhoidal hemorrhage	2 (1.6%)
Increased tendency to bruise	2 (1.6%)
Mouth hemorrhage	2 (1.6%)

*Patient is only counted once based on the most severe AE.
[Source: ADAE.xpt]

Serious bleeding was reported in 8% of patients in the extension trial. Serious bleeding experienced by more than one patient were epistaxis, GI hemorrhage and petechiae.

Table 91 C788-049: Serious Bleeding

Preferred Term	Fostaminib (n=123)
Any serious bleeding	10 (8.1%)
Epistaxis	3 (2.4%)
Gastrointestinal hemorrhage	2 (1.6%)
Petechiae	2 (1.6%)
Haematochezia	1 (0.8%)
Rectal hemorrhage	1 (0.8%)
Purpura	1 (0.8%)

[Source: ADAE.xpt]

Gastrointestinal Toxicities:

Pooled analysis of 047 and 048 during the placebo-controlled period:
In the pooled analysis of 047 and 048 trials, a total of 42 patients (41%) in the fostamatinib arm vs. 10 patients (21%) in the placebo arm reported GI toxicities. All of the GI toxicities were mild or moderate in severity except one patient in fostamatinib arm who had severe diarrhea. Diarrhea (fostamatinib: 31%, placebo: 15%) and nausea (fostamatinib: 19%, placebo: 8%) were the most commonly reported GI toxicities. Most of the incidences of diarrhea were Grade 1 or Grade 2 (fostamatinib: 29%, placebo: 15%). A total of 2 patients (2%) in the fostamatinib arm had Grade 3 diarrhea. One patient in the fostamatinib arm reported serious diarrhea that resulted in hospitalization. No patients in the placebo arm had serious diarrhea. One patient in each arm had diarrhea that resulted in study treatment discontinuation. A total of 2 patients (2%) in the fostamatinib arm had the dose reduced of the study treatment vs. none of the patients in the placebo arm due to diarrhea. A total of 3 patients (3%) in the fostamatinib arm and no patients in the placebo arm had the study drug interrupted due to diarrhea.

Table 92 Pooled analysis of C788-047 and C788-048: The Incidences of Diarrhea and Treatment Modification that Occurred During the Placebo-Controlled Period (Safety Population)

	Fostaminib (n=102)	Placebo (n=48)
All diarrhea AEs	32 (31.4%)	7 (14.6%)
Grade 1 or 2	30 (29.4%)	7 (14.6%)
Grade 3	2 (2.0%)	0
Serious diarrhea	1 (1.0%)	
Treatment discontinuation	1 (1.0%)	1 (2.1%)
Dose reduction	2 (2.0%)	0
Dose interruption	3 (2.9%)	0

[Source: ADAE.xpt]

All AEs of nausea were mild (fostaminib: 16%, placebo: 8%) or moderate (fostamatinib: 3%, placebo: 0) in severity. No patients discontinued study treatment due to nausea.

Other GI toxicities included abdominal pain (fostaminib: 7%, placebo: 4%) and vomiting (fostamatinib: 4%, placebo: 6%). One patient in each arm discontinued study treatment due to abdominal pain. No patients withdrew study drug due to vomiting.

C788-049:
During the extension trial, GI toxicities were reported for 40 patients (33%). Most of the reported AEs were due to diarrhea (24%). Serious diarrhea was reported for one patient who resulted in discontinuation of fostamatinib. Three additional patients (including one patient with severe event) discontinued treatment with fostamatinib due to diarrhea. In addition, abdominal pain, nausea and vomiting were reported in 9%, 8% and 6% of patients, respectively, and all events were mild or moderate in severity.

Hypertension:

Hypertension events were reported using the JNC 7, 2003 hypertension guidelines (the Seventh Report of the joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure) and not the new 2017 American College of Cardiology/American Heart Association (ACC/AHA) high blood pressure clinical practice guidelines. Using the 2017 definition, the incidences of hypertension would be greater than as reported due to more conservative blood pressure cutoff levels in the 2017 guidelines. To be eligible for the 047 or 048 trial, patients with uncontrolled or poorly controlled hypertension defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg (whether the patient was receiving anti-hypertensive treatment) were excluded.

Pooled analysis of 047 and 048 during the placebo-controlled period:
Hypertension was reported for 28% of patients in the fostamatinib arm vs. 13% in the placebo arm. A higher proportion of patients in the fostamatinib arm experienced hypertension AEs that were mild (fostamatinib: 17%, placebo: 10%) or moderate (fostamatinib: 9%, placebo: 0) in severity. Two patients (2%) in the fostamatinib arm and one patient (2%) in the placebo arm had severe hypertension. Among the two patients in the fostamatinib arm, one patient ((b) (6) had a severe and serious event of hypertensive crisis that resulted in hospitalization (the narrative for this patient has been presented under the Serious Adverse Events section above). The narrative for the other patient ((b) (6)) was not provided, however, according to the dataset, this patient had severe worsening elevated blood pressure that resolved without fostamatinib treatment modification. Both patients in the fostamatinib arm completed the study (047 or 048). One patient (2%) in the placebo arm and no patient in the fostamatinib arm discontinued treatment with the study drug due to hypertension. Overall, a total of 2 patients (2%) in fostamatinib arm and none of the patients in the placebo arm had the dose of the study treatment reduced due to hypertension and 2 patients (2%) and no patient in the fostamatinib and placebo arms, respectively, had treatment interrupted.

Table 93 Pooled analysis of C788-047 and C788-048: The Incidences of Hypertension and Treatment Modification that Occurred During the Placebo-Controlled Period (Safety Population)

	Fostaminib (n=102)	Placebo (n=48)
All hypertension AEs	28 (27.5%)	6 (12.5%)
Mild or moderate	26 (25.5%)	5 (10.4%)
Severe	2 (2.0%)	1 (2.1%)
Serious hypertension	1 (<1%)	0
Treatment discontinuation	0	1 (2.1%)
Dose reduction	2 (2.0%)	0
Dose interruption	2 (2.0%)	0

[Source: ADAE.xpt]

Among patients who developed hypertension, the median number of days to onset was 30 days (range: 2 to 171 days) in the fostamatinib arm and 43 days (range: 14 to 70 days) in the placebo arm. The median duration of the events was 15 days (range: 1 to 78 days) in the fostamatinib arm and 15 days (range: 6 to 16 days) in the placebo arm.

At baseline, blood pressure values were largely similar between the treatment arms. Twenty-eight percent and 35% of patients in the fostamatinib and placebo arms, respectively, had SBP<120 and DBP<80; and 2% and 0% of patients in the fostamatinib and placebo arms, respectively, had SBP≥140 and/or DBP≥90. During the placebo-controlled period, the proportion of patients with SBP≥140 and/or DBP≥90 had increased to 34% and 15% in the fostamatinib and placebo arms, respectively.

Table 94 Pooled analysis of C788-047 and C788-048: Blood Pressure During the Placebo-Controlled Period (Safety Population)

Blood pressure (mmHg)	Fostaminib (n=102)	Placebo (n=48)
At baselline		
SBP<120 and DBP<80	29 (28.4%)	17 (35.4%)
SBP≥120 and <140 and/or DBP≥80 and <90	71 (69.6%)	31 (64.6%)
SBP≥140 and <160 and/or DBP≥90 and <100	2 (2.0%)	0
Post-baseline		
SBP<120 and DBP<80	0	5 (10.4%)
SBP≥120 and/or DBP≥80	102 (100%)	43 (89.6%)
SBP≥140 and/or DBP≥90	35 (34.3%)	7 (14.6%)
SBP≥160 and/or DBP≥100	9 (8.8%)	0
SBP≥180 and/or DBP≥110	1 (1.0%)	0

[Source: ADVS.xpt and ISS-ITP]

The table below summarizes changes in blood pressure by shift analysis during the placebo-controlled period. A higher proportion of patients in the placebo-arm retained the baseline blood pressure (fostamatinib: 45 patients [44%), placebo: 28 patients [58%]). Increase in blood pressure was observed more frequently among patients in the fostamatinib arm by one-category (fostamatinib: 45 patients [44%], placebo: 18 patients [38%]), two-category (fostamatinib: 9 patients [9%], placebo: 1 patient [2%]), and three-category increases (fostamatinib: 3 patients [3%], placebo: 0 patient). Higher proportion of patients in the fostamatinib arm had increases in blood pressure to between 140/90 and 160/100 mm Hg (elevation in either systolic or diastolic pressure) compared to baseline (fostamatinib: 25 patients [25%], placebo: 7 patients [15%]); and to between 160/100 and 180/110 mm Hg (fostamatinib: 8 patients [8%], placebo: 0 patient). One (1%) and no patient in the fostamatinib and placebo arms, respectively, had a blood pressure increase to ≥180/110 mm Hg (the patient in the fostamatinib arm had a baseline blood pressure value between 120/80 and <140/90 mm Hg).

Table 95 Pooled analysis of C788-047 and C788-048: Shift Table for Blood Pressure for Baseline vs Highest Value During the Placebo-Controlled Period for Patients in Both Arms (Safety Population)

Maximum post dose value (mmHg)	Baseline value (mmHg)			
	SBP<120 and DBP<80	SBP≥120 and <140 and/or DBP≥80 and <90	SBP≥140 and <160 and/or DBP≥90 and <100	SBP≥160 and/or DBP≥100
Fostamatinib (n=102)				
SBP<120 and DBP<80	0	0	0	0

SBP≥120 and <140 and/or DBP≥80 and <90	23 (22.5%)	*44 (43.1%)**	0	0
SBP≥140 and <160 and/or DBP≥90 and <100	4 (3.9%)	21 (20.6%)	*1 (1.0%)**	0
SBP≥160 and <180 and/or DBP≥100 and <110	2 (2.0%)	5 (4.9%)	1 (1.0%)	0
SBP≥180 and/or DBP≥110	0	1 (1.0%)	0	0
Placebo (n=48)				
SBP<120 and DBP<80	*4 (8.3%)**	1 (2.1%)	0	0
SBP≥120 and <140 and/or DBP≥80 and <90	12 (25.0%)	*24 (50.0%)**	0	0
SBP≥140 and <160 and/or DBP≥90 and <100	1 (2.1%)	6 (12.5%)	0	0
SBP≥160 and/or DBP≥100	0	0	0	0

*Indicates no worsening from baseline in blood pressure.
[Source: ADVS.xpt and ISS-ITP]

During the placebo-controlled period, a total of 10 patients (10%) in the fostamatinib arm versus 3 patients (6%) in the placebo arm had the dose of the concomitant antihypertensive medication increased and a new antihypertensive medication was started in 17 patients (17%) and 6 patients (13%) in the fostamatinib and placebo arms, respectively.

C788-049:
In the 049 trial, a total of 21 patients (17%) developed hypertension and all were mild to moderate in severity. One patient ([redacted] (b) (6)) had hypertension that required treatment interruption and dose reduction of the study drug. Another patient ([redacted] (b) (6)) had inadequately controlled blood pressure that was managed with dose reduction of the study drug. No other cases of dose reduction, interruption or discontinuation of the study treatment were reported.

At baseline, 28% of patients had SBP<120 and DBP<80; and 2% had SBP≥140 and/or DBP≥90. Post-baseline, the proportion of patients who had SBP≥140 and/or DBP≥90 was increased to 27%.

Table 96 C788-049: Maximum Blood Pressure Values* (Safety Population)

Blood pressure (mmHg)	Fostamatinib (n=121)
At baseline	
SBP<120 and DBP<80	34 (28.1%)
SBP≥120 and <140 and/or DBP≥80 and <90	85 (70.2%)
SBP≥140 and <160 and/or DBP≥90 and <100	1 (<1%)

SBP≥160 and/or DBP≥100	1 (<1%)
Post-baseline	
SBP≥140 and/or DBP≥90	33 (27.3%)
SBP≥160 and/or DBP≥100	2 (1.7%)
SBP≥180 and/or DBP≥110	1 (<1%)

*Percentages are based on the number of patients with at least 1 post-baseline measurement.
[Source: ADVS.xpt and ISS-ITP]

During the extension trial, a total of 16 patients (13%) started treatment on new anti-hypertensive medication and 7 patients (6%) had the dose of the current anti-hypertensive medication increased.

A request for information was sent to the applicant to provide the numbers of patients who developed hypertension and had undergone fostamatinib dose modification, interruption, discontinuation or other intervention (addition or increase dose of anti-hypertensive medication) in the ITP studies, the rheumatoid arthritis studies and the healthy volunteer studies and to provide cases that did not resolve after these interventions. On December 21, 2017, the applicant provided the following information:

- In the ITP studies (study 047, 048 and 049), hypertension AEs identified as 'not resolved' at the last study visit were reported in a total of 7 patients (5%). Six of the 7 patients received new or increased anti-hypertensive treatment. In general, blood pressure in these patients was reported to have subsided to levels below 140/90 mm Hg with the majority going below 130/80 mm Hg. However, according to FDA analysis, the proportion of patients who had ongoing hypertension at the last study visit was higher in the 047, 048 and 049 studies; a total of 17 patients (12%) who received fostamatinib were identified as not resolved.

- In the placebo-controlled RA studies, hypertension AEs that were not resolved at the last study visit were reported in a total of 119 patients (5%) in the fostamatinib arm (70 [5.4%] in higher dose fostamatinib group, 49 [4.4%] in lower dose fostamatinib group) and 27 patients (2.3%) in the placebo arm. Blood pressure increases in these RA studies were treated until they were consistently below the mandated level of 140/90 mm Hg. Less than 1.0% of patients was reported to have blood pressure of > 140/90 mmHg at their last study visit.

- Hypertension was reported for 2 subjects in the healthy volunteer studies. Both AEs were mild in intensity and resolved without action taken on fostamatinib or need for any other intervention.

2017 ACC/AHA Hypertension Guidelines:
On November 13, 2017, the ACC/AHA published new guidelines on diagnosis and treatment of

hypertension. In the new guidelines, the definition of high blood pressure is lowered to account for complications that can occur at lower numbers and to allow for earlier intervention. The categories of blood pressure in the new guidelines are as follows:

- Normal: Less than 120/80 mm Hg;
- Elevated: Systolic between 120-129 and diastolic less than 80;
- Stage 1: Systolic between 130-139 or diastolic between 80-89;
- Stage 2: Systolic at least 140 or diastolic at least 90 mm Hg;
- Hypertensive crisis: Systolic over 180 and/or diastolic over 120, with patients needing prompt changes in medication if there are no other indications of problems, or immediate hospitalization if there are signs of organ damage.

In the 2017 guidelines, patients with stage 1 hypertension (BP 130-139/80-89 mm Hg) who have clinical ASCVD (atherosclerotic cardiovascular disease) or estimated CVD risk of ≥10% are recommended to initiate blood pressure-lowering medication in addition to nonpharmacological therapy. In the 047 and 048 trials, blood pressure was to be kept below 140/90 mmHg and for patients with increased cardiovascular risk, diabetes or renal insufficiency, maintaining the blood pressure below 130/80 mm Hg was considered.

On December 21, 2017, the applicant provided the incidences of hypertension based on the 2017 ACC/AHA hypertension guidelines. The datasets were not provided. Table 97 summarizes the incidences of hypertension that occurred in the 047 and 048 studies based on the new guidelines. The incidence of post-baseline maximum blood pressure in the elevated category was higher in the placebo arm (fostamatinib: 9%, placebo: 17%). For stage 1, the incidences were similar between the arms (fostamatinib: 57%, placebo: 58%) whereas for stage 2, the incidence was higher in the fostamatinib arm (fostamatinib: 33%, placebo: 15%).

Table 97 Pooled analysis of C788-047 and C788-048: The Incidences of Hypertension that Occurred During the Placebo-Controlled Period Based on the 2017 ACC/AHA Guideline (Safety Population)

Maximum post-baseline	Fostaminib (n=102)	Placebo (n=48)
Elevated	9 (8.8%)	8 (16.7%)
Stage 1	58 (56.9%)	28 (58.3%)
Stage 2	34 (33.3%)	7 (14.6%)
Hypertension crisis	1 (1.0%)	0

[Source: Applicant's response to information request]

In addition, the applicant provided shift tables of post-baseline maximum blood pressure (tables 98 and 99). The incidences of post-baseline elevated category in patients who had baseline normal blood pressure was higher in the placebo arm (fostamatinib: 3%, placebo: 8%); the incidence of post-baseline stage 1 category in patients who had baseline normal or elevated blood pressure was slightly higher in the fostamatinib arm (fostamatinib: 36%, placebo: 31%); the incidences of post-baseline stage 2 category in patients who had baseline

normal/elevated/stage 1 blood pressure was higher in the fostamatinib arm (fostamatinib: 31%, placebo: 15%); and post-baseline hypertensive crisis occurred in a total of 1 patient randomized to the fostamatinib arm in the 047/048 trials (this patient had baseline stage 1 hypertension).

Table 98 Pooled analysis of C788-047 and C788-048: Shift Table of Post-Baseline Maximum Blood Pressure Categories that Occurred During the Placebo-Controlled Period Based on the 2017 ACC/AHA Guideline (Fostamatinib Arm, Safety Population)

Maximum post-baseline	Baseline					
	Normal	Elevated	Stage 1	Stage 2	Hypertensive Crisis	Total
Normal	*0*	0	0	0	0	0
Elevated	3 (2.9%)	*3 (2.9%)*	3 (2.9%)	0	0	9 (8.8%)
Stage 1	20 (19.6%)	17 (16.7%)	*21 (20.6%)*	0	0	58 (56.9%)
Stage 2	6 (5.9%)	11 (10.8%)	15 (14.7%)	*2 (2.0%)*	0	34 (33.3%)
Hypertension crisis	0	0	1 (1.0%)	0	*0*	1 (1.0%)
Total	29 (28.4%)	31 (30.4%)	40 (39.2%)	2 (2.0%)	0	102 (100%)

[Source: Applicant's response to information request]

Table 99 Pooled analysis of C788-047 and C788-048: Shift Table of Post-Baseline Maximum Blood Pressure Categories that Occurred During the Placebo-Controlled Period Based on the 2017 ACC/AHA Guideline (Placebo Arm, Safety Population)

Maximum post-baseline	Baseline					
	Normal	Elevated	Stage 1	Stage 2	Hypertensive Crisis	Total
Normal	*4 (8.3%)*	1 (2.1%)	0	0	0	5 (10.4%)
Elevated	4 (8.3%)	*2 (4.2%)*	2 (4.2%)	0	0	8 (16.7%)
Stage 1	8 (16.7%)	7 (14.6%)	*13 (27.1%)*	0	0	28 (58.3%)
Stage 2	1 (2.1%)	3 (6.3%)	3 (6.3%)	*0*	0	7 (14.6%)
Hypertension crisis	0	0	0	0	*0*	0
Total	17 (35.4%)	13 (27.1%)	18 (37.5%)	0	0	48 (100%)

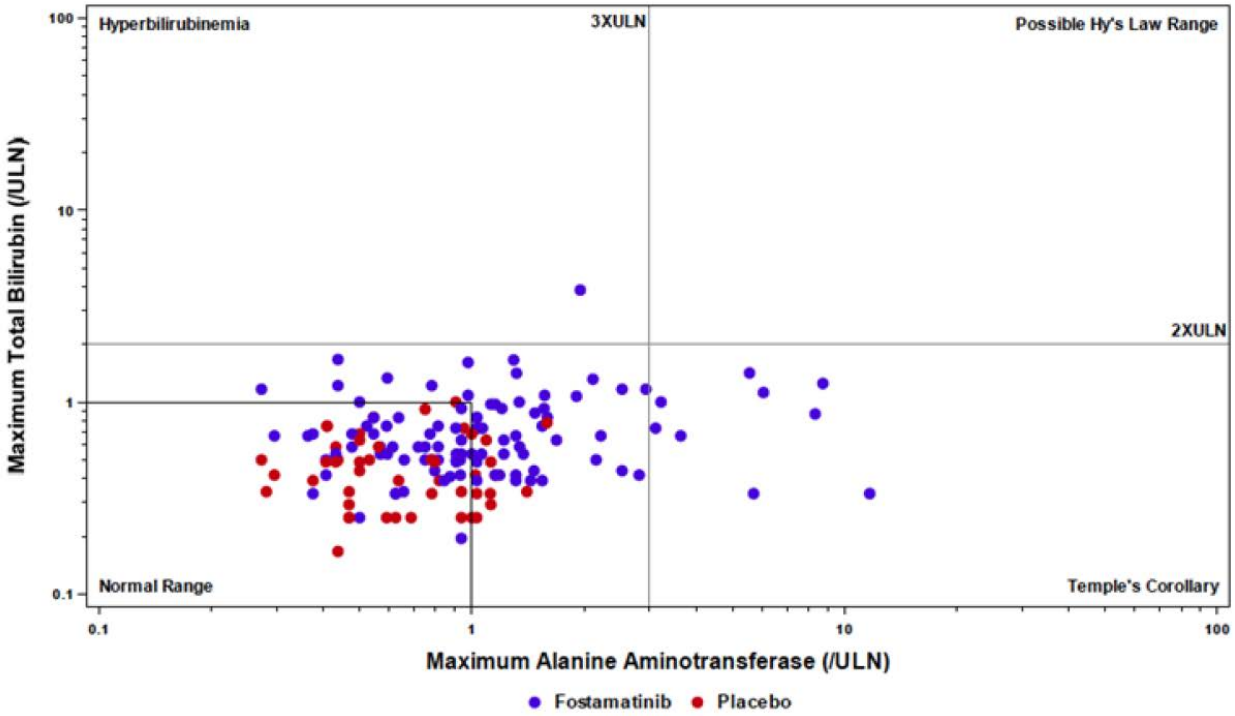
[Source: Applicant's response to information request]

Liver Function Test Abnormalities:

<u>Pooled analysis of 047 and 048 during the placebo-controlled period:</u>

Liver Transaminase Elevation:
Overall, a total of 14 patients (14%) in the fostamatinib arm and no patients in the placebo arm had elevation in liver transaminase. All AEs were mild or moderate in severity. The study treatment was interrupted in 5 patients (5%) and dose reduced in 2 patients (2%). No patient met the criteria for Hy's law. The figure below depicts the incidences of maximum total bilirubin and maximum ALT that occurred in both treatment arms during the placebo-controlled period.

Figure 13 Pooled analysis of C788-047 and C788-048: Maximum Total Bilirubin vs Maximum ALT During the Placebo-Controlled Period



[Source: 120-day safety update, summary of clinical safety]

One patient [redacted] (b) (6)) required treatment discontinuation due the transaminase elevation. The narrative of this patient is presented below:

Patient [redacted] (b) (6) had an increase in ALT ≥ 5 x ULN. Screening and Day 1 ALT levels were both 17 U/L. The patient received fostamatinib 100 mg bid. At Week 6 ([redacted] (b) (6) the ALT/AST were increased to 178 U/L and 114 U/L (normal range 16 to 19 U/L and <40 U/L). Total bilirubin was 1.6 mg/dL (normal range 0.1 to 1.2 mg/dL) with an indirect bilirubin of 1.0 mg/dL, and alkaline phosphatase was 63 U/L (normal range 45 to 108 U/L). Fostamatinib was temporarily interrupted ([redacted] (b) (6) On [redacted] (b) (6) the patient complained of mild nausea. At Week 8 [redacted] (b) (6) AST and bilirubin had returned to within normal limits, but ALT remained slightly elevated at 60 U/L. On [redacted] (b) (6) fostamatinib was restarted at a reduced dose of 150 mg once daily. Four days later ([redacted] (b) (6) ALT level was increased to 218 U/L, and study drug was withdrawn. The ALT returned to within normal limits (< 30 U/L) within one month ([redacted] (b) (6) No other cause of liver toxicity was identified. The investigator assessed the ALT increase as moderate in intensity and possibly related to the study drug.

A total of 9 (9%) and no patient in the fostamatinib and placebo arms, respectively, had ALT/AST levels >3xULN. Among the 9 patients with ALT/AT levels >3xULN, 3 patients (3%) had ALT/AST levels between >3 and ≤5xULN, 5 patients (5%) had ALT/AST levels between >5 and ≤10xULN, and 1 patient (1%) had ALT/AST levels >10xULN. Below is the narrative of the patient who had elevation of ALT>10xULN:

Patient (b) (6) had ALT levels ≥ 10 x ULN and AST levels > 5 x ULN. ALT and AST were increased at Week 6 ((b) (6) to 102 and 72 U/L, respectively, and continued to increase to a maximum of 374 U/L for ALT and 255 U/L for AST ((b) (6) Study drug was withheld, and the transaminase levels returned to within normal limits by Week 8 for AST (28 U/L) and by Week 10 for ALT (28 U/L). Study drug was re-introduced at a reduced dose. The subject's ALT was slightly elevated at Week 24 (35 U/L) and at Month 2 (38 U/L) in Study 049.

Table 100 Pooled analysis of C788-047 and C788-048: Maximum ALT and AST Post-Baseline Values During the Placebo-Controlled Period (Safety Population)

Maximum post-baseline values	Fostaminib (n=102)	Placebo (n=48)
ALT		
>3xULN	9 (8.8%)	0
>5xULN	6 (5.9%)	0
>10xULN	1 (1.0%)	0
>20xULN	0	0
AST		
>3xULN	2 (2.0%)	0
>5xULN	1 (1.0%)	0
>10xULN	0	0
>20xULN	0	0

A patient can appear in more than 1 category.
[Source: ADLB.xpt and ISS-ITP]

Bilirubin Elevation:
Post-baseline bilirubin elevation was observed in 2 patients in the fostamatinib arm and none of the patients in the placebo arm. Both were mild in severity and it has been reported that the bilirubin increase in both patients was almost exclusively due to unconjugated bilirubin. Both patients recovered. Of the 2 patients, the study treatment was interrupted in one patient ((b) (6)) who had elevated total bilirubin of >2 x ULN. No patient had post-baseline elevation in bilirubin and concurrent increase in ALT or AST. No patient required dose reduction or discontinuation due the bilirubin elevation.

C788-049:

Transaminase Elevation:

Elevation of transaminases was reported for 8 patients (7%). No patients meeting the Hy's law criteria were identified.

A total of 2 patients ([redacted] (b) (6)) had severe elevations in transaminases:

The first patient ([redacted] (b) (6)) was assigned to the placebo arm in the 047 trial and continued on the extension trial (049). After 120 days on the fostamatinib treatment, the patient had elevations in ALT and AST that were greater than 20 x ULN that required dose reduction of the study treatment. At the Week 16 visit of the extension trial, the AST was 868 IU/L (reference range [RR] 0 – 32) and AST 849 IU/L (RR 0 – 40 IU/L). The narrative for this patient was not provided. However, according to the datasets, the AE was assessed as 'unlikely related' to the study treatment that resolved. This patient discontinued from the extension study on Day 209 (Month 7).

The second patient ([redacted] (b) (6)) was treated with fostamatinib in the 048 trial and continued on the extension trial. The AE was also considered serious and resulted in discontinuation of fostamatinib. The event resolved after study drug discontinuation. See the narrative for this patient under Serious Adverse Events above.

In addition, another patient ([redacted] (b) (6)) discontinued study treatment due to transaminase elevation.

Patient [redacted] (b) (6) was a 27-year-old white male with a history of chronic ITP, diagnosed on [redacted] (b) (6) On [redacted] (b) (6) in the previous blinded study C788-048, the subject initiated placebo, 100 mg bid. On [redacted] (b) (6) the subject rolled over into this study (C788-049) and initiated open-label fostamatinib 100 mg bid. On [redacted] (b) (6) fostamatinib was increased to 150 mg bid due to platelet count < 50,000/mcL. At Month 3 visit on [redacted] (b) (6) the liver enzymes were increased: ALT 59 u/L (RR 0 – 44 u/L), AST 109 u/L (RR 0 – 40 u/L), ALP 64 (RR 44 - 102 u/L), and bilirubin 7 umol/L (RR 7 – 21 umol/L). At Month 4, the ALT was 64 and AST 39; bilirubin remained within the normal range. The subject had repeated liver function tests monthly, with periodic mild elevations for ALT/AST. At the month 9 visit, [redacted] (b) (6) ALT 205 u/L, AST 101 u/L, ALP 93 u/L, and bilirubin 13 umol/L (RR 2 – 21 umol/L). Transaminases slowly declined, although on [redacted] (b) (6) ALT remained 83 and AST was 47. Study drug was interrupted on [redacted] (b) (6) transaminases declined to normal range rapidly. On [redacted] (b) (6) (Month 10 visit), fostamatinib was resumed at 100 mg bid; ALT 65 u/L (RR 0 – 44 u/L), AST 48 u/L (RR 0 – 40 u/L), ALP 105 u/L (RR 44 – 102 u/L), and bilirubin 7 umol/L (RR 2 – 21 umol/L). ALT and AST continued to fluctuate between 2–3 x the upper limit of normal. On [redacted] (b) (6) ALT was 167 and AST 88, bilirubin remained in the normal range. Fostamatinib 100 mg bid was discontinued on [redacted] (b) (6). On [redacted] (b) (6) the LFTs were: ALT 49 u/L (RR 0 – 44 u/L), AST 34 u/L (RR 0 - 44 u/L), ALP 81 u/L (RR 44 – 102 u/L), and bilirubin 8 umol/L (RR 2 – 21 u/L). This case shows positive re-challenge of fostamatinib on transaminase elevation.

The table below summarizes the incidences of post-baseline maximum ALT and AST values that occurred in the extension trial up to the data cut-off date.

Table 101 C788-049: Post-Baseline Maximum ALT and AST Values (Safety Population)

	Fostamatinib (n=116)				
	≤3xULN	>3xULN and <5xULN	≥5xULN and <10xULN	≥10xULN <20xULN	≥20xULN
ALT	111 (95.7%)	3 (2.6%)	1 (0.9%)	0	1 (0.9%)
AST	114 (98.3%)	1 (0.9%)	0	0	1 (0.9%)

Percentages are based on the number of patients with at least 1 post-baseline measurement.
[Source: ADLB.xpt and ISS-ITP]

Throughout the 047, 048 and 049 trials, a total of 16 patients treated with fostamatinib had ALT or AST increase to > 3x ULN. The median number of days of liver enzymes elevation was 21 days (Start Day range, Day 43 to Day 296; and End Day range, Day 57 to Day 308). In general, transaminases recovered to baseline levels within 8 to 37 days after fostamatinib dose modification.

Bilirubin Elevation:
A total of 3 patients (2%) had increased blood bilirubin or hyperbilirubinemia in the 049 trial. All were mild or moderate in severity. One patient discontinued treatment with fostamatinib; the increased bilirubin in this patient was reported as predominantly indirect upon fractionation. This patient had no other liver function abnormalities. According to the applicant, the profile of this patient was consistent with the known effects of fostamatinib on UGT1A1, particularly in patients with Gilbert's phenotype.

Neutropenia:

<u>Pooled analysis of 047 and 048 during the placebo-controlled period:</u>
Neutropenia was reported in 7 patients (7%) in the fostamatinib arm and none of the patients in the placebo arm. A total of 2 patients had severe neutropenia; one (b) (6) patient had a SAE of neutropenic fever due to an unknown infection (see the narrative under the Serious Adverse Events section) and the other patient developed upper respiratory infection approximately 10 days following the onset of neutropenia. Dose reduction and interruption of the study treatment occurred in 2 patients each. One patient discontinued study treatment due to neutropenia.

Most of the patients in the 047 and 048 trials had post-baseline neutrophil counts of ≥ 1.5 x 10^9/L (fostamatinib: 91%, placebo: 98%). No patients had decrease in neutrophils <0.5 x 10^9/L. Decrease in neutrophils to between ≥ 1 and < 1.5 x 10^9/L was observed in a total of 8 patients (fostamatinib: 7 patients [7%], placebo: 1 patient [2%]) and between ≥ 0.5 and < 1 x 10^9/L in 2% of patients in the fostamatinib arm and none in the placebo arm.

Table 102 Pooled analysis of C788-047 and C788-048: Post-Baseline Minimum Neutrophil Values During the Placebo-Controlled Period (Safety Population)

Minimum post-baseline values	Fostaminib (n=100)*	Placebo (n=48)
< 0.5 x 10^9/L	0	0
≥ 0.5 to < 1 x 10^9/L	2 (2.0%)	0
≥ 1 to < 1.5 x 10^9/L	7 (7.0%)	1 (2.1%)
≥ 1.5 x 10^9/L	91 (91.0%)	47 (97.9%)

All patients had baseline neutrophil values ≥ 1.5 x 10^9/L.
*Subject with a neutrophil measurement at baseline and at least 1 post-baseline measurement.
[Source: ADLB.xpt and ISS-ITP]

C788-049:
A total of 5 patients (4%) had neutropenia. All events were mild or moderate in severity and all resolved except one patient ((b) (6) , no further information was provided for this patient). Treatment discontinuation of fostamatinib occurred in patient ((b) (6)) due to moderate neutropenia. None were associated with infection. The incidences of post-baseline neutrophil counts were similar with those during the placebo-controlled period. Six percent of patients had decrease in neutrophils to between ≥ 1 and < 1.5 x 10^9/L and 2% had decrease to between ≥ 0.5 and < 1 x 10^9/L. No patient had decrease in neutrophils <0.5 x 10^9/L.

Infection:

Pooled analysis of 047 and 048 during the placebo-controlled period:
Overall, infection was reported in 30% of patients in the fostamatinib arm and 21% in the placebo arm. Respiratory tract infections were the most frequently reported AEs in this category (fostamatinib: 14%, placebo: 6%). Infections that occurred in at least 2% greater in the fostamatinib arm were bronchitis (fostamatinib: 3%, placebo: 0%), influenza like illness (fostamatinib: 3%, placebo: 0%) and urinary tract infection (fostamatinib: 3%, placebo: 0%). Severe infection occurred in one patient in each arm (fostamatinib: pneumonia, placebo: sepsis). The patient who had sepsis ((b) (6)) in the placebo arm died.

C788-049:
During the extension trial, infection was reported in 23% of patients. The type of infections that occurred in >1% of patients were respiratory infection (9%); and nasal pharyngitis, gastroenteritis, oral candidiasis and viral infection (all, 2%). One patient had sepsis ((b) (6) that resulted in fatal outcome (see the narrative for this patient under the Deaths section above). Other AEs were all mild or moderate in severity.

7.4.6. Safety Analyses by Demographic Subgroups

Safety analyses by age:

Table 103 summarizes adverse events by age (<65 years vs. ≥65 years). In general, the adverse event incidences were similar by age between the two arms, except in the ≥65 years category higher proportion of patients in the fostamatinib arm experienced any AEs (93% vs. 55%) and SAEs (21% vs. 9%) while in the <65 years category, a higher proportion of patients in the placebo arm experienced SAEs (10% vs. 27%).

Among patients who received fostamatinib, the incidences of AEs, SAEs, AEs leading to treatment withdrawal and AEs leading to death were all higher in patients in the ≥65 years category than in the <65 years category.

Table 103 Pooled analysis of C788-047 and C788-048: AEs by Age (<65 Years vs. ≥65 years) that Occurred During the Placebo-Controlled Period (Safety Population)

	Fostaminib (n=102)		Placebo (n=48)	
	<65 years (n=74)	≥65 years (n=28)	<65 years (n=37)	≥65 years (n=11)
All AEs	59 (79.7%)	26 (92.9%)	31 (83.8%)	6 (54.5%)
Serious AEs	7 (9.5%)	6 (21.4%)	10 (27.0%)	1 (9.1%)
AEs leading to withdrawal	5 (6.8%)	5 (17.9%)	2 (5.4%)	2 (18.2%)
AEs leading to death	0	1 (3.6%)	0	1 (9.1%)

[Source: ADAE.xpt]

The table below summarizes AEs reported in ≥ 10% of patients by age. Among patients ≥65 years, in general the incidences of AEs were higher in the fostamatinib arm compared to the placebo arm.

Among patients who received fostamatinib, the incidences of AEs were higher in patients ≥65 of age years except nausea, headache and ALT/AST increased. Hypertension occurred at a higher incidence in patients ≥65 years (39%) compared to patients <65 years of age (24%).

Table 104 Pooled analysis of C788-047 and C788-048: AEs by Age (<65 Years vs. ≥65 years) Reported in ≥10% of Patients in Any Arm that Occurred During the Placebo-Controlled Period (Safety Population)

Preferred Term	Fostaminib (n=102)		Placebo (n=48)	
	<65 years (n=74)	≥65 years (n=28)	<65 years (n=37)	≥65 years (n=11)
Diarrhea	19 (25.7%)	11 (39.3%)	7 (18.9%)	0
Hypertension[1]	18 (24.3%)	11 (39.3%)	4 (10.8%)	2 (18.2%)
Nausea	14 (18.9%)	5 (17.9%)	4 (10.8%)	0
Headache	11 (14.9%)	0	9 (24.3%)	0
ALT increased	9 (12.2%)	2 (7.1%)	0	0
AST increased	8 (10.8%)	1 (3.6%)	0	0
Epistaxis	8 (10.8%)	7 (25.0%)	4 (10.8%)	1 (9.1%)
Dizziness	6 (8.1%)	5 (17.9%)	4 (10.8%)	0

Rash[2]	6 (8.1%)	3 (10.7%)	1 (2.7%)	0
Fatigue	3 (4.1%)	3 (10.7%)	1 (2.7%)	0
Hypokalemia	0	3 (10.7%)	0	0

Incidences are based on the number of patients, not the number of events. Although a patient may have had 2 or more clinical AEs, the patient is counted only once in a category. The same patient may appear in different categories.
1. Hypertension includes blood pressure increased, blood pressure diastolic increased and blood pressure systolic increased.
2. Rash includes rash erythematous and rash macular.
[Source: ADAE.xpt]

Safety analyses by gender:
The table below summarizes adverse events by gender. No clinically meaningful differences were observed between the treatment arms.

Table 105 Pooled analysis of C788-047 and C788-048: AEs by Gender that Occurred During the Placebo-Controlled Period (Safety Population)

	Fostaminib (n=102)		**Placebo (n=48)**	
	Female (n=61)	Male (n=41)	Female (n=30)	Male (n=18)
All AEs	52 (85.2%)	33 (75.0%)	24 (80.0%)	13 (72.2%)
Serious AEs	8 (13.1%)	5 (12.2%)	8 (26.7%)	3 (16.7%)
AEs leading to withdrawal	7 (11.5%)	3 (7.3%)	4 (13.3%)	0
AEs leading to death	1 (<1%)	0	1 (3.3%)	0

[Source: ADAE.xpt]

7.4.7. Specific Safety Studies/Clinical Trials

A prospective short-term (4-week) ambulatory blood pressure study was performed in patients with rheumatoid arthritis (RA). Over 130 patients (half with pre-existing hypertension) were randomized to receive either fostamatinib 100 mg BID or placebo for 28 days. After 28 days of treatment, mean changes from baseline in 24-hour mean systolic blood pressure were 4.3 mm Hg and 1.3 mm Hg in the fostamatinib and placebo arms, respectively; and mean changes in 24-hour mean diastolic blood pressure were 4.4 mm Hg and 0.7 mm Hg in the fostamatinib and placebo arms, respectively. After the 1-week washout (Day 36), mean changes in systolic blood pressure from the discontinuation visit (Day 29) of -3.3 mm Hg and -0.5 mm Hg were observed for the fostamatinib and placebo arms, respectively. The effects on blood pressure had generally reversed 1 week after discontinuing fostamatinib. Among patients who were on antihypertensive medication at baseline, maximum blood pressure of ≥ 140/90 mm Hg occurred in 11 patients (35.5%) and 7 patients (21.9%) in the fostamatinib and placebo arms, respectively, compared with 10 patients (27.0%) and 3 patients (8.6%) in the fostamatinib and placebo arms, respectively, without antihypertensive medication use at baseline. Patients with pre-existing hypertension may be more susceptible to the hypertensive effects of fostamatinib. Treatment discontinuation due to hypertension occurred in 0.7% of patients in the fostamatinib arm and 0.1% of patients in the placebo arm.

7.4.8. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

In the C788-047, C788-048 and C788-049 trials, only one patient experienced an AE (plasma cell myeloma) in the Neoplasms benign, malignant, and unspecified SOC.

Pediatrics and Assessment of Effects on Growth

In the C788-047, C788-048 and C788-049 trials, patients who were younger than 18 years of age were excluded. The safety and effectiveness of fostamatinib have not been established in pediatric patients.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No cases of drug overdose were reported in the fostamatinib clinical trials. In the RA trials, dose-related TEAEs differences included hypertension, nausea, dizziness, and vomiting.

In the fostamatinib clinical trials, no patient was identified with TEAE indicative of potential of drug abuse, withdrawal or rebound effects.

120 Day Safety Update

The applicant submitted the 120-day safety update on August 15, 2017. The submission contained safety data up to the clinical cut-off date of April 14, 2017, providing 7 months of additional safety information from the follow-up patients in the ongoing extension C788-049 trial. Based on the total of 146 patients that received fostamatinib throughout the placebo-controlled period (047 or 048 trial) and the extension 049 trial, the median days of fostamatinib exposure in the 120-day safety update was 204 days (range: 8 to 929 days) and 67% of patients received fostamatinib for more than 24 weeks.

Table 106 Extend of Exposure

	Placebo-controlled period (047/048) (n=150)		**047/048/049 fostamatinib-treated patients in the original NDA submission**	**047/048/049 fostamatinib-treated patients up to the 120-day safety update**
	Fostaminib (n=102)	**Placebo (n=48)**	**Fostamatinib (n=146)**	**Fostamatinib (n=146)**
Duration (days)				
Mean	105.1	92.2	228.2	305.0
Median	86.0	85.0	179.0	204.0
Range	8-183	16-173	8-712	8-929

[Source: 120-day safety update, summary of clinical safety]

Overall, the safety profile of fostamatinib was generally consistent with the initial NDA submission (see table below). No new safety signals or major changes in AEs were identified with the 120-day safety update.

Table 107 Comparison of Overall Summary of Safety (Safety Population)

	Placebo-controlled period (047/048)		**047/048/049 fostamatinib-treated patients in the original NDA submission**	**047/048/049 fostamatinib-treated patients upto the 120-day safety update**
	Fostaminib (n=102)	**Placebo (n=48)**	**Fostamatinib (n=146)**	**Fostamatinib (n=146)**
All Deaths	1 (<1%)	1 (2.1%)	2 (1.4%)	3 (2.1%)
TEAEs	85 (83.3%)	36 (75.0%)	120 (82.2%)	125 (85.6%)
Mild	33 (32.4%)	20 (41.7%)	31 (21.2%)	31 (21.2%)
Moderate	37 (36.3%)	9 (18.8%)	60 (41.1%)	60 (41.1%)
Severe	15 (14.7%)	7 (14.6%)	29 (19.9%)	34 (23.3%)
Treatment-related TEAEs	60 (58.8%)	13 (27.1%)	90 (61.6%)	94 (64.4%)
TESAEs	13 (12.7%)	10 (20.8%)	31 (21.2%)	38 (26.0%)
AEs leading to any study drug withdrawal	10 (9.8%)	4 (8.3%)	22 (15.1%)	25 (17.1%)

[Source: 120-day safety update, summary of clinical safety]

At the time of the 120-day safety update cut-off date, a total of 49 of the 123 enrolled patients (40%) remained in the C788-049 study. No new patients were enrolled.

Between the NDA submission and the 120-day safety update, a total of 8 new SAEs were reported (melena, nephrolithiasis, thrombocytopenia, menorrhagia, obstructive cholecystitis, loss of consciousness, chest pain, and pneumonia). All of the SAEs except the pneumonia SAE were reported as recovered/resolved. One additional death was reported (the above SAE of pneumonia had a fatal outcome). The narrative of this patient is summarized below:

Patient (b) (6) was a 70-year-old white male with a history of chronic kidney disease (stage 3), previous alcohol excess, hypertension, and gout, was found dead at home approximately 3 weeks after the study drug had been interrupted on (b) (6) due to the new left leg symptoms of foot drop (278 days after the start of fostamatinib). MRI confirmed a structural cause (L4/L5 disc protrusion) for the symptoms of left foot drop; therefore, the investigator did not believe this was related to the study drug. From (b) (6) to (b) (6) in the previous blinded study (047), the subject received fostamatinib 100 mg bid, which was increased to 150 mg bid on (b) (6) On (b) (6) the subject initiated open-label treatment (049) with fostamatinib at 150 mg bid. The baseline platelet count in study 049

was 19 x 10^9/L (RR 150-400 10^9/L). The last platelet count obtained on (b) (6) was 66 x 10^9/L. An autopsy diagnosed bilateral lobar pneumonia as the cause of death. The investigator assessed the pneumonia as severe in intensity and unlikely related to the study drug.

A total of 2 additional patients discontinued fostamatinib treatment due to an AE (diarrhea and the above event of pneumonia).

Liver Function Test Abnormalities:
No cases of Hy's law were reported. Between the time of the NDA cutoff and the 120-day cutoff, maximum ALT/AST levels > 3 × ULN post-baseline occurred in one additional patient and the elevation was between > 3 and ≤ 5 × ULN. Patient (b) (6) had ALT/AST>3x ULN and total bilirubin >2xULN (identified in Figure 15, upper right quadrant), however, the bilirubin elevation occurred in isolation and was not concurrent with the transaminase elevation. The narrative for this patient is as follows:

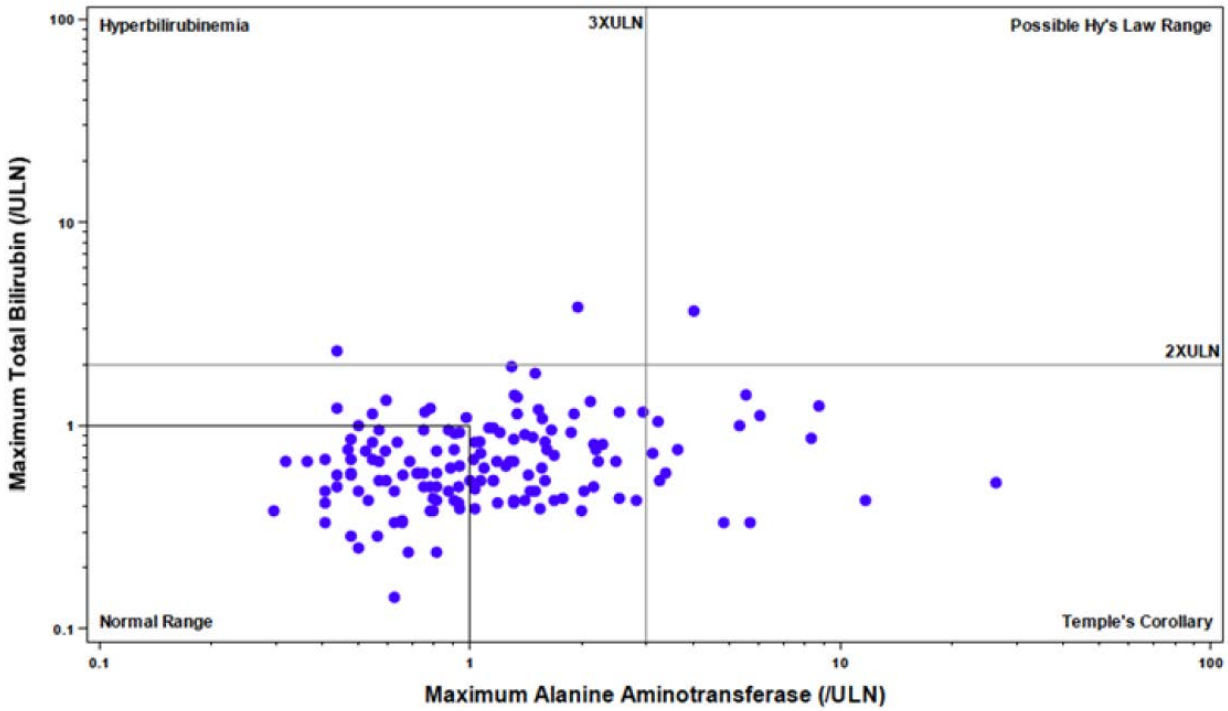
Patient (b) (6) switched from placebo to fostamatinib after rolling over into Study 049. The patient developed an ALT/AST elevation >3 x ULN (ALT was 4 x ULN) with ALP <2 x ULN, and more than a month later, a TBL>2 x ULN (see figure 14 below) during the extension study. The ALT elevation was reported as an AE of mild severity. Later, AEs were reported for diarrhea (mild) and oral pain (moderate) and the patient discontinued Study 049 after approximately 4 months. Due to nonconcurrent transaminase and TBL elevations, the Hy's Law criteria was not met.

Figure 14 Liver Function Tests Over Time in Patient (b) (6)

(b) (6)

[Source: 120-day safety update, summary of clinical safety]

Figure 15 Maximum Total Bilirubin vs. Maximum ALT: Fostamatinib-Exposure in ITP Studies (120-Day Safety Update)



[Source: 120-day safety update, summary of clinical safety]

Hypertension:
One additional new severe hypertension AE was reported in the 120-day safety update. The table below summarizes the blood pressure changes by shift analysis. In general, the results provided in the 120-day safety update is consistent with those included in the initial NDA submission.

Table 108 Shift Table for Blood Pressure (Safety Population)

Maximum post dose value (mmHg)	Baseline value			
	SBP<120 and DBP<80	SBP≥120 and <140 and/or DBP≥80 and <90	SBP≥140 and <160 and/or DBP≥90 and <100	SBP≥160 and <180 and/or DBP≥100 and <110
Fostamatinib during the placebo-controlled period (n=102)				
SBP<120 and DBP<80	0	0	0	0
SBP≥120 and <140 and/or DBP≥80 and <90	23 (22.5%)	*44 (43.1%)**	0	0
SBP≥140 and <160 and/or DBP≥90 and <100	4 (3.9%)	21 (20.6%)	*1 (1.0%)**	0
SBP≥160 and <180 and/or	2 (2.0%)	5 (4.9%)	1 (1.0%)	0

DBP≥100 and <110				
SBP≥180 and/or DBP≥110	0	1 (1.0%)	0	0
Fostamatinib exposure up to the 120-day safety update (n=146)				
SBP<120 and DBP<80	*3 (2.1%)**	0	0	0
SBP≥120 and <140 and/or DBP≥80 and <90	26 (17.8%)	*59 (40.4%)**	0	0
SBP≥140 and <160 and/or DBP≥90 and <100	9 (6.2%)	35 (24.0%)	*1 (0.7%)**	1 (0.7%)
SBP≥160 and <180 and/or DBP≥100 and <110	2 (1.4%)	6 (4.1%)	1 (0.7%)	0
SBP≥180 and/or DBP≥110	1 (0.7%)	2 (1.4%)	0	0

*Indicates no worsening from baseline in blood pressure.
[Source: 120-day safety update, summary of clinical safety]

7.4.9. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Fostamatinib is a new molecular entity and is not approved for marketing in any country at this time. There is no post-marketing experience with fostamatinib.

Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed in the clinical trials.

7.4.10. Integrated Assessment of Safety

The safety review of fostamatinib was primarily based on a total of 150 patients with ITP (fostamatinib: 102 patients, placebo: 48 patients) who participated in the two identical phase 3, registrational trials (C788-047 and C788-048); and on the 44 patients who received placebo during the C788-047 and C788-048 trials and continued on the open-label, extension trial (C788-049) and received treatment with fostamatinib. Patients who received treatment with fostamatinib initially were dosed on the 100 mg twice daily regimen and in majority of patients (87%) the dose was increased to 150 mg twice daily starting at Week 4. The median average daily dose of fostamitinib was 248 mg reflecting the general administered daily dose ranges of 200 mg to 300 mg. The median duration of study treatment was 85 days (fostamatinib: 86 days, placebo: 85 days) during the placebo-controlled period. Based on the total of 146 patients who received fostamatinib throughout the placebo-controlled and the extension trials, the median duration of fostamatinib exposure was 179 days (range, 8 to 712 days). The safety review was conducted on the pooled data of the two phase 3 randomized trials and separately on the extension trial. The safety findings of the review are as follows:

<u>Deaths:</u>

A total of 2 patients (fostamatinib: 1 patient [<1%], placebo: 1 patient [2%]) died in the C788-047 and C788-048 trials. The deaths were due to multiple myeloma and sepsis in the fostamatinib and placebo arms, respectively. In the C788-049 trial, one additional patient (<1%) died due to sepsis 19 days after the last dose of fostamatinib. No deaths were attributed to the study treatment.

Serious Adverse Events:

- Studies C788-047 and C788-048: Serious AEs were reported more frequently in the placebo arm (fostamatinib: 13%, placebo: 21%). Most of the SAEs were related to bleeding (fostamatinib: 4%, placebo: 10%) and thrombocytopenia (fostamatinib: 2%, placebo: 4%). Other SAEs that occurred in the fostamatinib arm were febrile neutropenia, hypertensive crisis, pneumonia, syncope, bronchitis, retinal tear, plasma cell myeloma, diarrhea, ITP flare and transient ischemic attack.
- Study C788-049: SAEs occurred in 17% of patients during the extension trial. SAEs reported in more than 1 patient were thrombocytopenia (4%) and related to bleeding (epistaxis, petechiae and GI hemorrhage, all 2%).

Treatment Discontinuation due to Adverse Events:

- Studies C788-047 and C788-048: Similar percentage of patients in each arm discontinued study treatment due to AEs (fostamatinib: 10%, placebo: 8%). There were no AEs that lead to study treatment withdrawal in more than 1 patient in the fostamatinib arm.
- Study C788-049: The incidence of treatment discontinuation due to AEs (10%) in the extension trial was similar to that in the fostamatinib arm in the randomized trials. Diarrhea (3%) and increased liver transaminases (AST/ALT) (2%) were the only AEs that lead to treatment discontinuation in more than one patient.

Significant Adverse Events:

- Studies C788-047 and C788-048: The incidences of severe AEs (defined as life-threatening or fatal) were similar between the treatment arms (both 15%). Severe AEs that occurred in more than one patient in the fostamatinib arm were thrombocytopenia/platelet count decreased, blood pressure increased/hypertensive crisis and dyspnea (2% each).
- Study C788-049: Severe AEs occurred in 15% of patients. Severe AEs that were reported for more than 1 patient were thrombocytopenia/platelet count decreased (6%), gastrointestinal hemorrhage and hepatic enzyme increased/transaminases increased (both 2%).

Treatment Emergent Adverse Events:

- Studies C788-047 and C788-048: The incidence of TEAEs was higher in the fostamatinib arm (83%) compared to the placebo arm (75%). Most of the patients experienced mild (fostamatinib: 32%, placebo: 42%) or moderate (fostamatinib: 36%, placebo: 19%) TEAEs as the greatest severity. TEAEs that occurred in at least 10% of patients and at

greater than two-fold higher incidence in the fostamatinib arm compared to the placebo arm were diarrhea, hypertension, nausea, AST/ALT increased, rash, neutropenia, chest pain, fatigue, abdominal pain, and contusion.

- Study C788-049: In the extension trial, 72% of patients had an TEAE. Most of the TEAEs were mild (24%) or moderate (34%) in severity. The most frequently reported TEAEs (>10%) were diarrhea, hypertension, petechiae, and epistaxis.

Adverse Events of Specific Interest:
Adverse events of specific interest that occurred > 10% more often in the fostamatinib arm compared to the placebo arm were GI toxicity (fostamatinib: 41%, placebo: 21%), hypertension (fostamatinib: 28%, placebo: 13%) and liver toxicity (fostamatinib: 14%, placebo: 0).

Gastrointestinal Toxicity:

- Studies C788-047 and C788-048: Diarrhea (fostamatinib: 31%, placebo: 15%) and nausea (fostamatinib: 19%, placebo: 8%) were the most frequently reported GI toxicities. Other than the one case of severe diarrhea that occurred in the fostamatinib arm, all of the GI toxicities were mild or moderate in severity.
- Study C788-049: In the extension trial, GI toxicities occurred in 33% of patients and most were due to diarrhea (24%). Study treatment discontinuation was reported in 3% of patients due to diarrhea.

Gastrointestinal toxicities should be managed with supportive care management strategies (dietary changes, hydration, anti-emetics, and/or antidiarrheal medication). Dose reduction, treatment interruption or discontinuation of fostamatinib should be considered if supportive care management strategies are not effective.

Hypertension:

- Studies C788-047 and C788-048: Most hypertension AEs were mild or moderate in severity (fostamatinib: 26%, placebo: 10%). Two percent of patients in each arm had severe hypertension. One patient in the fostamatinib arm had a severe and serious event of hypertensive crisis that resulted in hospitalization. Ten percent of patients in the fostamatinib arm versus 6% in the placebo arm had the dose of the concomitant antihypertensive medication increased and a new antihypertensive medication was started in 17% and 13% of patients in the fostamatinib and placebo arms, respectively.
- Study C788-049: In the extension trial, 17% of patients developed hypertension and all were mild to moderate in severity. Thirteen percent of patients started treatment on new anti-hypertensive medication and 6% had the dose of the current anti-hypertensive medication increased.

Blood pressure should be monitored every 2 weeks until stable, then monthly. Anti-hypertensive therapy should be adjusted or initiated to ensure maintenance of blood pressure control. Dose interruption, or reduction or discontinuation of fostamatinib should be considered.

Liver Toxicity:

- Studies C788-047 and C788-048: Overall, 14% of patients in the fostamatinib arm and no patients in the placebo arm had elevation in liver transaminase. All AEs were mild or moderate in severity. Nine percent of patients in the fostamatinib arm had post-baseline ALT/AST levels >3xULN; 3% of patients had ALT/AST levels between >3 and ≤5xULN, 5% had ALT/AST levels between >5 and ≤10xULN, and 1% had ALT/AST levels >10xULN. Post-baseline bilirubin elevation was reported in 2% of patients in the fostamatinib arm and no patients in the placebo arm. No cases of Hy's law were reported.
- Study C788-049: In the extension trial, 7% of patients had elevation of liver transaminases (ALT/AST) including 1 patient with post-baseline ALT and AST that were greater than 20 x ULN that required dose reduction of the fostamatinib treatment. No patients meeting the Hy's law criteria were identified.

Throughout the 047, 048 and 049 trials, 11% of patients had ALT or AST increase to > 3x ULN. The median number of days of liver enzymes elevation was 21 days (Start Day range, 43 to 296; and End Day range, 57 to 308). In general, transaminases recovered to baseline levels within 8 to 37 days after dose modification of fostamatinib.

Liver function tests should be monitored monthly during fostamatinib treatment. If ALT or AST increases to ≥ 3 x ULN and <5 x ULN, LFTs should be re-checked every 72 hours until ALT/AST values are no longer elevated. If ALT or AST increases to ≥ 5 x ULN, fostamatinib should be discontinued. Dose interruption, reduction, or discontinuation of fostamatinib should be considered.

SUMMARY AND CONCLUSIONS

7.5. Statistical Issues

Due to the small sample size and high rates of attrition in Study 047 and 048, the statistical interpretation of the primary efficacy results was heavily dependent on the number of responders in the placebo arm in each study. The sensitivity analyses show that the missing data did not have an impact on the study conclusions. The LOCF imputation may not reflect the true platelet value. Furthermore, due to the high discontinuation in both arms and in both studies, imputations have considerable weight on the efficacy results. In Study 047, the following secondary endpoints were statistically significant: platelet response at Week 12, platelet response at Week 24. These are supportive of the primary results, however platelet response at Week 24 needs to interpreted with caution; at Week 24, there were no patients with platelet counts in the placebo arm and only 11 patients with platelet counts in the fostamatinib arm.

7.6. Conclusions and Recommendations

This reviewer recommends regular approval of fostamatinib for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment.

The efficacy of fostamatinib was studied in two identical phase 3, double-blind, placebo-controlled, randomized trials (C788-047 and C78-048) and an open-label, extension trial (C788-049). The primary endpoint in the phase 3 randomized trials was stable platelet response defined as achievement of platelet count of ≥ 50 $x10^9$/L on at least 4 of the 6 visits between Weeks 14 to 24. In the C788-047 trial, the difference of response between the two treatment arms was 17.6% [95% CI (-6.1%, 40.3%), exact confidence interval], [95% CI (7.2%, 28.1%), normal approximation], p-value 0.03. In the C788-048 trial, the difference of response between the two arms was 11.8% [95% CI (-13.0%, 35.7%), exact confidence intervals], [95% CI (-1.1%, 24.8%), normal approximation], p-value: 0.26. Although the primary efficacy result of the C788-048 trial was not statistically significant, this was primarily based on one patient in the control arm whose post-baseline platelet counts fluctuated from 420,000/mcL (at Week 2) to 16,000/mcL (at Week 16) with no rescue therapy. In addition, although the number of patients who received a prior TPO receptor agonist therapy was small in these trials, in this subgroup the differences of stable platelet response between the two arms were 15.4% and 15.0% in the C788-047 and C788-048 trials, respectively. The patients who had received a prior TPO receptor agonist and responded to fostamatinib therapy and had discontinued the TPO medication due to loss of response.

There were no multiplicity adjustments for Study 049 hence the analyses were considered explorative. There were two pre-specified versions of the primary efficacy endpoint. Following the sponsor's most recent data submission, a total of 18 patients maintained a stable response per Version 1 (achievement of a platelet count ≥ 50,000/mcL within 12 weeks of starting treatment and maintained for at least 12 months). Of these 18 patients, 6 patients were treated with placebo in Study 047/048. The proportion of placebo patients who maintained a stable platelet response (per Version 2, defined as achievement of a platelet count ≥ 50,000/mcL within 12 weeks of starting treatment and maintained for at least 12 weeks) was 20.5% (95% CI: 8.5, 32.4). These results are supportive of the efficacy results of the Study 047 and Study 048.

The safety review of fostamatinib was primarily based on a total of 146 patients that received at least one dose of fostamatinib in the two phase 3 trials and the extension trial. The main safety concerns of fostamatinib include hypertension, liver toxicity, gastrointestinal toxicity and neutropenia. The prescribing information provides adequate monitoring and mitigation strategies for these toxicities. The safety profile of fostamatinib is acceptable.

In conclusion, the benefit-risk assessment of fostamatinib for the treatment of thrombocytopenia in adult patients with chronic ITP who have had an insufficient response to a previous treatment is acceptable. Fostamatinib could provide an alternative therapy for

patients who do not tolerate or do not respond to existing therapies.

X X

Stella Karuri, PhD
Primary Statistical Reviewer

Yuan-Li Shen, Dr PH
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X X

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8 Advisory Committee Meeting and Other External Consultations

This application was not presented to the Oncologic Drug Advisory Committee or any other external consultants.

9 Pediatrics

The safety and efficacy of fostamatinib have not been evaluated in pediatric patients. Pediatric patients with ITP were not enrolled in fostamatinib clinical trials.

10 Labeling Recommendations

10.1. Prescribing Information

The following are recommended major changes to the fostamatinib prescribing information based on this review:

- **1 INDICATIONS and USAGE:** Remove "persistent" from the proposed indication,

"treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment" to be consistent with the diagnostic criteria for chronic ITP.

- **2 DOSAGE AND ADMINISTRATION:** Revise the recommendations for dose modifications for hypertension to be consistent with the 2017 American College of Cardiology/ American Heart Association (ACC/AHA) high blood pressure clinical practice guidelines.

- **5 WARNINGS AND PRECAUTIONS:** Add a new subsection for "Embryo-Fetal Toxicity".

- **6 ADVERSE REACTIONS:** Revise the incidence of common (≥ 5%) adverse reactions table with groupings of relevant Preferred Terms for diarrhea, hypertension, respiratory infections, rash, abdominal pain and neutropenia. Add a table for "elevations in hepatic transaminases" that occurred during studies C788-047 and C788-048.

- **8 USE IN SPECIFIC POPULATIONS:** Update information to be consistent with the Pregnancy and Lactation Labeling Rule Guidance. Revised the Geriatric Use subsection to reflect the safety and efficacy results from studies C788-047 and C788-048. Remove the [redacted] (b) (4) per 21CFR201.57 (i.e., because there were no clinically relevant differences in response, safety, or recommendations for use of fostamatinib in these patient populations).

- **14 CLINICAL STUDIES:** For the presentation of the primary endpoint results for studies C788-047 and C788-048, include proportions of patients in both arms that rolled over into the open-label extension study (C788-049) at Week 12 and proportions of patients that completed the study. Remove information regarding [redacted] (b) (4) that was not pre-specified as endpoints in studies C788-047 and C788-048. Add the results of the first version of the primary endpoint of the extension study (C788-049).

- **17 PATIENT COUNSELING INFORMATION:** Revise the section to be consistent with the updated WARNINGS AND PRECAUTIONS section.

10.2. Patient Labeling

The Patient Package Insert was revised to be consistent with the updated Prescribing Information and FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

11 Risk Evaluation and Mitigation Strategies (REMS)

There are no additional risk management strategies proposed beyond recommended labeling. Review of the application and of the findings from the review teams, the Division of Risk Management in the Office of Surveillance and Epidemiology agree that a REMS is not necessary to ensure that the benefits of fostamatinib outweigh its risks. Therefore, the subsequent sections are not applicable and have been omitted.

12 Postmarketing Requirements and Commitments

Chemistry, Manufacturing and Controls (CMC) review recommended two post marketing commitments (PMC) with timelines as follows (See separate CMC Reviews for details):

- Develop a test method for [redacted] (b) (4) and hardness for the drug product and submit the validation data to the FDA. Include tests for [redacted] (b) (4) and hardness for drug product release and stability specifications with adequate justification.

  This PMC has a study completion date of June 30, 2018.

- Test [redacted] (b) (4) for elemental impurities and submit the data to FDA. [redacted] (b) (4)

  This PMC has a study completion date of June 30, 2018.

13 Appendices

13.1. References

1. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190-4207.
2. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. Blood 2010;115(2):168-186.
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4. FDA statistical review of Nplate (romiplostim) 2007.
5. Page LK, Psaila B, Provan D, et al. The immune thrombocytopenic purpura (ITP) bleeding score: assessment of bleeding in patients with ITP. British journal of haematology 2007;138(2):245-8.
6. Fogarty PF, Tarantino MD, Brainsky A, et al. Selective validation of the WHO Bleeding Scale in patients with chronic immune thrombocytopenia. Curr Med Res Opin 2012;28(1):79-87.
7. Robinson ES, Khankin EV, Karumanchi SA, et al. Hypertension induced by vascular endothelial growth factor signaling pathway inhibition: mechanisms and potential use as a biomarker. Semin Nephrol 2010;30(6): 591-601.
8. Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. J Pharmacol Exp Ther 2005;315(3): 971-979.
9. Promacta prescribing information.
10. Nplate prescribing information.
11. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017; Nov 13:[Epub ahead of print].
12. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 2009.

13.2. Financial Disclosure

The applicant provided financial disclosure information for all covered clinical studies including the ITP (C788-047, C788-048 and C788-049), oncology and rheumatoid arthritis studies. The FDA financial certification form 3454 was included and was signed by Ryan Maynard, the executive vice president and chief financial officer for Rigel Pharmaceuticals, dated April 6, 2017.

Covered Clinical Study (Name and/or Number): C788-047

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 189		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): C788-048

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 81		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study (Name and/or Number): C788-049

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 184		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____		

Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Nonclinical Pharmacology/Toxicology

The carcinogenic potential of fostamatinib was investigated in 104-week studies conducted in Crl:CD1(ICR) mice and Crl:CD(SD) rats. The studies were conducted under a SPA with concurrence from the ECAC. No tumor findings achieved statistical significance in either sex or species.

13.4. OCP Appendices (Technical documents supporting OCP recommendations)

13.4.1. Clinical PK

Healthy subjects PK

The PK parameters of R406 after single dose and multiple dose have been evaluated in healthy subjects in the following 27 studies (Table 109). Due to the formulation development, it is hard to compare the concentration profile of R406 across studies as various fostamatinib formulations was used, such as, oral suspension, (b) (4) tablet, BFC tablet, OFC-I tablet and OFC tablet.

Table 109: List of Biopharmaceutical and Clinical Pharmacology Studies in Healthy Subjects

Study Number and Description	Healthy Subjects	Fostamatinib Dose	Dose Strength
C406-001 PK of single and multiple doses of R406	59 male	A single R406 dose of 80, 250, 400, 500, 600 mg R406 100, 200, or 300 mg BID, 7 days,	Oral solution of R406
C788-001 PK for single and multiple doses of	34 male	Part A: a single dose of 80, 250, 400 mg	Fostamatinib (b) (4) in orange juice as

fostamatinib, food effect and ketoconazole DDI		Part B: 160 mg, BID, 7 days, Part C: a single dose of fostamatinib 80 mg	an oral suspension
C788-003 PK of 21-day dosing with fostamatinib	5M/5F	250 mg, BID, 20 days	Fostamatinib (b) (4) in orange juice as an oral suspension
C788-005 Relative bioavailability	10M/8F	A single dose of 100 mg (b) (4) suspension (~ 80 mg fostamatinib (b) (4)); A single dose of 75 mg (b) (4) tablet	Fostamatinib (b) (4) in orange juice as an oral suspension 25 mg (b) (4)% w/w (b) (4) tablet
C788-008 Relative bioavailability	12 male	A single dose of 100 mg (b) (4)% w/w (b) (4) tablet 100 mg (b) (4)% w/w (b) (4) tablet 200 mg % w/w (b) (4) tablet 300 mg % w/w (b) (4) tablet	25 mg (b) (4)% w/w (b) (4) tablet 100 mg (b) (4)% w/w (b) (4) tablet
C788-014 ADME study of a single radiolabeled fostamatinib dose	6 male	A single dose of 150 mg sodium salt suspension 100 µCi of ^{14}C-R788 in 150 mg oral suspension	Fostamatinib sodium salt oral suspension
C788-016 Relative bioavailability and food Effect	18 male	A single dose of 100 mg BFC tablet 100 mg GFC tablet	100 mg (b) (4)% w/w BFC tablet 50 mg (b) (4)% w/w GFC tablet
C788-013 QT/QTc study	114M/94F	100 or 300 mg tablet, BID, 3 days,	100 mg (b) (4)% w/w BFC tablet
C788-018 CYP3A4 substrate (midazolam) DDI	16 male	Fostamatinib, 100 mg tablet, BID, 7 days,	100 mg % w/w BFC tablet
C788-052 Bioequivalence	42 male	A single dose of 150 mg OFC-I tablet (AZ) 150 mg OFC-I tablet (b) (4)	150 mg (b) (4)% w/w OFC-I tablet
C788-054 Bioequivalence	42 male	A single dose of 150 mg (b) (4)% w/w OFC-I tablet (AZ) 150 mg % w/w OFC tablet (Patheon)	150 mg OFC-I tablet 150 mg OFC tablet
D4300-007 PK of single and multiple ascending dose of fostamatinib	56 male (40 Japanese and 16 white)	Single Dose Japanese: 50, 100, 150, 200 mg White : 150 mg Multiple Dose Japanese: 50, 100, 150, and 200 mg, BID, 10 days White: 150 mg, BID, 10 days	50 mg (b) (4)% w/w BFC tablet
D4300-009 PK of R406 in subjects with RI compared with healthy subjects	8 with normal renal function,	A single dose of 150 mg tablet	50 mg (b) (4)% w/w BFC tablet
D4300-010 PK of R406 in subjects with varying degrees of HI and in healthy	8 healthy subjects	A single dose of fostamatinib 150 mg	50 mg (b) (4)% w/w BFC tablet

subjects.			
D4300-011 Verapamil DDI	15 male	A single dose of fostamatinib 150 mg	50 mg (b)(4)% w/w BFC tablet
D4300-012 Oral contraceptive DDI	33 female	Fostamatinib, 100 mg tablet, BID , 21 days	50 mg % w/w BFC tablet
D4300-013 Warfarin DDI	14M/1F	Fostamatinib, 100 mg tablet, BID on Days 8-20	50 mg % w/w BFC tablet
D4300-014 pioglitazone (a CYP2C8 substrate) DDI	15 male	Fostamatinib, 100 mg, BID on Days 1-8	50 mg % w/w BFC tablet
D4300-015 Rifampicin (a CYP3A4 inducer) DDI	15 male	A single dose of fostamatinib 150 mg	50 mg (b)(4)% w/w BFC tablet
D4300-016 Relative bioavailability (four-way crossover)	24 male	A single dose of 100 mg (b)(4)% w/w BFC tablet 100 mg % w/w BFC tablet (high dissolution) 100 mg (b)(4)% w/w BFC tablet (medium dissolution) 100 mg (b)(4)% w/w BFC tablet (low dissolution)	50 mg % w/w BFC tablet 100 mg (b)(4)% w/w BFC tablet
D4300-018 Relative bioavailability	24 male	A single dose of 100 mg BFC tablet 150 mg BFC tablet 100 mg (b)(4)% w/w OFC-I tablet 150 mg % w/w OFC-I tablet	50 mg (b)(4)% w/w BFC tablet 100 mg (b)(4)% w/w OFC-I tablet 150 mg (b)(4)% w/w OFC-I tablet
D4300-019 IVIVC, food effect, ranitidine DDI	28 males	A single dose of 150 mg OFC-I tablet Reference batch 150 mg OFC-I tablet Variant A 150 mg OFC-I tablet Variant B 150 mg BFC tablet	150 mg (b)(4)% w/w OFC-I tablet 50 mg (b)(4)% w/w BFC tablet
D4300-020 Bioequivalence	88 males	A single dose of 100 mg OFC-I tablet 150 mg OFC-I tablet 100 mg BFC tablet 150 mg BFC tablet	50 mg (b)(4)% w/w BFC tablet 100 mg (b)(4)% w/w OFC-I tablet 150 mg % w/w OFC-I tablet
D4300-026 Digoxin DDI	23 male	Fostamatinib ,100 mg, BID on Days 9-15	50 mg (b)(4)% w/w BFC tablet
D4300-027 absolute BA of a single oral dose of fostamatinib with respect to an IV microtracer dose of ^{14}C-R406	10 male	A single dose of 150 mg fostamatinib 100 µg solution of ^{14}C-R406 for IV infusion	50 mg (b)(4)% w/w BFC tablet

D4300-032 PK of oral fostamatinib after single and multiple doses.	24 male Japanese	A single dose of 100, 200 mg 100 or 200 mg BID, 10 days	50 mg (b)(4)% w/w BFC tablet
D4300-039 Rosuvastatin and simvastatin DDI	42M and female	Fostamatinib, 100 mg, BID on Days 1-7	50 mg (b)(4)% w/w BFC tablet

The mean (CV%) PK parameters of R406 following a single dose of the commercial 150 mg OFC tablet are estimated in the Study C788-054, as well as those of the 150 mg OFC-I tablet (Table 110). The plasma concentrations of R406 increased rapidly reaching maximum levels within 1.5 hours. Mean C_{max} and $AUC_{0\text{-}inf}$ were 550 ng/mL and 7080 ng•h/mL, respectively. The mean $t_{½}$ was about 15 hours.

Table 110: Summary of Mean PK Parameters (CV%) of R406 in Study C788-054

	150 mg OFC-I tablet Reference 1	150 mg OFC-I tablet Reference 2	150 mg OFC tablet
$AUC_{0\text{-}inf}$ (ng*h/mL)	7120 (39%)	7310 (32%)	7080 (37%)
C_{max} (ng/mL)	582 (55%)	604 (48%)	550 (57%)
T_{max} (hr)*	2 (1, 4)	2 (1, 4)	1.5 (1, 4)
$t_{1/2}$ (hr)	15 (25%)	16 (35%)	15 (28%)
Note: * Data presented are median (minimum, maximum)			

(Data Source: Table 7 on page 46 in the CSR of Study C-935788-054)

Dose Proportionality

Dose proportionality of R406 following a single dose of fostamatinib was observed in the dose range of 50 to 300 mg in healthy subjects as shown in the

Table 111. After multiple doses of fostamatinib, the exposure increased in a dose proportional manner up to 200 mg BID. Exposure was slightly higher than dose proportional at doses higher than 200 mg BID.

Table 111: Dose-Normalized C_{max} and AUC of R406 following a single dose or multiple doses of fostamatinib

Study	Dose	Dose Ratio	C_{max} Ratio	AUC Ratio
Single Dose				
C788-008	100, 200, and 300 mg white tablets	300/100	3.5	2.9
		200/100	2.5	2.7

D4300-007	50, 100, 150, and 200 mg BFC tablets	200/50	2.4	2.0
		150/50	3.8	2.8
		100/50	2.1	1.9
D4300-018	100 and 150 mg BFC tablets	150/100	1.5	1.5
D4300-020	100 and 150 mg OFC-I tablets	150/100	1.3	1.4
D4300-032	100 and 200 mg BFC tablets	200/100	2.0	1.9
Multiple Doses				
C788-013	100 and 300 mg BFC tablets BID	300/100	3.9	4.0
D4300-007	50, 100, and 200 mg BFC tablets BID	200/50	5.1	5.5
		100/50	1.8	1.8
D4300-032	100 and 200 mg BFC tablets BID	200/100	3.3	3.4

(Data Source: Table 4 on page 41 in the summary of clinical pharmacology studies)

Patient PK

Rich PK samples were collected from a subset of 12 subjects following150 mg fostamatinib BID in extension Study C788-049 after the first dose on day of the visit at Month 2. Blood samples were collected at perdose, 0.5, 1, 2, 4, 6, and 8 hours postdose. The PK parameters for R406 in 12 ITP patients were listed in the Table 112. The average C_{max} was 810 ± 289 ng/mL and the average $AUC_{0\text{-}8hr}$ was 4340 ± 1640 ng•h/mL at steady state. Inter-subject variability for R406 was 35% and 38% for C_{max} and $AUC_{0\text{-}8hr}$, respectively. The estimated $AUC_{0\text{-}12hr}$ for R406 was 5450 ± 2210 ng•h/mL, suggesting that daily exposure at steady state (AUCss) is approximately 11000 ng•h/mL.

Overall, the steady-state AUC and C_{max} estimated in this study were within the range of those observed in subjects dosed with 100 to 150 mg BID of fostamatinib in healthy volunteer studies.

Table 112: Mean PK Parameters (± SD) for R406 at Steady State in ITP Patients in Study C788-049 Following 150 mg Fostamatinib BID

	Number of Patients	Mean (± SD)
T_{max} (h)	12	2.17 ± 2.33
C_{max} (ng/mL)	12	810 ± 289
$AUC_{0\text{-}8hr}$ (ng•h/mL)	12	4340 ± 1640
$AUC_{0\text{-}12hr}$ (ng•h/mL)	10	5450 ± 2210

Sparse PK samples were collected in Study C788-047 and Study C788-048. Blood samples for PK analysis were collected within 12 hours post dose during Weeks 2, 6, and 24. An additional PK sample was collected from subjects whose dose was escalated, at the visit following dose escalation. Mean plasma R406 concentrations in Study C788-047 ranged from 300 to 537 ng/mL at Week 2, 406 to 775 ng/mL at Week 6, and 361 to 1160 ng/mL at Week 24. The mean plasma

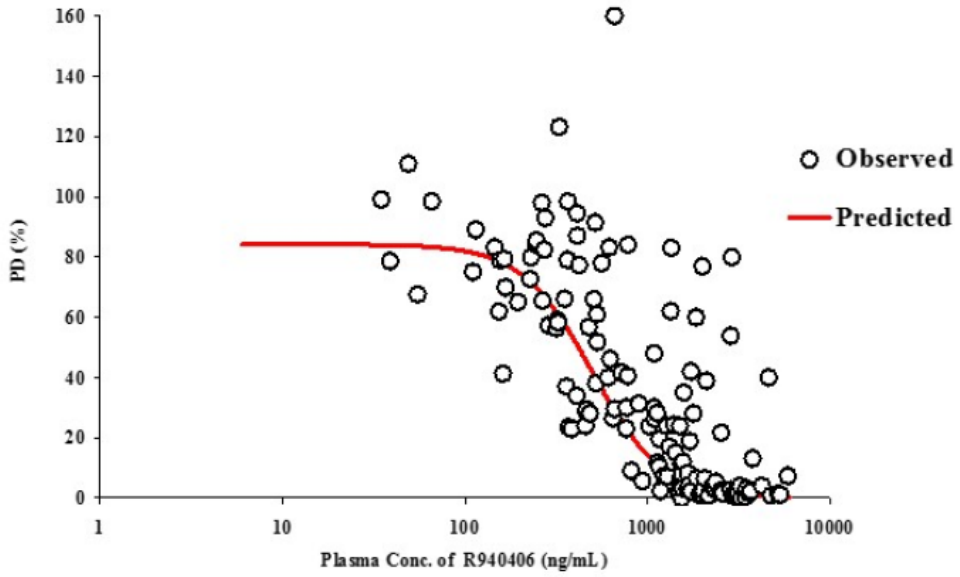
R406 concentrations in Study C788-048 ranged from 386 to 945 ng/mL at Week 2, 424 to 1700 ng/mL at Week 6, and 165 to 851 ng/mL at Week 24.The plasma concentration data of R406 in both studies were further applied in the population PK analyses.

13.4.2. Pharmacometrics Review

PK-PD

The effective concentration of R406, the active metabolite of fostamatinib, to inhibit Syk signaling was evaluated in heathy volunteers (Study C406-001). The percentage of CD63+ basophils stimulated by ex vivo anti-IgE were measured from blood samples in the healthy volunteers following administration of single oral doses at 80-600 mg and multiple doses at 100-300 mg BID. This PD effect was analyzed in relation to the plasma concentration of R406 at the corresponding time points. Using an E_{max} model, EC_{50} was estimated to be 496±42.2 ng/mL (~1.06 uM), which can be calculated to ~12,000 ng*hr/mL of daily AUC (Figure 16).

Figure 16. Correlation Between Plasma R406 Concentration and Percent Change of CD63+ Basophils in Healthy Volunteers After Single and Multiple Oral Doses of Fostamatinib



(Source: Summary of Clinical Pharmacology, Figure 3, page 57)

In the Phase 2b studies in RA patients (Studies C788-010 and C788-011), median AUC of R406 was 12,000-13,000 ng*hr/mL following 100 mg BID. In another study in RA patients (C788-006), significant decreases in MMP-3 and IL-6 were observed in the 100 mg and 150 mg BID treatment groups, but not in the 50 mg BID group. These data suggest that fostamatinib suppresses inflammatory processes in vivo at 100 mg BID or above.

Daily AUC at steady state (DAUCss) in patients with ITP was calculated using the final population PK model developed with data from Studies C788-047 and C788-049. Mean (±SD) DAUCss was 11,192 (±5,226) ng*hr/mL while mean (±SD) daily dose was 218 (±39.6) mg. There was no difference in AUC between patients with ITP and those with RA. In patients with RA, mean (±SD) DAUCss was 10,716 (±5,028) ng*hr/mL and mean (±SD) daily dose was 194 (±28.1) mg.

These results show that 100 mg dose could generate effective concentrations to inhibit Syk signaling and the exposure-response analysis also supports that the R406 exposure following administration of fostamatinib 100 mg BID has approximately 20% of probability of increasing platelet count to ≥ 50,000/uL.

General Dosing and Therapeutic Individualization

Over the course of the 24-week treatment period in both placebo-controlled Phase 3 studies, subjects were expected to visit the clinic 13 times. Safety assessments and platelet counts were performed at each visit to evaluate the safety and efficacy of fostamatinib/placebo, and to determine if a dose adjustment was necessary. From Week 4, the initial dose of fostamatinib 100 mg BID was increased to 150 mg BID on platelet count and tolerability. If dose-limiting adverse events were observed, the dose level was reduced to as low as 100 mg QD. Dose increase from 100 mg BID to 150 mg BID was required in majority of subjects randomized to fostamatinib. However, fostamatinib-induced hypertension was observed and it has a significant relationship with R406 exposure. Hypertension did not last long upon discontinuation of fostamatinib in clinical trials including those in patients with RA. Although hypertensive occurred in only one subject with ITP, the sample size was too small to predict its incidence in post-marketing setting.

Does the available clinical pharmacology information provide supportive evidence of effectiveness in immune thrombocytopenia (ITP)?

Yes. Daily AUC at steady state ($DAUC_{ss}$) in patients with ITP was calculated using the final population PK model developed with data from Studies C788-047 and C788-049. Mean (±SD) $DAUC_{ss}$ was 11,192 (±5,226) ng*hr/mL while mean (±SD) daily dose was 218 (±39.6) mg. The daily exposure was close to the estimated EC50 for inhibition of Syk signaling in healthy volunteers, which could be generated by 100 mg BID in patients with ITP.

Moreover, there is a notable exposure-response relationship between R406 concentration and response for platelet count ≥50,000/uL at Week 12. Even though dose was adjusted (mainly increased) based on platelet count from Week 4, the relationship was still significant.

Should the higher initial dosing regimen of 150 mg twice daily be recommended for the general population?

Not necessarily. During the treatment period in Study C788-47, dose was increased from 100 mg BID to 150 mg BID in 44 out of 50 subjects, then decreased back to 100 mg BID in 7 out of those 44 subjects, again decreased to 150 mg QD in 2 out of the 7 subjects. In Study C788-48, dose was increased from 100 mg BID to 150 mg in 44 out of 49 subjects, and decreased back to 100 mg BID in 5 out of those 44 subjects, again decreased to 150 mg QD followed by 100 mg QD in 1 out those 5 subjects. Overall, dose was increased and maintained at 150 mg BID in 75% of subjects (37/51 in C788-47 and 39/50 in C788-48) during the treatment.

Considering dose escalation occurred in majority of those subjects at Week 4, an alternative initial dose of 150 mg BID could be considered for potential clinical benefit, especially in those have lower baseline platelet count. From the reviewer's analysis, subjects who required to increase dose to 150 mg BID at Week 4 tended to have lower baseline platelet count (~15,000/uL) compared to that in subjects who maintained 100 mg BID at Week 4 (~22,000/uL).

However, exposure-safety analysis for blood pressure indicates that increases in both diastolic and systolic blood pressure are expected with increasing R406 concentration. Higher incidence of hypertension was observed in fostamatinib arm (20.6%) compared to placebo arm (4.2%). Although the incidence of hypertensive crisis that required dose adjustment was rare (1.1%) from the Phase 3 studies, considering small number of subjects enrolled in the Phase 3 studies, it is hard to predict the increase in risk for hypertensive crisis by increased initial dose, especially who are vulnerable to hypertensive crisis.

Fostamatinib is indicated for adults with chronic ITP that lasts longer than 6 months and requires long-term treatment, while acute form of ITP may require an urgent care such as transfusion of platelet concentrate. Moreover, there was no difference in stable response between during Weeks 2-12 and during Weeks 14-24 in the Phase 3 studies (16% vs. 18% in pooled studies, Table 113).

Table 113. Incidence of Stable Response

	C788-047		C788-048		Pooled Studies	
	Placebo (N = 25)	Fostamatinib (N = 51)	Placebo (N = 24)	Fostamatinib (N = 74)	Placebo (N = 49)	Fostamatinib (N = 101)
During Weeks 2 – 12						
Stable Responder	0/25	6/51 (12%)	1/24 (4%)	10/50 (20%)	1/49 (2%)	16/101 (16%)
Non-Responder	25/25 (100%)	45/51 (88%)	23/24 (96%)	40/50 (80%)	48/49 (98%)	85/101 (85%)
Difference (95% CI)	12% (3%, 21%)		16% (2%, 30%)		14% (6%, 22%)	
During Weeks 14 – 24						
Stable Responder	0/25	9/51 (18%)	1/24 (4%)	9/50 (18%)	1/49 (2%)	18/101 (18%)
Non-Responder	25/25 (100%)	42/51 (82%)	23/24 (96%)	41/50 (82%)	48/49 (98%)	85/101 (82%)
Difference (95% CI)	18% (7%, 28%)		14% (0%, 27%)		16% (7%, 24%)	

(Source: Summary of Clinical Efficacy, Table 28, page 71)

It should be also noted that 50% of stable responders (4/9 in C788-47, 5/9 in C788-48) continued to receive the initial dose 100 mg BID without dose escalation. Overall data suggest that potential benefit from initiating treatment at 150 mg BID may not be great enough to compensate the increased risk for hypertensive crisis compared to initiating treatment at 100 mg BID then escalating dose to 150 mg BID at Week 4 based on platelet count.

Applicant's Analysis

Population PK Analysis

The analysis dataset included 330 measurements from 113 patients with ITP (44 males and 69 females) from 3 phase 3 studies and received daily doses of 100 to 300 mg fostamatinib. The median age [range] was 53 [20, 88] years, and the median body weight [range] was 79 [47.2, 204] kg. First, the final population PK model was developed in healthy subjects and RA patients (N=2413) and then rerun after incorporating ITP patient data. There was no substantial change in parameter estimates with and without the ITP patient data (Table 114).

Table 114. Comparison of R406 PK Between Patients with RA and those with ITP

	RA Subjects					ITP Subjects				
	Daily Dose (mg)	Weight (kg)	CL (L/h)	V2 (L)	DAUCss (ng*h/mL)	Daily Dose (mg)	Weight (kg)	CL (L/h)	V2 (L)	DAUCss (ng*h/mL)
All doses										
N	1994	1994	1994	1994	1994	113	113	113	113	113
Mean	194	73.5	21.3	499	10716	218	80.5	22.0	537	11192
SD	28.1	18.0	8.88	185	5028	39.6	24.7	7.44	210	5226
Min	100	35	4.90	105	1295	150	47.2	6.53	278	4441
Median	200	70.5	19.98	467	9657	200	79	21.2	486	9971
Max	300	165	88.58	1711	43771	300	204	45.0	1523	45907

(Source: RIG-04-16, Table 3, page 14)

Second, the final population PK model was fitted to the ITP data after all model parameters were fixed to the population values, except for the inter-individual variability terms. As in the first approach, the individual predicted concentrations were highly correlated with the observed concentrations. In the covariate analysis, body weight was found to be a significant covariate on clearance and volume of distribution. The allometric exponents for clearance and volume of distribution were 0.662, and 1.23, respectively. The median AUC at steady state were 7232, 5183, and 3936 ng*hr/mL for subjects with body weight <50 kg, 50-90 g, and >90 kg, respectively.

Table 115. Summary Statistics of Estimated R406 PK Parameters in ITP Patients

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

(Source, RIG-04-16, Table 4, page 15)

Reviewer's comments: The results from the population PK analysis suggest that weight-based dosing may be desirable for fostamatinib targeting similar exposure across subjects with various body weight. However, doses are adjusted based on each patient's response, weight-based dosing does not seem to be practically beneficial to clinical outcomes. As shown in **Table 115**, *there was no difference in body weight between subjects who received 100 mg BID and those*

who received 150 mg BID, although patients who received 150 mg showed exactly 50% higher exposure than those who received 100 mg BID. Considering that dose was escalated based on each patient's response, the results indicate that baseline characteristics such as baseline platelet count may play an important role than exposure itself. If the exposure was a driving factor for dose escalation, then there would have been difference in body weight between subjects who escalated dose to 150 mg BID and those who maintained 100 mg BID.

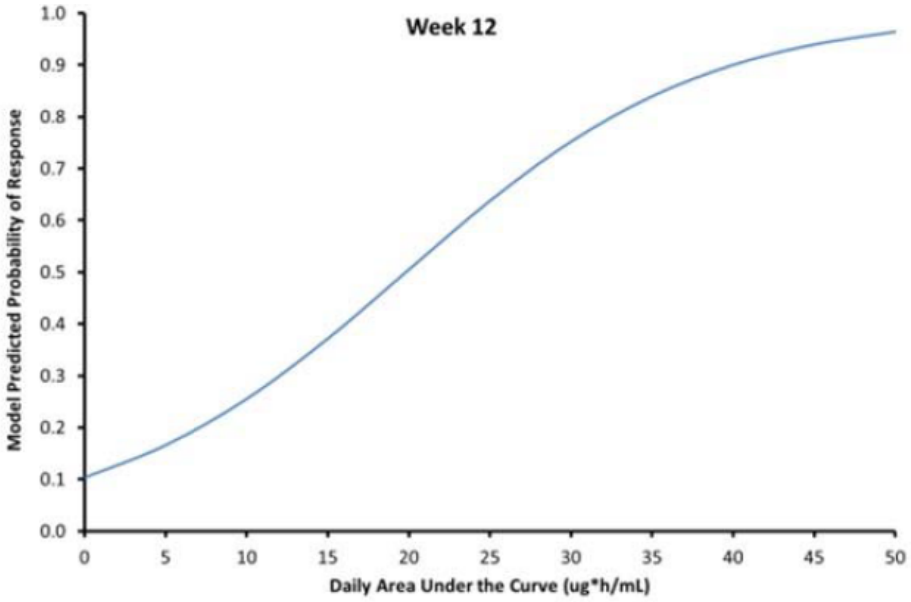
Exposure-Response Analysis

Exposure-Response for Primacy Efficacy Endpoints

The ER for efficacy was based on data from 2 Phase 3 studies in ITP patients. Platelet counts on Week 12, 14-24, and 24 were used as the efficacy endpoint. A total of 79 subjects (30 males and 49 females) of whom 27 subjects received placebo and 52 subjects received daily doses of 200 mg (100 mg BID) or 300 mg (150 mg BID) were included in the Week 12 analysis. A limited number of subjects were available for Weeks 14-24 (N=33) and Week 24 (N=27) analyses.

The exposure variable, daily AUC at steady state was calculated using clearance estimates from the final population PK model, which were then incorporated into the PK/PD datasets. Logistic regression for responding status at Week 12 show that the probability of achieving a target increase of ≥50,000/uL at Week 12 increases as R406 concentration increases (Figure 17). The applicant did not found any covariate which was a significant predictor of probability of response at Week 12.

Figure 17. Logistic Regression for Response at Week 12



(Source: Summary of Clinical Pharmacology, Figure 4, page 60)

Due to the small number of subjects and high variability in the platelet count, the relationship between exposure and probability of achieving the target increase at Weeks 14-24 or Week 24 could not be achieved. None of the applicant's attempted models including semi-mechanistic, direct response, and indirect response model were successful for the platelet count analysis as a continuous variable.

The applicant concluded that higher R406 exposure increased the likelihood of achieving a clinical response at Week 12, but not later. The variability in response to fostamatinib in ITP patients could not be solely attributed to PK variability among patients.

Exposure-Response for Primacy Safety Endpoints

The ER for safety was based on data from 5 Phase 2 and 3 studies in patients with RA and 2 phase 3 studies in patients with ITP. A total of 2435 patients of whom 878 received placebo and the remaining 1657 received repeated daily doses of 100 to 300 mg of fostamatinib. The safety variables included blood pressure, liver enzymes (ALT, AST), bilirubin, and absolute neutrophil count (ANC).

The results indicate that changes in AST, ALT, and bilirubin are not likely to increase as R406 concentration increases. The changes in ANC and neutrophil count were not clinically meaningful. However, blood pressure tended to increase as R406 concentration increases and the estimated E_{max} and EC_{50} were 10.2 mmHg and 16300 ng*hr/mL for systolic blood pressure, 9.21 mmHg and 17000 ng*hr/mL for diastolic blood pressure, respectively. Daily AUC following 150 mg BID is expected to be similar with those estimated EC_{50}.

Preclinical study results suggest that increase peripheral vascular resistance is a primary mechanism of fostamatinib-induced blood pressure elevation. It is hypothesized that the increased vascular resistance is a consequence of impaired vasorelaxation, resulting from reduced endothelial nitric oxide availability. This hypothesis is also applied to other kinase inhibitors whose pharmacological profiles are similar with fostamatinib, e.g., inhibition of VEGFR2.

Reviewer's Analysis

Introduction

Since dose was escalated up 150 mg BID from 100 mg BID in majority of subjects at Week 4, potential baseline characteristics that required a higher dose were investigated to evaluate the adequacy of the proposed initial dosing.

Objectives

- To compare distribution of baseline platelet counts by subjects whose dose was escalated to 150 mg BID at Week 4 or not.

Datasets

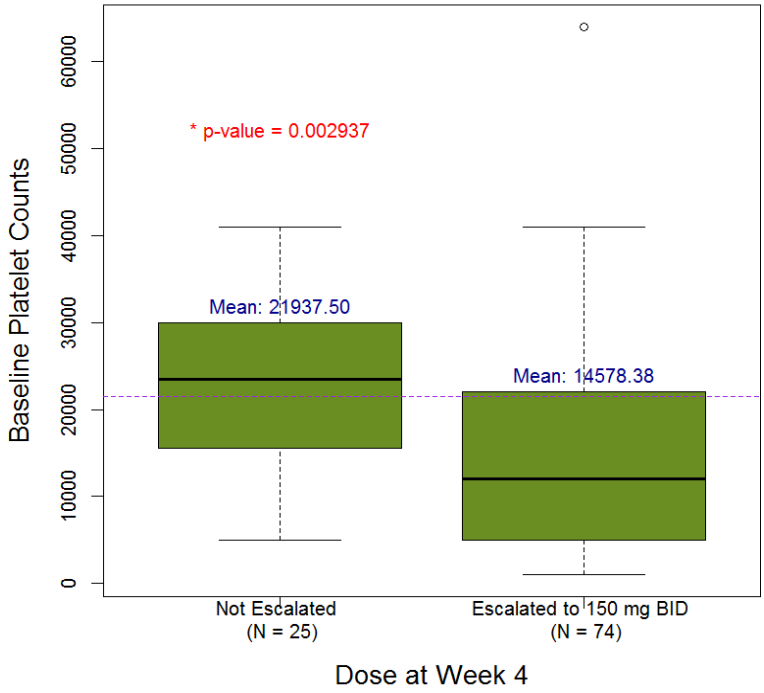
Datasets utilized for the analysis are summarized in below.

Study Number	Name	Link to EDR
ISE IPT Efficacy	Adeff.xpt	//CDSESUB1/evsprod/NDA209299/0001/m5/datasets/ise-itp/analysis/adam/datasets
ISE ITP Dosing	Adex.xpt	//CDSESUB1/evsprod/NDA209299/0001/m5/datasets/ise-itp/analysis/adam/datasets

Results

There was a significant difference in baseline platelet count between subjects who stayed at 100 mg BID (~22,000/uL) and those who increase dose to 150 mg BID (~15,000/uL) at Week 4. It is not surprising that subjects with lower platelet count are more prone to dose escalation for efficacy. The result suggests there is a potential benefit of higher initial dose in patients with lower platelet count (Figure 18). However, the benefit should be assessed in relation to potential risk associated with higher exposure.

Figure 18. Distribution of Baseline Platelet Count



(Source: Reviewer's analysis)

14 Division Director (DHOT)

X

John Leighton, PhD

15 Division Director (OCP)

X

NAM Atiqur Rahman, PhD

16 Division Director (OB)

X

Rajeshwari Sridhara, PhD

17 Division Director (Clinical)

Immune thrombocytopenia is a severe life-threatening sometimes fatal disorder characterized by immunologic destruction of platelets and decreased platelet production resulting in thrombocytopenia and a predisposition to bleeding. Despite availability of approved products and use of labeled and off-label strategies (including chemotherapeutic agents), a need for additional products exists. Fostamatinib is a prodrug of the active compound R940406 which is an orally active, ATP competitive, small molecule inhibitor of spleen tyrosine kinase. Fostamatimib is postulated to act through a reduction of FcγR-mediated platelet destruction and elimination. Fostamatinib resulted in durable platelet responses in adult patients with chronic ITP in two randomized trials and an extension trial. No data was provided on pediatric usage. Diarrhea and hypertension were the two most common adverse reactions in clinical trials followed by nausea, dizziness, hepatotoxicity (transaminase elevation), infection, rash, pain, fatigue and neutropenia. Febrile neutropenia was reported in 6% of fostamatinib-treated patients. Nonclinical studies identified embryofetal lethality and decreased fetal weights at high doses. Teratogenic effects were observed in both species in the form of soft tissue and skeletal abnormalities. Therefore, the label will advise females of reproductive potential to use effective contraception during treatment and for at least 1 month following the last dose of the drug. Additionally, the Clinical Pharmacology review recommended that a dose reduction is recommended when concomitantly taking a strong CYP3A inhibitor and avoidance of concomitant use with fostamatinib is recommended when concomitantly taking a strong CYP3A inducer. Two Chemistry, Manufacturing and Controls post marketing commitments will be in the approval letter one for a test method for (b) (4) and hardness for the drug product and a second for elemental impurities and submit the data to FDA.

The application did not have data on patient-reported outcomes.

X

Ann. T. Farrell, MD

18 Office Director (or designated signatory authority)

Richard Pazdur, MD

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/s/

RACHEL S MCMULLEN
04/16/2018

HYON-ZU LEE
04/16/2018

BRIAN D CHOLEWA
04/17/2018

CHRISTOPHER M SHETH
04/17/2018

JOHN K LEIGHTON
04/17/2018

RUNYAN JIN
04/17/2018

JEE E LEE
04/17/2018

QI LIU
04/17/2018

JIANG LIU
04/17/2018

NAM ATIQUR RAHMAN
04/17/2018
I concur.

STELLA W KARURI
04/17/2018

YUAN L SHEN
04/17/2018

RAJESHWARI SRIDHARA
04/17/2018

KATHY M ROBIE SUH
04/17/2018

Cross-Discipline Team Leader Memorandum

Date	April 17, 2018
From	Kathy M. Robie-Suh, M.D., Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 209299
Applicant	Rigel Pharmaceuticals, Inc.
Date of Submission	April 15, 2017; received April 17, 2017
PDUFA Goal Date	April 17, 2018
Proprietary Name / **Established (USAN) names**	Tavalisse/ fostamatinib
Dosage forms / Strength	Oral tablet/ 100 mg and 150 mg
Proposed Indication(s)	For the treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment
Recommended:	Approval

The Cross-Discipline Team Leader Review for the application is incorporated as part of the Multidisciplinary Review and Evaluation which has been entered into DARRTS.

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/s/

KATHY M ROBIE SUH
04/17/2018

NDA 209299

Division Director Review is part of the unireview

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/s/

ANN T FARRELL
04/16/2018

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 209299
Supplement #:	NME
Drug Name:	Tavalisse ™ (fostamatinib)
Indication(s):	Treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.
Applicant:	Rigel Pharmaceuticals, Inc.
Date(s):	April 15, 2017
Review Priority:	Standard
Biometrics Division:	Division of Biometrics V
Statistical Reviewer:	Stella Karuri, Ph.D.
Concurring Reviewers:	Yuan-Li Shen, Ph.D., Team Leader
	Rajeshwari Sridhara, Ph.D., Division Director
Medical Division:	Division of Hematology Products
Clinical Team:	Hyon-Zhu Lee, M.D., Kathy Robie Suh, M.D.,
	Anne Farrell, M.D.
Project Manager:	Rachel McMullen

The statistical review is complete and has been added to the Multidisciplinary Review and Evaluation. Refer to the Multidisciplinary Review and Evaluation for additional details. From a statistical standpoint, this NDA is acceptable to support approval.

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/s/

STELLA W KARURI
03/01/2018

YUAN L SHEN
03/05/2018

Clinical Memorandum

Application Type	New Drug Application (NDA)
Application Number	209299
Priority or Standard	Standard
Submit Date	April 17, 2017
Received Date	April 17, 2017
PDUFA Goal Date	April 17, 2018
Division/Office	DHP/OHOP
Reviewer Name	Hyon-Zu Lee, Pharm.D.
Team Leader	Kathy Robie-Suh, M.D., Ph.D.
Review Completion Date	December 15, 2017
Established Name	Fostamatinib
Trade Name	Tavalisse
Applicant	Rigel Pharmaceuticals, Inc.
Formulation	Tablet
Dosing Regimen	The initial dose of fostamatinib is 100 mg orally twice daily. After 4 weeks increase to 150 mg twice daily if platelet count has not increased to at least 50 x 10^9/L
Applicant Proposed Indication/Population	Treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.
Recommendation on Regulatory Action	Approval
Recommended Indication/Population (if applicable)	Treatment of thrombocytopenia in adult patients with chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment.

The clinical review is complete and has been added to the Multidisciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

HYON-ZU LEE
02/26/2018

KATHY M ROBIE SUH
02/26/2018

MEMORANDUM

Date: December 29, 2017
From: Christopher M. Sheth, PhD
Nonclinical Pharmacology/Toxicology Supervisor
Division of Hematology Oncology Toxicology (DHOT)
for Division of Hematology Products (DHP)
To: NDA 209299 Tavalisse (fostamatinib)
Re: Nonclinical Secondary Review

Nonclinical Pharmacology/Toxicology Secondary Review is complete. There are no nonclinical issues that would prevent approval of this application. My recommendation for this application is it's approvable from the perspective of Pharmacology/Toxicology.

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/s/

CHRISTOPHER M SHETH
12/26/2017

MEMORANDUM

Date: December 20, 2017
From: Brian Cholewa, PhD
Nonclinical Reviewer
Division of Hematology Oncology Toxicology (DHOT)
for Division of Hematology Products (DHP)
Through: Christopher M. Sheth, PhD
Nonclinical Supervisor
To: NDA 209299 Fostamatinib
Re: Nonclinical Review

Fostamatinib is a kinase inhibitor that binds spleen tyrosine kinase indicated for the treatment of adult patients with chronic immune thrombocytopenia who have had an insufficient response to a previous treatment. The nonclinical review is complete and has been added to the Multidisciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Refer to the Multi-disciplinary Review and Evaluation for additional details. There are no nonclinical issues that would prevent approval of this application.

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/s/

BRIAN D CHOLEWA
12/26/2017

CHRISTOPHER M SHETH
12/26/2017

Office of Clinical Pharmacology Memo

NDA or BLA Number	209299
Link to EDR	\\CDSESUB1\evsprod\NDA209299\0001
Submission Date	4/15/2017
Submission Type	Standard
Brand Name	Tavalisse
Generic Name	Fostamatinib
Dosage Form and Strength	Tablets: 150 mg, 100 mg
Route of Administration	Oral
Proposed Indication	For the treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment
Proposed Dosing Regimen	Initially 100 mg taken orally twice daily; after a month, if platelet count has not increased to ≥ 50 x 10^9/L, increase dose to 150 mg twice daily
Applicant	Rigel Pharmaceuticals Inc
Associated IND	74939
OCP Review Team	Runyan Jin, Ph.D., Jee Eun Lee, Ph.D., Jiang Liu, Ph.D., Qi Liu, Ph.D.
OCP Final Signatory	Nam Atiqur Rahman, Ph.D. Division Director Division of Clinical Pharmacology V

The Office of Clinical Pharmacology (OCP) review is complete and has been added to the NDA 209299 Multidisciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. Based on our analyses of the submitted PK, efficacy, and safety data, our recommendation for this application is approvable from a clinical pharmacology perspective.

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/s/

RUNYAN JIN
12/14/2017

QI LIU
12/14/2017

JEE E LEE
12/14/2017

JIANG LIU
12/14/2017

NAM ATIQUR RAHMAN
12/14/2017
I concur.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	209299
Supporting document/s:	1
Applicant's letter date:	4/17/2017
CDER stamp date:	4/17/2017
Product:	Fostamatinib
Indication:	Immune Thrombocytopenic Purpura (ITP)
Applicant:	Rigel Pharmaceuticals Inc.
Review Division:	Division of Hematology Oncology Toxicology (for Division of Hematology Products)
Reviewer:	Brian Cholewa, PhD
Supervisor/Team Leader:	Christopher M. Sheth, PhD
Division Director:	John Leighton, PhD Ann Farrell, MD (DHP)
Project Manager:	Rachel McMullen, MPH, MHA

- 1 Executive Summary

1.1 Introduction

Fostamatinib (R935788) is a prodrug that rapidly metabolizes to the active compound R940406 [R406]). R406 is a small molecule spleen tyrosine kinase (SYK) inhibitor. SYK plays a role in the immune system by mediating signal transduction of Fc-activating receptors and is involved in B-cell maturation. NDA 209299 seeks approval of Tavalisse (fostamatinib) taken orally at a maximum dose of 300 mg/day in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment. In support of this application the Sponsor has provided the final report for the following carcinogenicity studies:

- G-935788-0015 - R788 NA: “A 104-Week Oral Gavage Carcinogenicity Study in Mice”
- G-935788-0013 - R788 NA: “A 104-Week Oral Gavage Carcinogenicity Study in Rats”

1.2 Brief Discussion of Nonclinical Findings

The carcinogenic potential of fostamatinib was studied in 104-week studies in the rat and mouse. In Crl:CD1(ICR) mice, fostamatinib was administered by oral gavage (dose volume of 10/5 mL/kg) twice daily at doses of 50, 150, 500/250, or 1200 mg/kg/day and compared to vehicle or water control. In Crl:CD(SD) rats, fostamatinib was administered by oral gavage (dose volume of 10 mL/kg) twice daily at doses of 10, 25, 45, or 80 mg/kg/day in males, and 5, 12, 24, or 40 mg/kg/day in females and compared to vehicle control.

In mice, fostamatinib administered at 1200 mg/kg/day was terminated on Day 14 for males and Day 44 for females due to toxicity and mortality. Terminal sacrifice for the 500/250 mg/kg/day dose was conducted on Day 555 for males and Day 494 for females after reaching 15 surviving animals. At terminal sacrifice, the lower doses had a survival rate that was similar to controls but the FDA survival analysis did show a statistically significant dose response relationship in mortality across two controls and treated groups in both male and female mice.

In rats, fostamatinib administered to males at 80 mg/kg/day exceeded the maximum tolerated dose and animals were euthanized on Day 95. Dosing was ceased for females administered 40 mg/kg/day on Day 410 due to rapidly decreasing survival. Dosing was ceased on Day 612 for males administered 45 mg/kg/day and on Day 619 for females administered 24 mg/kg/day after reaching 20 surviving animals. At terminal sacrifice, the lower doses had a survival rate that was similar to controls but the FDA survival analysis showed a statistically significant dose response relationship in mortality in

males and females.

The Sponsor did not find any statistically significant increases in neoplasms in either species; however, the FDA's analysis showed statistically significant positive dose-repose relationships in hemangioma in ovaries in female mice (p=0.0062) when the water control or the vehicle control was used in the analysis. The pairwise comparisons of this tumor type incidence rates against the water control and vehicle controls separately were statistically significant for 500/250 mg/kg/day dose groups (p=0.0429). The exposure (AUC_{0-6}) of female mice administered fostamatinib at 500 mg/kg/day was 52010 and 42282 ng*h/mL on Days 1 and 91, respectively. Of note, toxicokinetic sampling occurred prior to the administration of the second dose.

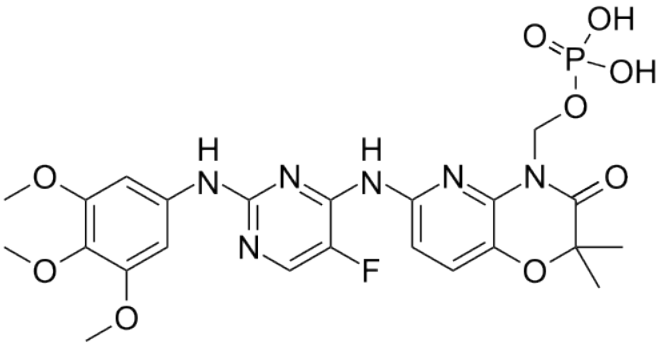
Exposure to the active metabolite of fostamatinib, R406 (C_{max} and AUC_{0-t}), had gender and species related differences. In mice, exposure was markedly higher in males than in females at lower doses (50 mg/kg/day) but the differences were attenuated at higher doses. In contrast, when fostamatinib was administered to rats, females had a higher exposure than males. There was no apparent accumulation of fostamatinib in either species.

With respect to the dose in which a statistically significant increase in hemangioma in ovaries was observed in mice (500 mg/kg/day) by FDA analysis, the more conservative measurement of AUC_{0-6} (actual dose 250 mg/kg) on day 91 (last reported level, $AUC_{0-\infty}$ not provided) was 42282 ng*h/mL, which is ~6 fold greater than the mean $AUC_{0-\infty}$ level of 7080 ng•h/mL in humans following oral dosing of 150 mg. In humans, R406 accumulates approximately 2- to 3-fold upon twice daily dosing at 100–200 mg. Overall, these data suggest a potential concern for the carcinogenic potential of fostamatinib to result in hemangioma in ovaries at relevant human exposures.

2 Drug Information

2.1 Drug

CAS Registry Number	901119-35-5
Generic Name	Fostamatinib (R935788)
Chemical Name	Phosphoric acid mono-{6-[5-fluoro-2-(3,4,5-trimethoxyphenylamino)-pyrimidin-4-ylamino]-2,2-dimethyl-3-oxo-2,3-dihydro-pyrido[3,2-b][1,4]oxazin-4-ylmethyl} ester-, disodium salt, hexahydrate
Molecular Formula/ Molecular Weight	$C_{23}H_{24}FN_6Na_2O_9P.6H_2O$

Structure or Biochemical Description	
Pharmacologic class	Kinase inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

- Primary nonclinical review and SPAs for the carcinogenicity studies were performed under IND (b) (4) submitted to DPARP.
- IND 074939 was the original IND submitted to DHP for the indication of ITP.

2.7 Regulatory Background

- As reported under IND (b) (4), the initial IND for R935788 was submitted to the Division by Rigel Pharmaceuticals on 9/20/2005. The drug development program was taken over by AstraZeneca in April, 2010. AstraZeneca decided not to proceed with regulatory filings for Fostamatinib and returned the rights to the compound to Rigel on 6/11/13.
- Following the previous report, there are two active commercial INDs ((b) (4) and (b) (4) and two active research INDs ((b) (4) and (b) (4)).

8 Carcinogenicity

Study Title: 104-Week Oral Gavage Carcinogenicity Study in Mice

Study no.:	G-935788-0015
Study report location:	eCTD 4.2.3.4.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	December 4, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Fostamatinib; TYKRK002, RM03L027A0, LTRGGA1005; 97.8%, 99.0%, 99.3%

Adequacy of Carcinogenicity Studies:

- Dose levels were concurred by ECAC.

Appropriateness of Test Models:

- The study evaluated four doses of fostamatinib based 4- and 13-week studies. The MTD was not reached in previous studies, thus the high dose was selected to reach a saturated exposure and was expected to hit a target AUC of ~600,000 ng*h/mL.
- The study report provided sufficient histopathology data from the designated organs and tissues to evaluate both the non-neoplastic and neoplastic effects at all dose levels that did not exceed the MTD. Additionally, data on survival, body weights, and toxicokinetics were provided.

Evaluation of Tumor Findings:

Key Study Findings

- The FDA tumor analysis showed statistically significant positive dose-repose relationships in hemangioma in ovaries in female mice (p=0.0062) when the water control or the vehicle control was used in the analysis.
- The FDA survival analysis demonstrated a statistically significant dose response relationship in mortality across two controls and treated groups in both male and female mice (p<0.001).
- Exposure to fostamatinib at lower doses (50 mg/kg/day) was markedly higher in males than in females but the gender differences decreased as doses increased.

Methods

Doses:	0, 50, 150, 500/250, or 1200 mg/kg/day
Positive Control:	None
Frequency of dosing:	Twice daily for 728 days
Dose volume:	10/5 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.1% Carboxymethylcellulose Sodium, 0.1% Methylparaben Sodium and 0.02% Propylparaben Sodium in Purified Water (w/w)
Basis of dose selection:	Results of 4 and 13-week study
Species/Strain:	Crl:CD1(ICR) mice
Number/Sex/Group	60/sex/group
Age:	~9 weeks
Animal housing:	Individually housed in wire-mesh cages
Paradigm for dietary restriction:	Food and water available *ad libitum*
Dual control employed:	None
Interim sacrifice:	Not conducted

Observations and times:

Mortality:	Twice daily with the addition of an evening mortality

	check after Week 53
Clinical signs:	Detailed observations performed weekly, cageside observations performed twice daily.
Body weights:	Once weekly
Food consumption:	Once weekly for 14 weeks, every two weeks until Week 28, every 4 weeks thereafter
Hematology:	Not conducted
Urinalysis:	Not conducted
Gross pathology:	At necropsy on main study animals
Histopathology:	Conducted for all main study animals

Study Design

Group Assignments			
Group Number	Dose Level (mg/kg/day)	Number of Animals	
		Male	Female
	Main Study		
1	0 (Water Control)	60	60
2	0 (Vehicle Control)	60	60
3	50	60	60
4	150	60	60
5	500/250	60	60
6	1200	60	60
7 [a]	NA	25	25
	Toxicokinetic		
8	0 (Water Control)	12+3	12+3
9	0 (Vehicle Control)	12+3	12+3
10	50	72+6	72+6
11	150	72+6	72+6
12	500/250	72+6	72+6
13	1200	72+6	72+6

[a]Sentinel animals included for health screening purposes

Results

Mortality

- Fostamatinib administered at 1200 mg/kg/day was terminated on Day 14 for males and Day 44 for females due to toxicity and mortality. Terminal sacrifice for the 500/250 mg/kg/day dose was conducted on Day 555 for males and Day 494 for females after reaching 15 surviving animals. Survival of animals at the lower doses of 50 and 150 mg/kg/day were generally similar to controls, although males administered 150 mg/kg/day had a lower survival rate when compared to male controls.

Table 1 Survival of rats in the 2-year carcinogenicity study

	Males				Females			
Dose (mg/kg/day)	**0 Water**	**0 Vehicle**	**50**	**150**	**0 Water**	**0 Vehicle**	**50**	**150**
Animals initially in study	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Animals surviving to terminal necropsy	26 43%	32 53%	27 45%	22 37%	23 38%	23 38%	27 45%	32 53%

Clinical Signs

- Primary clinical observations included teeth broken, teeth cut, malocclusion, and limb function impairment. Clinical signs were observed across all male dose groups but with a higher incidence occurring in the high dose females, although observations in females did not occur in a dose dependent manner.

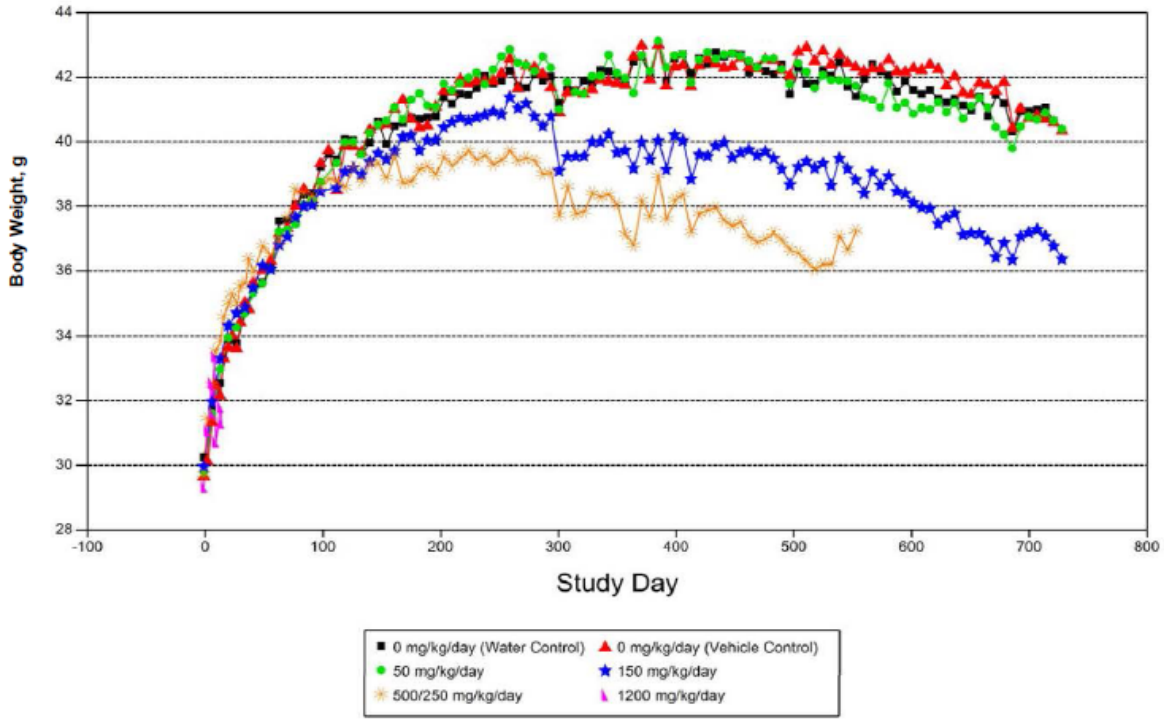
Table 2 Summary of clinical observations

	Males					Females				
Dose (mg/kg/day)	**0 Water**	**0 Vehicle**	**50**	**150**	**0 Water**	**0 Vehicle**	**50**	**150**	**0 Water**	**0 Vehicle**
Teeth Broken	50/1	27/1	93/3	125/5	20/10	54/2	57/2	0/0	76/8	1428/44
Teeth Cut	148/12	440/23	460/46	869/45	13/5	300/13	395/10	200/11	344/19	1434/59
Malocclusion	22/1	399/7	472/8	444/10	20/5	189/4	350/5	114/2	155/5	384/6
Limb function impaired	13/6	4/2	14/5	74/14	2/1	218/3	0/0	0/0	80/9	245/19

Body Weights

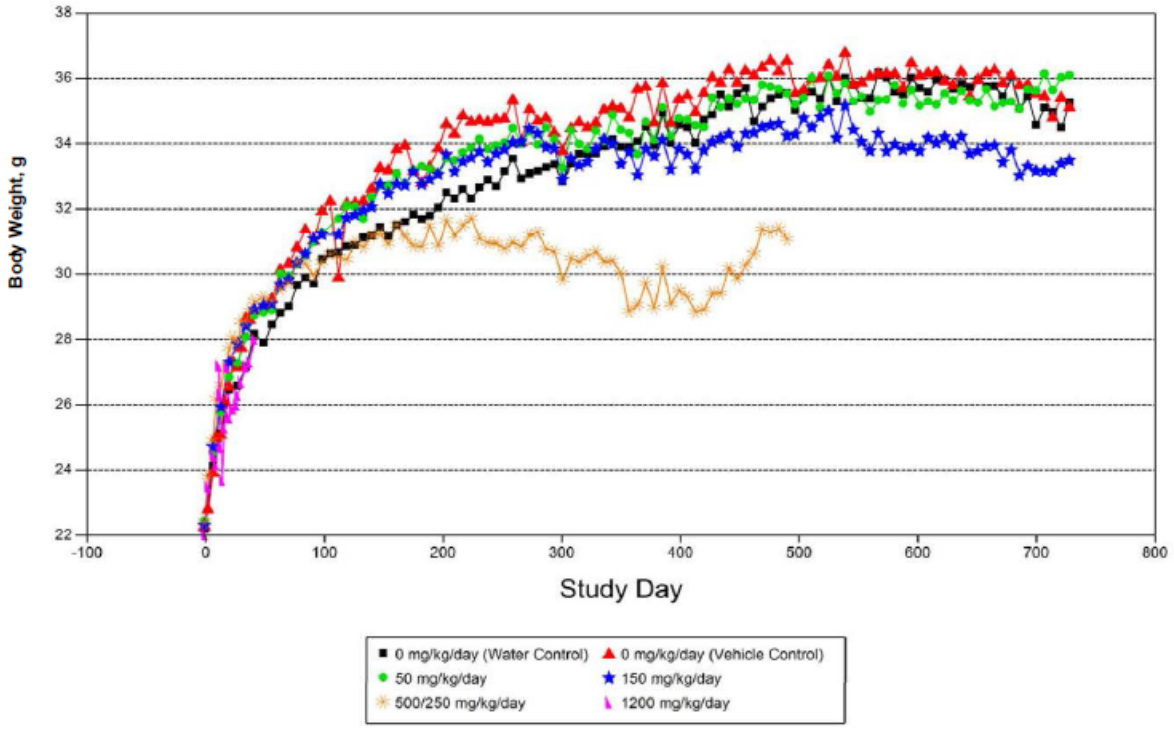
- Body weights of both males and females administered 150 and 500/250 mg/kg/day fostamatinib were considerably decreased when compared to controls.

Figure 1 Male body weight data



(Excerpted from Sponsor NDA)

Figure 2 Female body weight data

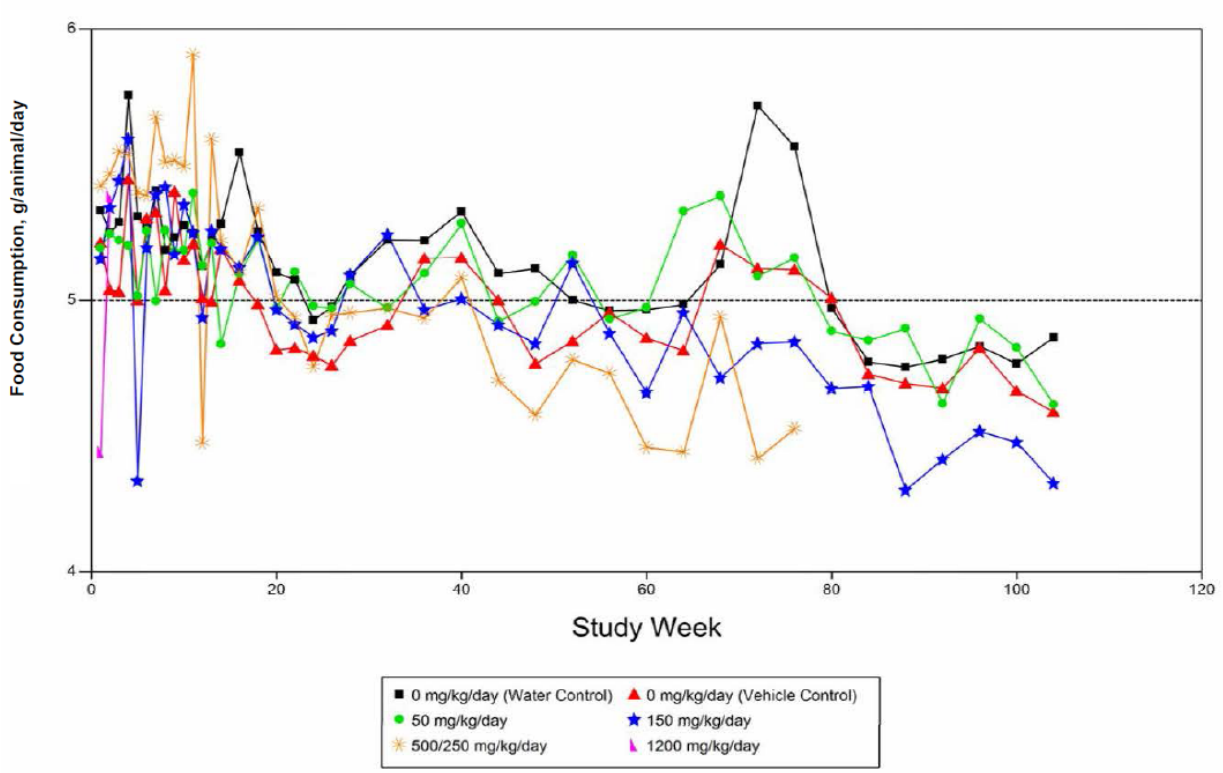


(Excerpted from Sponsor NDA)

Food Consumption

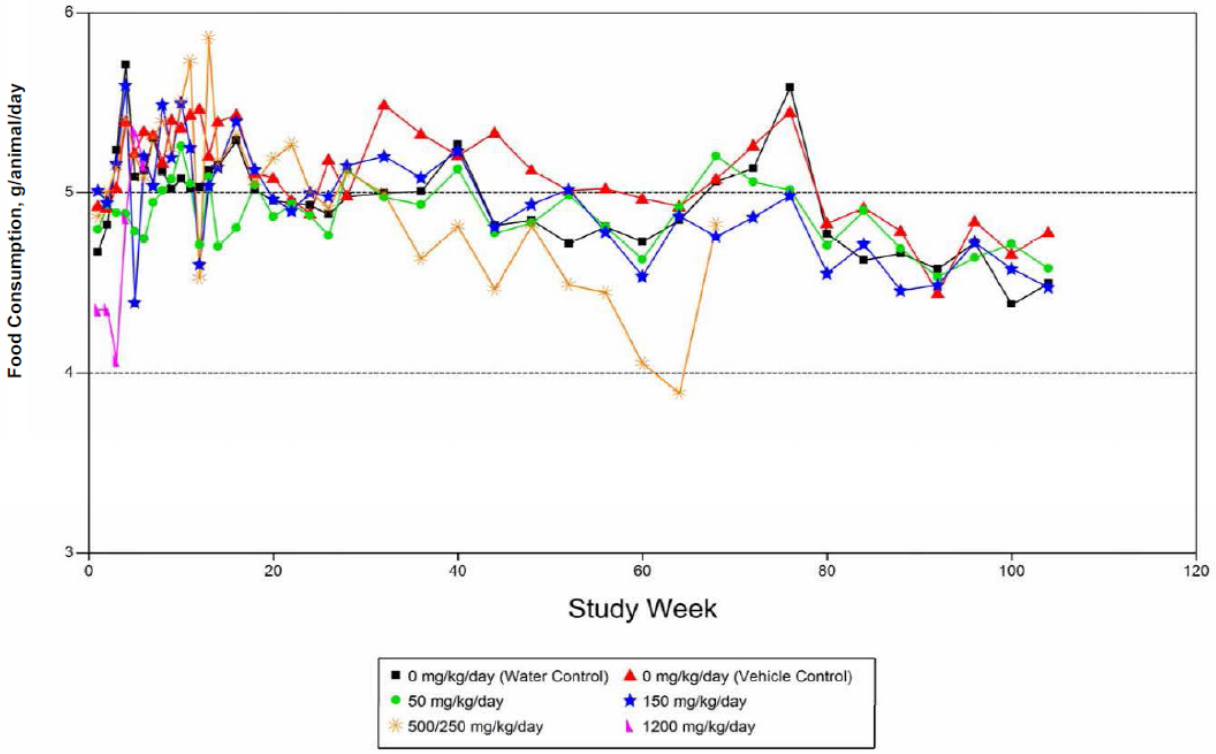
- Decreased food consumption was correlated to decreased bodyweights in animals administered 150 and 500/250 mg/kg/day fostamatinib. The exception is females administered 150 mg/kg/day, which presented with decreased body weight but had similar food consumption when compared to controls.

Figure 3 Male food consumption data



(Excerpted from Sponsor NDA)

Figure 4 Female food consumption data



(Excerpted from Sponsor NDA)

Gross Pathology

- Primary macroscopic observations included bone deformity/malformation and surface irregularities involving the sternum in males and females at ≥ 150 mg/kg/day and in the vertebra of males and females at 500 mg/kg/day.

Histopathology

Peer Review: Yes; reviewed and certified by a pathologist from AstraZeneca Pharmaceutical, Inc.

Neoplastic

- There were no statistically significant increases in neoplasms reported in this study. However, the FDA tumor analyses showed statistically significant positive dose-repose relationships in hemangioma in ovaries in female mice (p=0.0062) when the water control or the vehicle control was used in the analysis. The pairwise comparisons of this tumor type incidence rates against the water control and vehicle controls separately were statistically significant for 500/250 mg/kg/day dose groups (p=0.0429).

Table 3 Tumor Types with Statistical Significant Dose Response Relationships and Pairwise Comparisons of Treated Groups and Control

Animal	Organ name	Tumor name	Water/Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
Female Mice	ovaries	HEMANGIOMA [m]	0/60 (44) 0.0062 *	0/60 (45)	0/60 (46)	2/60 (12) 0.0429 **

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed. NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.
Note: In all tumor tables, a tumor marked with "s" is a secondary tumor and marked with "m" is a multicentric tumor. The tumors without any mark are the primary tumors.

Non-neoplastic

- Non-neoplastic findings were noted primarily in the bone.

Table 4 Non-neoplastic findings

	Male					Female				
Dose (mg/kg/day)	**0**	**0**	**50**	**150**	**500/250**	**0**	**0**	**50**	**150**	**500/250**
No. examined	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Bone, sternum										
thickening, growth plate										
minimal	7	13	17	25	12	10	9	14	19	9
mild	5	2	5	10	21	6	3	1	7	22
moderate	1	1	0	0	5	0	1	0	0	9
Bone, femur (proximal with head)										
thickening, growth plate										
mild	0	0	0	0	8	2	1	1	1	8
moderate	0	0	0	0	7	2	1	0	0	19
severe	0	0	0	0	2	0	0	0	0	6

* P≤0.05 ** P≤0.01

Toxicokinetics

- Fostamatinib is rapidly metabolized to the active metabolite R406, which is the reported toxicokinetic parameter.
- The exposure (C_{max} and $AUC_{0\text{-}t}$) to fostamatinib had gender related differences. Exposure to fostamatinib at lower doses (50 mg/kg/day) was markedly higher in males than in females but the gender differences decreased as doses increased.
- Exposure increased greater than dose proportional for females and generally less than dose proportional for males. There was no apparent accumulation of fostamatinib during the study.

Table 5 Toxicokinetic parameters of R406

Day	Dose (mg/kg/day)	Gender	C_{max} (ng/mL)	t_{max}[a] (h)	t_{last}[a] (h)	AUC_{0-6} (ng·h/mL)	AUC_{last} (ng·h/mL)
1	50	Male	2785	1	8	4437	6207
		Female	534	8	8	779	1328
	150	Male	9558	1	8	22821	28624
		Female	6563	1	8	10608	13745
	500	Male	15516	2	24	74225	218793
		Female	11659	4	8	52010	66636
	1200	Male	19636	8	24	95969	314512
		Female	17928	6	24	82609	274325
28	50	Male	3809	1	8	7253	10558
		Female	626	1	8	838	1173
	150	Male	8881	1	8	17109	24469
		Female	6529	8	8	8298	14964
	500	Male	14467	1	8	46449	63568
		Female	12772	8	24	32523	150480
91	50	Male	4296	1	8	7278	9259
		Female	310	1	8	544	693
	150	Male	6771	8	24	16423	77704
		Female	6802	1	8	9457	14380
	500	Male	11614	8	24	39426	147638
		Female	15363	8	8	42282	59223
364	50	Male	3410	1	8	6296	8559
		Female	880	1	8	1465	1756
	150	Male	5998	1	8	16008	21851
		Female	8032	1	24	12560	76346
	500 / 250[b]	Male	7733	1	6	21264	ND[c]
		Female	8661	1	2	ND[d]	ND[d]

AUC_{0-6} is the area under the plasma concentration-time curve over the first b.i.d. dose (from 0 to 6 hours).
AUC_{last} is the area under the plasma concentration-time curve from 0 to the time of the last quantifiable concentration.
[a] Relative to the first b.i.d. dose.
[b] The dose was reduced from 500 to 250 mg/kg/day starting on Day 352
[c] Samples were collected to 6 h.
[d] Samples were collected to 2 h.
The 1200 mg/kg/day dose was terminated after Day 1 samples were collected. No additional TK samples were collected from this group after Day 1.
NC: Not Calculated
ND: Not Determined

Dosing Solution Analysis

- All dose formulations met the acceptance criteria for accuracy and precision.

Study title: A 104-Weeek Oral Gavage Carcinogenicity Study in Rats

Study no.:	G-935788-0013
Study report location:	eCTD 4.2.3.4.1
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 11, 2008
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	Fostamatinib; TYKRK002, RM03L027A0, LTRGGA1005; 97.8%, 99.0%, 99.3%

Adequacy of Carcinogenicity Studies:

- Dose levels were concurred by ECAC.

Appropriateness of Test Models:

- The study evaluated four doses of fostamatinib based on the results of the 26-week study. The high dose was selected based on hematology parameters in males and reduced body weight gain in females. The dose spacing was based on AUC exposures not being dose proportional and the gender accounted for the increased exposure in females.
- The study report provided sufficient histopathology data from the designated organs and tissues to evaluate both the non-neoplastic and neoplastic effects at all dose levels. Additionally, data on survival, body weights, and toxicokinetics were provided.

Evaluation of Tumor Findings:

Key Study Findings

- The FDA survival analysis showed a statistically significant dose response relationship in mortality in males and females.
- No statistically significant tumors were observed.
- The exposure (C_{max} and AUC_{0-t}) to fostamatinib had gender related difference with females having a higher exposure than males. Exposures were slightly greater than dose proportional and there was no apparent accumulation during the study.

Methods

Doses:	Males: 0, 10, 25, 45, or 80 mg/kg/day Females: 0, 5, 12, 24 or 40 mg/kg/day
Positive Control:	None
Frequency of dosing:	Twice daily for 728 days
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.1% Carboxymethylcellulose Sodium, 0.1%

	Methylparaben Sodium and 0.02% Propylparaben Sodium in Purified Water (w/w)
Basis of dose selection:	Results of 26-week study
Species/Strain:	Crl:CD(SD) rats
Number/Sex/Group:	60/sex/group
Age:	~8 weeks
Animal housing:	Individually housed in wire-mesh cages
Paradigm for dietary restriction:	Food and water available *ad libitum*
Dual control employed:	None
Interim sacrifice:	Not conducted

Observations and times:

Mortality:	Twice daily with the addition of an evening mortality check after Week 53
Clinical signs:	Detailed observations performed weekly, cageside observations performed twice daily.
Body weights:	Once weekly for 14 weeks, every two weeks until Week 28, every 4 weeks thereafter
Food consumption:	Once weekly for 14 weeks, every two weeks until Week 28, every 4 weeks thereafter
Hematology:	Not conducted
Urinalysis:	Not conducted
Gross pathology:	At necropsy on main study animals
Histopathology:	Conducted for all main study animals

Study Design

Group Number	Dose Level (mg/kg/day)	Number of Animals	
		Male	Female
	Main Study		
1	0	60	
2	10	60	
3	25	60	
4	45	60	
5	80	60	
6[a]	NA	25	
	Toxicokinetic		
7	0	3	
8	10	12	
9	25	12	
10	45	12	
11	80	12	
	Main Study		
12	0		60
13	5		60
14	12		60
15	24		60
16	40		60
17[a]	NA		25
	Toxicokinetic		
18	0		3
19	5		12
20	12		12
21	24		12
22	40		12

[a]Sentinel animals included for health screening purposes
NA – Not applicable

Results

Mortality

- Fostamatinib administered to males at 80 mg/kg/day exceeded the maximum tolerated dose and animals were euthanized on Day 95. Dosing was ceased for females administered 40 mg/kg/day on Day 410 due to rapidly decreasing survival. Dosing was ceased on Day 612 for males administered 45 mg/kg/day and on Day 619 for females administered 24 mg/kg/day after reaching 20 surviving animals. At lower doses, survival of males administered 10 and 25

mg/kg/day was similar to control and survival of females administered 5 and 12 mg/kg/day was greater than control.

Table 6 Survival of rats in the 2-year carcinogenicity study

	Males					Females				
Dose (mg/kg/day)	**0 Control**	**10**	**25**	**45**	**80**	**0 Control**	**5**	**12**	**24**	**40**
Animals initially in study	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Animals surviving to terminal necropsy	22 37%	19 32%	25 42%	16 27%	0 0%	16 27%	32 53%	28 47%	16 27%	15 25%

Clinical Signs

- Primary clinical observations included teeth broken, teeth cut, malocclusion, and limb function impairment. Clinical signs were observed across all male dose groups but with a higher incidence occurring in the high dose females, although observations in females did not occur in a dose dependent manner.

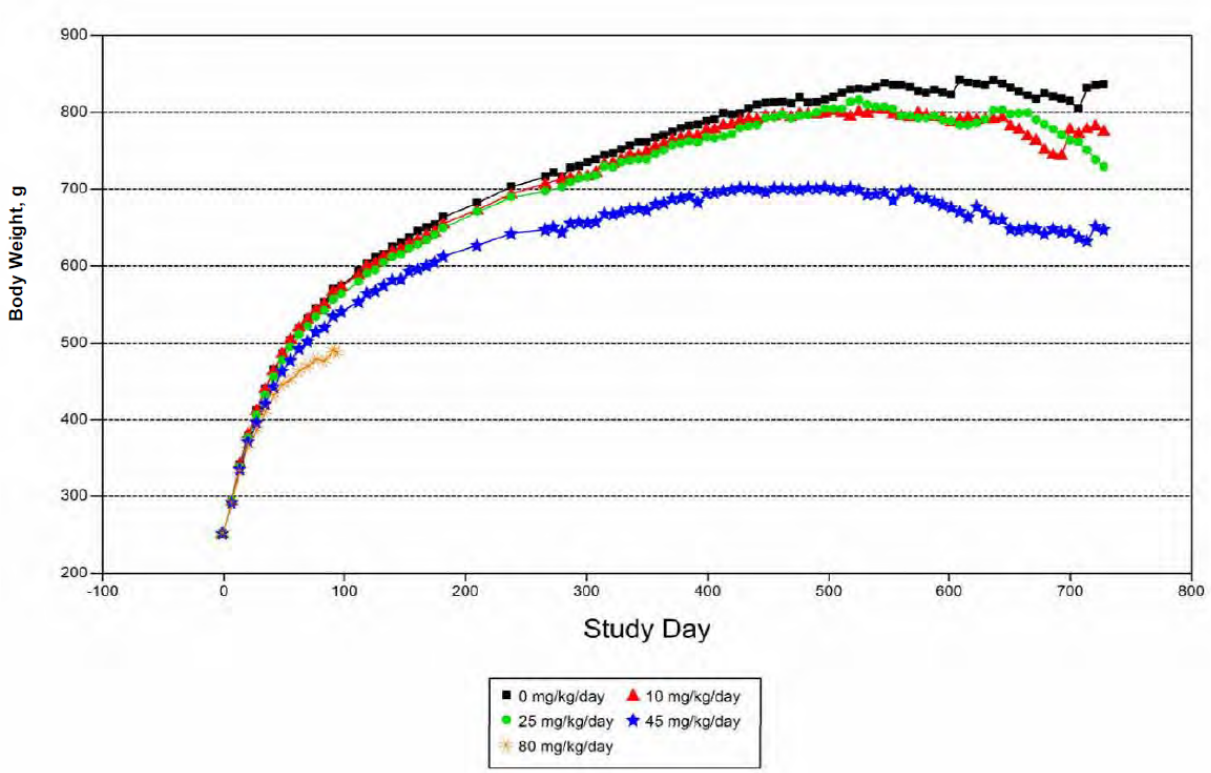
Table 7 Summary of clinical observations

	Males					Females				
Dose (mg/kg/day)	**0 Control**	**10**	**25**	**45**	**80**	**0 Control**	**5**	**12**	**24**	**40**
Teeth Broken	50/1	27/1	93/3	125/5	20/10	54/2	57/2	0/0	76/8	1428/44
Teeth Cut	148/12	440/23	460/46	869/45	13/5	300/13	395/10	200/11	344/19	1434/59
Malocclusion	22/1	399/7	472/8	444/10	20/5	189/4	350/5	114/2	155/5	384/6
Limb function impaired	13/6	4/2	14/5	74/14	2/1	218/3	0/0	0/0	80/9	245/19

Body Weights

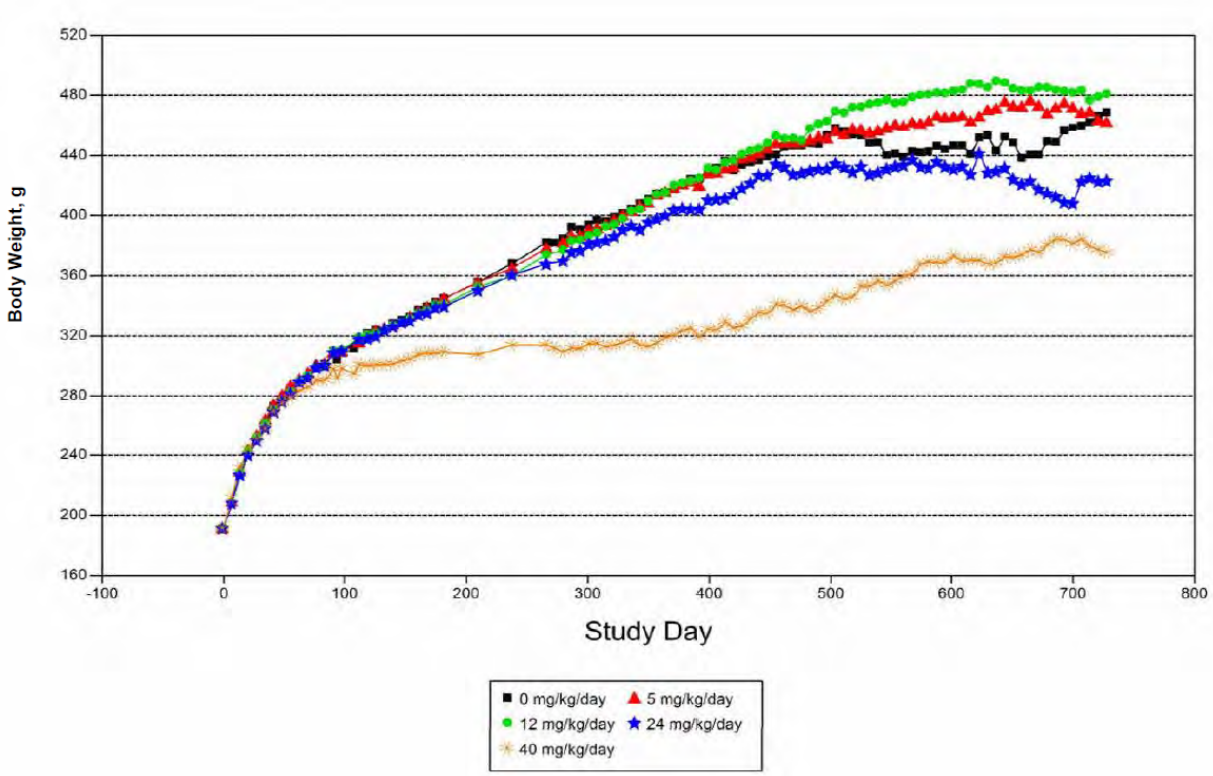
A marked decrease in body weights was observed in males administered ≥ 45 mg/kg/day and females administered 40 mg/kg/day and to a lesser extent in females administered 24 mg/kg/day.

Figure 5 Male body weight data



(Excerpted from Sponsor NDA)

Figure 6 Female body weight data

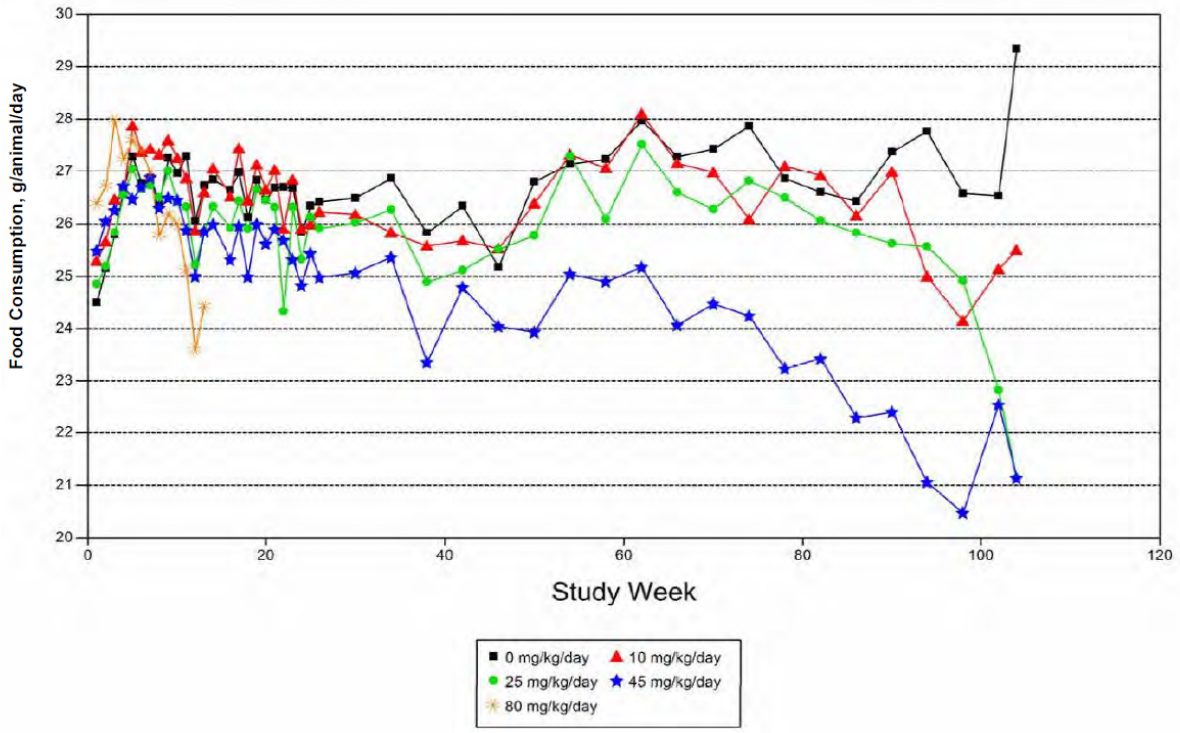


(Excerpted from Sponsor NDA)

Food Consumption

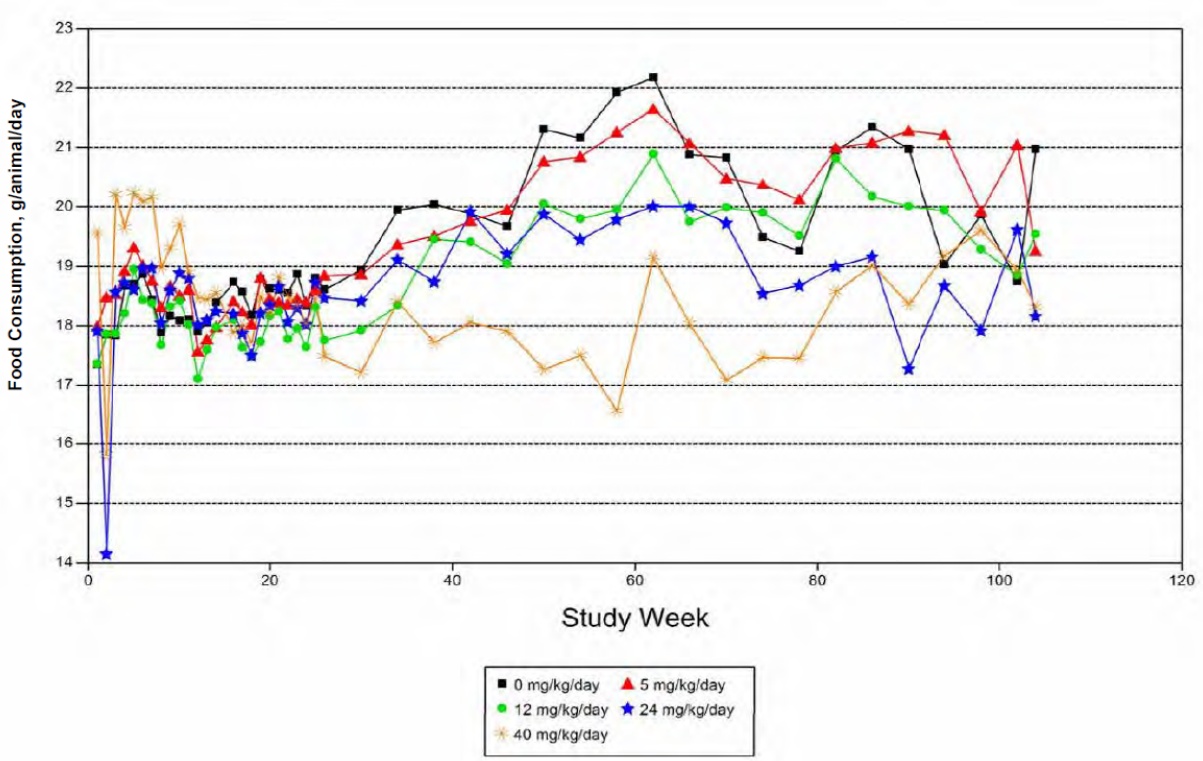
- Decreases in food consumption following administration of fostamatinib was more prominent in males than females. These findings are potentially associated with higher levels stomach erosion/ulcer observed in males when compared to females or control.

Figure 7 Male food consumption data



(Excerpted from Sponsor NDA)

Figure 8 Female food consumption data



(Excerpted from Sponsor NDA)

Gross Pathology

- Macroscopic were primarily found in the incisor teeth of both male and female rats and in the adrenal glands of female rats. Findings in the incisors included absent, broken, malocclusion, overgrown and/or discoloration of the teeth in males at all doses levels and in females at doses ≥ 24 mg/kg/day. An increased incidence of enlarged adrenal glands was observed in all females treated with fostamatinib.

Histopathology

Peer Review: Yes; reviewed and certified by a pathologist from AstraZeneca Pharmaceutical, Inc.

Neoplastic

- There were no statistically significant increases in neoplasms reported in this study.

- The FDA analysis found a significant increase ($p = 0.0475$) in adenoma hepatocellular in liver in male rats at 40 mg/kg/day when compared to control but was considered a common tumor and it didn't reach the statistical significant alpha level of 0.005.

Non-neoplastic

- Non-neoplastic findings were noted in the adrenal glands, bone, spleen, stomach and teeth.

Table 8 Non-neoplastic findings

	Male				Female				
Dose (mg/kg/day)	**0**	**10**	**25**	**45**	**0**	**5**	**12**	**24**	**40**
No. examined	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
Adrenal glands									
Angiectasis/cystic degeneration, focal cortical									
minimal	11	12	11	9	10	7	1	2	8
mild	6	7	7	7	16	15	9	8	11
moderate	1	4	7	10	28	31	35	13	21
severe	0	1	3	2	0	7	13	29	16
Bone, femur, head									
degenerative joint disease									
moderate	0	0	0	6	0	0	0	0	0
severe	0	0	0	1	0	0	0	0	0
Spleen									
depletion, lymphoid, generalized									
mild	3	0	2	7	0	0	0	7	7
moderate	0	4	4	13	2	1	1	8	15
severe	0	0	1	1	1	0	0	5	5
Stomach, nonglandular									
erosion/ulcer									
minimal	0	0	1	0	1	0	0	2	1
mild	2	0	1	2	3	1	1	1	3
moderate	1	1	2	4	0	0	0	1	0
severe	0	1	0	3	0	0	0	0	0
Tooth/teeth, incisor									
odontodysplasia									
minimal	0	4	2	8	0	0	0	2	13
mild	1	2	3	6	0	2	3	2	9
moderate	1	6	9	15	6	5	3	9	21

Toxicokinetics

- Fostamatinib is rapidly metabolized to the active metabolite R406, which is the reported toxicokinetic parameter.
- The exposure (C_{max} and AUC_{0-t}) to fostamatinib had gender related difference with females having a higher exposure than males. Exposures were slightly greater than dose proportional and there was no apparent accumulation during the study.

Table 9 Toxicokinetic parameters of R406 in males

Group	R788 Na Dose (mg/kg/day)	Sex	Day	t_{max} (h)[a]	C_{max} (ng/mL)	AUC_{0-6h} (ng·h/mL)	AUC_{last} (ng·h/mL)
8	10	Male	1	8	636	1550	2291
9	25			8	2082	4350	6729
10	45			8	3329	9535	13709
11	80			8	5110	20844	27519
8	10		28	8	733	2205	3129
9	25			8	1901	7069	9573
10	45			8	3408	10963	15473
11	80			8	6869	19889	29757
8	10		91	8	774	2570	3583
9	25			1	1914	6736	9180
10	45			8	3559	11461	16432
11	80			8	6617	17780	27059
8	10		182[b]	1	510	1602	2221
9	25			1	1564	4284	5930
10	45			1	2475	8769	12096
8	10		364[b]	1	514	1918	2433
9	25			1	1042	2898	3804
10	45			1	1746	5995	8118
8	10		546[b]	8	654	1890	2758
9	25			8	1432	4253	6096
10	45			8	2005	7953	11379
10	45		612[b]	8	2814	7853	11345
8	10		728[b]	1	678	2299	2937
9	25			2	1774	6442	7859

[a] Relative to the first b.i.d. dose.
[b] The 80 mg/kg/day dose was terminated on Day 95 with no TK sample collection from this group after Day 91, and the 45 mg/kg/day dose was terminated on Day 612 with limited TK sample collection, and no TK sample collection from this group after Day 612.

Table 10 Toxicokinetic parameters of R406 in females

Group	R788 Na Dose (mg/kg/day)	Sex	Day	t_{max} (h) [a]	C_{max} (ng/mL)	AUC_{0-6h} (ng·h/mL)	AUC_{last} (ng·h/mL)
19	5	Female	1	8	320	885	1277
20	12			8	1026	2836	4038
21	24			8	2852	7625	11024
22	40			8	4751	15747	21926
19	5		28	1	442	1223	1572
20	12			8	1258	3756	5373
21	24			8	3115	9307	13066
22	40			2	3604	14662	19349
19	5		91	1	408	1499	2005
20	12			8	1246	3989	5710
21	24			8	3643	10889	15244
22	40			8	5148	13926	20580
19	5		182	1	569	1344	1746
20	12			8	1209	3731	5370
21	24			8	3555	8545	12773
22	40			8	4727	12122	18404
19	5		364	1	418	1260	1677
20	12			8	1304	4454	6273
21	24			8	2269	8850	12066
22	40			8	3839	9871	14818
19	5		546[b]	1	386	1436	2027
20	12			8	1212	4665	6475
21	24			8	4107	9655	14929
21	24		619[b]	8	2648	6645	9936
19	5		728[b]	8	1317	934	2385
20	12			2	911	4137	4815

[a] Relative to the first b.i.d. dose.
[b] The 40 mg/kg/day dose was terminated and a single sample was collected from surviving animals on Day 410. No TK samples were collected from this group after Day 410 except for limited TK samples collected on Day 728 though dosing was terminated on Day 410.
The 24 mg/kg/day dose was terminated on Day 619 with limited TK sample collection. No TK samples were collected from this group after Day 619.

Dosing Solution Analysis

Dose formulations met accepted criteria except for the Week 1, 12 mg/kg/day dose. An investigation was conducted and a discrepancy was found between the replicates. The

reported dose outside the acceptance criteria was 127.4% and was not likely to impact the interpretation of the study results.

Conclusions for 104-week mouse and rat carcinogenicity studies

A statistical review of the tumor data in both 104-week carcinogenicity studies was requested. The statistical review was conducted by Dr. Feng Zhou of the Division of Biometrics in the Office of Biostatistics. Below are the summaries of the neoplastic statistical analyses of 104-week carcinogenicity studies conducted in mice and rats.

104-week carcinogenicity study in rats.

- Neither the Sponsor's nor the FDA's statistical analyses found a significant increase in neoplasms.

104-week carcinogenicity study in mice:

- There were no statistically significant increases in neoplasms reported in the study report. However, the FDA tumor analyses showed statistically significant positive dose-repose relationships in hemangioma in ovaries in female mice (p=0.0062) when the water control or the vehicle control was used in the analysis. The pairwise comparisons of this tumor type incidence rates against the water control and vehicle controls separately were statistically significant for 500/250 mg/kg/day dose groups (p=0.0429).

Table 11 Tumor Types with Statistical Significant Dose Response Relationships and Pairwise Comparisons of Treated Groups and Control

Animal	Organ name	Tumor name	Water/Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
Female Mice	ovaries	HEMANGIOMA [m]	0/60 (44) 0.0062 *	0/60 (45)	0/60 (46)	2/60 (12) 0.0429 **

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed. NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0.05 for a common tumor and a rare tumor, respectively.
Note: In all tumor tables, a tumor marked with "s" is a secondary tumor and marked with "m" is a multicentric tumor. The tumors without any mark are the primary tumors.

Based on these analyses and the FDA criteria for a positive carcinogenicity response presented below, FDA's conclusion is that there is a statistically significant increase in the risk of developing hemangioma in the ovaries based on the 104-week carcinogenicity study conducted in Crl:CD1(ICR) mice.

Table 12: FDA criteria for positive carcinogenicity response

Rare Tumors <1% in control/historical		Common Tumors (>1% control/historical)	
Trend Analysis	Pairwise Analysis	Trend Analysis	Pairwise Analysis
P<0.025	P<0.05	P<0.005	P<0.01
Both should be statistically significant in order to consider it a positive		Both should be statistically significant in order to consider it a positive	

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/s/

BRIAN D CHOLEWA
12/07/2017

CHRISTOPHER M SHETH
12/07/2017

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CARCINOGENICITY STUDIES

NDA/BLA #:	NDA 209299
Drug Name:	Fostamatinib
Indication(s):	Treatment of thrombocytopenia in adult patients with persistent or chronic immune thrombocytopenia (ITP) who have had an insufficient response to a previous treatment
Applicant:	Rigel Pharmaceuticals, Inc. 1180 Veterans Boulevard, South San Francisco, CA 94080, USA (b) (4)
Date(s):	Received 4/18/2017
Documents Reviewed:	Studies G-935788-0013 - R788 NA (rats) and G-935788-0015 - R788 NA (mice) were submitted on 4/17/2017 (via S0001) and the electronic tumor.xpt files were submitted on the same time.
Review Priority:	Priority Review
Biometrics Division:	Division of Biometrics VI
Statistical Reviewer:	Feng Zhou, M.S.
Concurring Reviewers:	Karl Lin, Ph. D., Team Leader
Medical Division:	Office of Hematology and Oncology Products/Division of Hematology Products (DHOT)
Pharmacology Team:	Brian Cholewa, Ph.D; Christopher Sheth, Ph.D
Project Manager:	Rachel McMullen, MPH, MHA
Keywords:	Carcinogenicity, Dose response

Table of Contents

1 Summary

This review evaluates statistically the data of 2-year oral carcinogenicity studies of R788 NA in rats and mice. The review analyzes the dose-response relationship of tumor incidence and mortality (including tumor-related mortality). The review concludes that R788 NA statistically decreased the survivals in males and females in both species. R788 NA caused statistically significant increases in the incidence of hemangioma in ovaries in female mice when compared with water or vehicle control individually. See Table 1 for tumor incidences and p-values of those tumor types that had significant dose-response relationships or pairwise comparisons.

Table 1: Tumor Types with Statistical Significant Dose Response Relationships and Pairwise Comparisons of Treated Groups and Control

Animal	Organ name	Tumor name	Water/Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
Female Mice	ovaries	HEMANGIOMA [m]	0/60 (44) 0.0062 *	0/60 (45)	0/60 (46)	2/60 (12) 0.0429 **

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed.
NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0 01 and 0 05 for a common tumor and a rare tumor, respectively.
Note: In all tumor tables, a tumor marked with "s" is a secondary tumor and marked with "m" is a multicentric tumor. The tumors without any mark are the primary tumors.

Rat Study: Rats (60/sex/dose) were dosed by oral gavage with 0 (VC), 10 (LD), 25 (MD), 45 (MH), and 80 (HD)-mg/kg/day R788 NA for male and 0 (VC), 5 (LD), 12 (MD), and 24 (MH), and 40 (HD)-mg/kg/day R788 NA for female twice daily for up to 104 weeks. The vehicle in the VC was 0.1% Carboxymethylcellulose Sodium, 0.1% Methylparaben Sodium and 0.02% Propylparaben Sodium in Purified Water (w/w) via the same twice daily dosing regimen. Due to low survival, males given 80 mg/kg/day were terminated starting in Week 12. Therefore, tissues were not microscopically examined for this terminated male dose group. The 80 mg/kg/day male rats group was not included in the analyses.

The survival analyses showed a statistically significant dose response relationship in mortality in males and females. Mortalities in the male MH group and female LD, MD, and, HD groups were significantly higher than that of the control group. The respective survival rates in the VC, LD, MD, MH, and HD groups at the termination were 37%, 32%, 42%, 27%, and 0% in males and 27%, 52%, 47%, 27%, and 25% in females. The tumor analysis didn't show any statistically significant positive dose-response relationships and pairwise comparison of any tumor type incidence.

Mouse Study: Mice (60/sex/dose) were dosed by oral gavage with 0 (WC), 0 (VC), 50 (LD), 150 (MD), 500 (MH), and 1200 (HD)-mg/kg/day R788 NA once daily for up to 104 weeks. The water and vehicle controls received water or 0.1% Carboxymethylcellulose Sodium, 0.1% Methylparaben Sodium and 0.02% Propylparaben Sodium in Purified Water (w/w) via the same twice daily dosing regimen. Due to low survival, effective on Day 352, the dose level for the animals at 500 mg/kg/day was reduced to 250 mg/kg/day (150 mg/kg/dose to 125 mg/kg/dose). The animals at 1200 mg/kg/day were terminated on Day 14 for males and Day 44 for females due to mortality and toxicity at this dose level, without any end of study

or postmortem evaluations. 1200 mg/kg/day dose groups were not included in any analyses.

The survival analysis did show a statistically significant dose response relationship in mortality across two controls and treated groups in both male and females mice ($p<0.001$). Mortalities in the male MH and female MH groups were significantly higher than the of the two control groups ($p<0.001$). The respective survival rates in the WC, VC, LD, MD, and MH groups at the termination were 43%, 52%, 45%, 37%, and 25% in males and 38%, 37%, 44%, 53%, and 25% in females.

The tumor analysis (Table 1) showed statistically significant positive dose-repose relationships in hemangioma in ovaries in female mice ($p=0.0062$) when the water control or the vehicle control was used in the analysis. The pairwise comparisons of this tumor type incidence rates against the water control and vehicle controls separately were statistically significant for MH dose groups ($p=0.0429$).

2 Background

Fostamatinib, a prodrug of R940406, is a potent and relatively selective spleen tyrosine kinase (SYK) inhibitor. The proposed indication for fostamatinib is for the treatment of adult patients (18 years and older) with persistent or chronic immune thrombocytopenia (ITP). Fostamatinib should not be used in children (until growth plate fusion) due to a potential safety risk seen in the rat and rabbit toxicology studies. The sponsor provided the nonclinical study report G-935788-0015 - R788 NA: "A 104-Week Oral Gavage Carcinogenicity Study in Mice" and G-935788-0013 - R788 NA: "A 104-Week Oral Gavage Carcinogenicity Study in Rats" on 4/18/2017 via submission NDA 20929/S0001. The electronic tumor.xpt data files were submitted on the same time.

The phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as dose increases. Results of this review have been discussed with the reviewing pharmacologist Dr. Brian Cholewa.

3 Rat Study- G-935788-0013 - R788 NA

Study Report: g-935788-0013.pdf (statistical report on page 2111)
SAS data: tumor.xpt

This study was conducted for AstraZeneca by (b) (4) to evaluate the carcinogenic potential of the test article, R788 Na, after twice daily oral gavage administration to male and female CD® [Crl:CD®(SD)] rats for up to 104 consecutive weeks. Four treatment groups of 60 male rats were administered the R788 Na at respective dose levels of 10, 25, 45, or 80 mg/kg/day. Four treatment groups of 60 female rats were administered the test article at respective dose levels of 5, 12, 24, or 40 mg/kg/day. Two additional groups of 60 animals each (one group of males and one group of females) served as the respective controls for each sex and received the vehicle, 0.1% Carboxymethylcellulose Sodium, 0.1% Methylparaben Sodium and 0.02% Propylparaben Sodium in Purified Water (w/w) via the same twice daily dosing regimen. This review refers these dose groups as the vehicle control (VC), low (LD), mid (MD), mid-high (MH), and high (HD) dose groups, respectively.

Assessment of toxicity was based on dose analysis, morbidity, mortality, injury, body weight, food consumption, clinical observations and masses, ophthalmology, clinical pathology, toxicokinetics, macroscopic observations, and microscopic evaluations.

3.1 Sponsor's Analyses

3.1.1 Survival Analysis

Intercurrent mortality data were analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups was conducted using a log-rank test[12]. Any animal with accidental injury that caused death or unscheduled sacrifice was censored in the estimation. In addition, all animals still alive at the end of the experimental period were censored at the following day. If this overall test was significant ($p < 0.05$) and there were more than two

groups, then a follow up analysis was done where each treatment group was compared to the control group using a log-rank test. Results of all pair-wise comparisons are reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's concluded results: On Day 95, at the request of the Sponsor with concurrence of the FDA, all remaining 80 mg/kg/day males were terminated (they had exhibited a 14% mean body weight decrease from Day 1 when compared to the control mean), as this dose level exceeded the maximum tolerated dose and would not be a viable dose level for a 2-year study duration. Therefore, tissues were not microscopically examined for this terminated male dose group. On Day 410, dosing ceased for all females at 40 mg/kg/day due to rapidly decreasing survival, as well as a mean body weight decrease (when compared to the control mean) that exceeded that of the 80 mg/kg/day males. On Day 612, dosing ceased for all males at 45 mg/kg/day after reaching a survival level of 20 animals. On Day 619, dosing ceased for all females at 24 mg/kg/day after reaching a survival level of 20 animals. The animals remained on study and protocol-designated parameters/evaluations were continued for these three main study groups until the scheduled terminal necropsy.

Thus, the overall incidence of main study survival was generally either comparable to controls in males at the lower dose groups (10 and 25 mg/kg/day) or statistically significantly greater than controls in females at the lower dose groups (5 and 12 mg/kg/day for females). Among the groups for which dosing ceased early, survival was statistically significantly decreased for 45 mg/kg/day males and 40 mg/kg/day females when compared with controls, but survival was similar to controls for 24 mg/kg/day females. The 40 mg/kg/day females were kept on study in order to assess reversibility (survival did stabilize).

3.1.2 Tumor Data Analysis

The Poly-3 method [13, 14] was used to assess prevalence of tumors. The survival-adjusted rates based on the risk weights are displayed. The tests of significance are included both an overall trend and pair-wise comparisons of each treatment group with the control. All p-values are reported using upper-tailed test, unless otherwise indicated. Evaluation criteria (p-values of significance) were applied differently for rare tumors (background rate of 1% or less) and common tumors (background rate greater than 1%) The evaluation criteria from the FDA are given in Table F (FDA) [15].

Table F. Evaluation Criteria for Common and Rare Tumors

Test for Positive Trends	Control-High Pair-wise Comparisons
Common and rare tumors will be tested at 0.005 and 0.025 significance levels, respectively	Common and rare tumors will be tested at 0.01 and 0.05 significance levels, respectively

Sponsor's concluded results:

There were no statistically significant increases in incidence of neoplasms in test article dosed groups compared to controls. Neoplasms seen in the study were of the type generally seen in rats of this strain.

3.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 4/18/2017 via submission NDA 20929/S0001. The tumor.xpt data included a variable (origin) which indicating the type of tumor as "primary", "secondary", "multicentric", or "undetermined". The sponsor's tumor analysis only included the "primary" tumors. This review included all type of tumors. Notes in all tumor tables, a tumor marked with "s" is a secondary tumor and marked with "m" is a multicentric tumor. The tumors without any mark are the primary tumors.

All remaining 80 mg/kg/day male rats were terminated on Day 95. The sponsor claimed that these animals had exhibited a 14% mean body weight decrease from Day 1 when compared to the control mean, as this dose level exceeded the maximum tolerated dose and would not be a viable dose level for a 2-year study duration. Therefore, tissues were not microscopically examined for this terminated male dose group. The male rats dosed with 80 mg/kg/day was not included in the tumor.xpt data file and therefore this dose group was not included in any analyses.

3.2.1 Survival Analysis

The survival distributions of rats in all treatment groups were estimated using the Kaplan-Meier product limit method. For control, low, medium, and high dose groups, the dose response relationship was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 1A and 1B in the appendix for male and female rats, respectively. The intercurrent mortality data are given in Tables 1A and 1B in the appendix for male and female rats, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 3A and 3B in the appendix for male and female rats, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death were 38 (63%), 41 (68%), 36 (60%), 45 (75%) in male rats and 44 (73%), 29 (48%), 32 (53%), 44 (73%) and 45 (75%) in female rats in the VC, LD, MD, MH, and HD groups, respectively. The survival analyses showed a statistically significant dose response relationship in mortality in males and females (Ps<0.0137). Mortalities in the male MH group and female LD, MD, and, HD groups were significantly higher than that of the control group (Ps<0.0375).

3.2.2 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of control group with each of the treated groups. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-k method described in the papers of Bailer and Portier [2] and Bieler and Williams [3]. In this method an animal that lives the full

study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of s_h =1. An animal that dies at week w_h without developing the tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}}\right)^k$ <1. The adjusted group size is defined as Σs_h. As an interpretation, an animal with score s_h =1 can be considered as a whole animal while an animal with score s_h < 1 can be considered as a partial animal. The adjusted group size Σs_h is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor of the tumor type being tested, otherwise the adjusted group size is less than N. These adjusted group sizes are then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used.

Multiple testing adjustments currently follow the rule displayed in Table 12.6. [5, 6]

Table 12.6 Recommended decision rules (levels of significance) for controlling the overall false positive rates for various statistical tests performed and submission types

Submission type		Tumor type	Decision rule			
			Trend test alone	Pairwise test alone	Joint test	
					Trend test	Pairwise test
Standard 2 year study with two sexes and two species		Common	0.005	0.01	0.005	0.05
		Rare	0.025	0.05	0.025	0.10
Alternative ICH Studies (One 2-year study in one species and one short- or medium-term alternative study, two sexes)	Two-year study	Common	0.005	0.01	0.005	0.05
		Rare	0.025	0.05	0.025	0.10
	Short- or medium-term alternative study	Common	0.05	0.05	0.05	0.05
		Rare	0.05	0.05	0.05	0.05
Standard 2 year studies with two sexes and one species		Common	0.01	0.025	0.01	0.05
		Rare	0.05	0.10	0.05	0.10

The adjusted levels of significance for testing a positive dose response in the 2-year rat study are 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The adjusted levels of significance for the pairwise comparison in the 2-year rat study are 0.01 and 0.05 for a common tumor and a rare tumor, respectively.

The tumor rates and the p-values of the tested tumor types are listed in Tables 5A and 5B in the appendix for male and female rats, respectively.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 either for dose response relationships or for pairwise comparisons of treated groups and control.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons of Treated Groups and Controls in Rats

Sex	Organ name	Tumor name	0mg|kg|day Vehicle (VC) (N=60) P - Trend	10mg|kg|day Low (L) (N=60) P - C vs. L	25mg|kg|day Mid (M) (N=60) P - C vs. M	40mg|kg|day M-High (MH) (N=60) P - C vs. MH
Male	Live	Adenoma, Hepatocellular	1/60 (43) 0.0078	1/60 (45) 0.7641	1/60 (42) 0.7471	5/60 (32) 0.0475
		C_Hepatocellular_A+C	1/60 (43) 0.0157	2/60 (46) 0.5256	1/60 (42) 0.7471	5/60 (32) 0.0475

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed. NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0 025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0.01 and 0 05 for a common tumor and a rare tumor, respectively.
Note: In all tumor tables, a tumor marked with "s" is a secondary tumor and marked with "m" is a multicentric tumor. The tumors without any mark are the primary tumors.

Based on the criteria of adjustment for multiple testing discussed above, adenoma hepatocellular in liver in male rats was considered as a common tumor and it didn't reach the statistical significant alpha level of 0.005. The pairwise comparison of these tumor type incidences against the vehicle controls was not statistically significant for any dosed groups.

For female rats, the tumor analysis did not show any statistically significant dose-response relationship and pairwise comparison in incidence in all tumor types tested.

4 Mouse Study- G-935788-0015 - R788 NA

Study Report: g-935788-0015.pdf (statistical report on page 1740)
SAS data: tumor.xpt

This study was conducted for AstraZeneca by (b) (4) to evaluate the carcinogenic potential of the test article, R788 Na, after twice daily oral gavage administration to male and female [Crl:CD1®(ICR)] mice for up to 104 consecutive weeks. Four treatment groups of 60 animals/sex were administered the R788 Na at respective dose levels of 50, 150, 500, or 1200 mg/kg/day. Two additional groups of 60 animals/sex served as the respective water and vehicle controls and received water or 0.1% Carboxymethylcellulose Sodium, 0.1% Methylparaben Sodium and 0.02% Propylparaben Sodium in Purified Water (w/w) via the same twice daily dosing regimen. This review refers these dose groups as the water control (WC), vehicle control (VC), low (LD), mid (MD), mid-high (MH), and high (HD) dose groups, respectively.

Assessment of toxicity was based on dose analysis, morbidity, mortality, injury, body weight, food consumption, clinical observations and masses, ophthalmology, clinical pathology, toxicokinetics, macroscopic observations, and microscopic evaluations.

Effective on Day 352, the dose level for the animals at 500 mg/kg/day was reduced to 250 mg/kg/day (and 150 mg/kg/dose to 125 mg/kg/dose) by reducing the dose volume from 10 mL/kg/dose to 5 mL/kg/dose. This was due to reduced survival and decreases in mean body weight. The animals dosed with 1200 mg/kg/day were terminated on Day 14 for males and Day 44 for females due to mortality and toxicity at this dose level, without any end of study or postmortem evaluations. The 1200 mg/kg/day dose groups were not included in any analyses.

4.1 Sponsor's Analyses

4.1.1 Survival Analysis

The sponsor used the same survival analysis methods for the rat study in this mouse study.

Sponsor's concluded results: The overall incidence of main study survival was generally comparable to that of both of the control groups (water control and vehicle control) in both males and females at 50 and 150 mg/kg/day, but was statistically significantly decreased when compared with both control groups in males and females at 500/250 mg/kg/day (surviving 15 males necropsied were on Day 555 and surviving 15 females were necropsied on Day 494 in this group; dosing had ceased on Day 515 for males and on Day 449 for females after reaching a survival of 20).

4.1.2 Tumor Data Analysis

The sponsor used the same tumor data analysis methods for the rat study in this mouse study.

Sponsor's findings: There were no R788 Na-related carcinogenic findings. There were no statistically significant increases in the incidence of neoplasms in the test article dosed groups compared to controls. All neoplasms in the study were of the type generally seen in mice of this age and strain.

4.2 Reviewer's Analyses

To verify the sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this review analyzed the SAS data sets of these studies received on 4/18/2017 via submission NDA 20929/S0001. This study included water control and vehicle control; this review analyzed the dose-response relationship of tumor incidence and mortality (including tumor-related mortality) against two controls separately.

4.2.1 Survival Analysis

The Kaplan-Meier curves for survival rates of all treatment groups are given in Figures 2A and 2B in the appendix for male and female mice, respectively. The intercurrent mortality data of all treatment groups are given in Tables 2A and 2B in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals for control, low, medium, and high dose groups are given in Tables 4A and 4B in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percent) of death were 34 (57%), 28 (47), 33 (57%), 38 (63%), and 45 (75%) in male mice and 37 (62%), 38 (63%), 33 (57%), 28 (47%), and 45 (75%) in female mice in the WC, VC, LD, MD, MH groups, respectively. The death rates were similar compared to the controls. Mortalities in MH dose group were significantly higher than the individual control (WC and VC) for both male and female mice ($p<0.0001$). The tests showed a statistically significant dose-response relationship in mortality across two controls and treated groups in males and females

(p<0.0001). Please note of, the high dose groups for male and female mice were included in the analysis.

4.2.2 Tumor Data Analysis

The tumor data were analyzed for dose response relationships and pairwise comparisons of the water control group and the vehicle control group separately with each of the treated groups using the same method that was used for the rat study. The tumor rates and the p-values of the tested tumor types are listed in Tables 6A, 6B, 6C, and 6D in the appendix for male and female mice, respectively.

Reviewer's findings: Following table displays the tumor types showing p-values less than or equal to 0.05 either for dose response relationships or for pairwise comparisons of treated groups and control.

Tumor Types with P-Values ≤ 0.05 for Dose Response Relationship or Pairwise Comparisons of Treated Groups and Water Control or Vehicle Control in Mice

Sex	Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
Male	epididymides	LYMPHOMA m	4/60 (48) 0 0464	0/60 (44) 1 0000	5/60 (42) 0 4146	3/60 (16) 0 2346
	pituitary gland	LYMPHOMA m	0/60 (46) 0 0393	0/60 (44)	2/60 (41) 0 2192	1/60 (14) 0 2333
	seminal vesicles	LYMPHOMA m	2/60 (47) 0 0384	0/60 (44) 1 0000	4/60 (42) 0 2860	2/60 (15) 0 2443
	small intestine, i	LYMPHOMA m	2/60 (47) 0 0079	0/60 (44) 1 0000	5/60 (42) 0 1732	3/60 (16) 0 0989
	small intestine, j	LYMPHOMA m	1/60 (47) 0 0183	0/60 (44) 1 0000	3/60 (41) 0 2583	2/60 (15) 0 1425
Female	ovaries	HEMANGIOMA m	0/60 (44) 0 0062 *	0/60 (45)	0/60 (46)	2/60 (12) 0 0429 **

Sex	Organ Name	Tumor Name	Vehicle Control 0 m/k/d (N=60)	Low Dose 50 m/k/d (N=60)	Mid Dose 150 m/k/d (N=60)	M-High Dose 500/250 m/k/d (N=60)
Male	epididymides	LYMPHOMA m	4/60 (48) 0 0464	0/60 (44) 1 0000	5/60 (42) 0 4146	3/60 (16) 0 2346
	liver	LYMPHOMA m	5/60 (49) 0 0292	3/60 (45) 0 8369	8/60 (43) 0 1966	4/60 (16) 0 1426
	lung	LYMPHOMA m	2/60 (47) 0 0220	2/60 (44) 0 6663	5/60 (41) 0 1644	3/60 (16) 0 0989
	lymph node, mesent	LYMPHOMA m	5/60 (49) 0 0386	4/60 (45) 0 7125	8/60 (43) 0 1966	4/60 (16) 0 1426
	seminal vesicles	LYMPHOMA m	1/60 (46) 0 0132	0/60 (44) 1 0000	4/60 (42) 0 1531	2/60 (15) 0 1468
	small intestine, i	LYMPHOMA m	3/60 (48) 0 0208	0/60 (44) 1 0000	5/60 (42) 0 2844	3/60 (16) 0 1595
Female	ovaries	HEMANGIOMA m	0/60 (44) 0 0062 *	0/60 (45)	0/60 (46)	2/60 (12) 0 0429 **

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed.
NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0 01 and 0 05 for a common tumor and a rare tumor, respectively.
Note: In all tumor tables, a tumor marked with "s" is a secondary tumor and marked with "m" is a multicentric tumor. The tumors without any mark are the primary tumors.

Based on the criteria of adjustment for multiple testing discussed above, hemangioma in ovaries in female mice were considered to have a statistically significant positive dose response relationship ($p=0.0062<0.025$) when the water control or the vehicle control was used in the analysis. The pairwise comparisons of this tumor type incidence rates against the water control and the vehicle controls separately were statistically significant for mid-high dosed groups ($p=0.0429<0.05$).

Feng Zhou
Mathematical Statistician

Concurring Reviewer: Karl Lin, Ph.D., Team Leader, Biometrics-6

cc:
Dr. Christopher Sheth
Dr. Brian Cholewa
Dr. Yi Tsong
Dr. Karl Lin
Ms. Patrician

5 Appendix

Table 1A: Intercurrent Mortality Rate in Male Rats

	Vehicle Control 0mg|kg|day		Low Dose 10mg|kg|day		Mid Dose 25mg|kg|day		M-High Dose 45mg|kg|day	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	3	5.00	1	1.67	5	8 33	9	15.00
53 - 78	9	20.00	7	13.33	12	28.33	16	41.67
79 - 92	13	41.67	16	40.00	11	46.67	17	70.00
93 - 104	13	63.33	17	68.33	7	58.33	2	73.33
Terminal sacrifice	22	36.67	19	31.67	25	41.67	16	26.67
Total	60	.	60	.	60	.	60	.

All Cum. %Cumulative Percentage except for Terminal sacrifice

Table 1B: Intercurrent Mortality Rate in Female Rats

	Vehicle Control 0mg|kg|day		Low Dose 5mg|kg|day		Mid Dose 12mg|kg|day		M-High Dose 24mg|kg|day		High Dose 40mg|kg|day	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	2	3.33	1	1.67	1	1.67	9	15.00	21	35.00
53 - 78	15	28.33	5	10.00	8	15.00	21	50.00	16	61.67
79 - 92	16	55.00	12	30.00	8	28.33	11	68.33	4	68.33
93 - 104	11	73.33	10	46.67	15	53.33	3	73.33	4	75.00
Terminal sacrifice	16	26.67	32	51.67	28	46.67	16	26.67	15	25.00
Total	60	.	60	.	60	.	60	.	60	.

All Cum. %Cumulative Percentage except for Terminal sacrifice

Table 2A: Intercurrent Mortality Rate in Male Mice

	Water Control 0mg|kg|day		Vehicle Control 0mg|kg|day		Low Dose 50mg|kg|day		Mid Dose 150mg|kg|day		M-High Dose 500/250mg|kg|day	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	2	3.33	4	6.67	6	10.00	6	10.00	26	43.33
53 - 78	8	16.67	10	23.33	7	21.67	12	30.00	17	71.67
79 - 92	9	31.67	7	35.00	9	36.67	13	51.67	2	75.00
93 - 104	15	56.67	7	46.67	10	53.33	7	63.33	.	.
Accidental Death	.				1	1.67	.	.	.	.
Terminal sacrifice	26	43.33	32	53.33	27	45.00	22	36.67	15	25.00
Total	60		60	.	60	.	60	.	60	.

All Cum. %Cumulative Percentage except for Terminal sacrifice

Table 2B: Intercurrent Mortality Rate in Female Mice

	Water Control 0mg|kg|day		Vehicle Control 0mg|kg|day		Low Dose 50mg|kg|day		Mid Dose 150mg|kg|day		M-High Dose 500/250mg|kg|day	
Week / Type of Death	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %	No. of Death	Cum %
0 - 52	4	6.67	4	6.67	3	5.00	6	10.00	30	50.00
53 - 78	10	23.33	7	18.33	10	21.67	8	23.33	15	75.00
79 - 92	8	36.67	12	38.33	4	28.33	4	30.00	.	.
93 - 104	15	61.67	14	61.67	15	55.33	10	46.67	.	.
Accidental Death	.		.		1	1.67	.	.	.	.
Terminal sacrifice	23	38.33	23	38.33	27	45.00	32	53.33	15	25.00
Total	60		60	.	60	.	60	.	60	.

All Cum. %Cumulative Percentage except for Terminal sacrifice

Table 3A: Intercurrent Mortality Comparison in Male Rats

Test	All Dose Groups	Control vs. Low	Control vs. Mid	Control vs. Mid-High	Control vs. High
Dose-Response (Likelihood Ratio)	0.0137	0.8420	0.9066	0.0173	.
Homogeneity (Log-Rank)	0.0169	0.8397	0.9058	0.0151	.

#All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level.

Table 3B: Intercurrent Mortality Comparison in Female Rats

Test	All Dose Groups	Control vs. Low	Control vs. Mid	Control vs. Mid-High	Control vs. High
Dose-Response (Likelihood Ratio)	<.0001	0.0022	0.0066	0.2676	0.0375
Homogeneity (Log-Rank)	<.0001	0.0019	0.0056	0.2601	0.0338

#All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level.

Table 4A: Intercurrent Mortality Comparison in Male Mice

Test	All Dose Groups	Water Control vs. Low	Water Control vs. Mid	Water Control vs. Mid-High
Dose-Response (Likelihood Ratio)	<.0001	0.9326	0.1772	<.0001
Homogeneity (Log-Rank)	<.0001	0.9318	0.1720	<.0001
Test	**All Dose Groups**	**Vehicle Control vs. Low**	**Vehicle Control vs. Mid**	**Vehicle Control vs. Mid-High**
Dose-Response (Likelihood Ratio)	<.0001	0.4317	0.0587	<.0001
Homogeneity (Log-Rank)	<.0001	0.4278	0.0567	<.0001

#All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level.

Table 4B: Intercurrent Mortality Comparison in Female Mice

Test	All Dose Groups	Water Control vs. Low	Water Control vs. Mid	Water Control vs. Mid-High
Dose-Response (Likelihood Ratio)	<.0001	0.4949	0.1455	<.0001
Homogeneity (Log-Rank)	<.0001	0.4891	0.1426	<.0001
Test	**All Dose Groups**	**Vehicle Control vs. Low**	**Vehicle Control vs. Mid**	**Vehicle Control vs. Mid-High**
Dose-Response (Likelihood Ratio)	<.0001	0.5253	0.1531	<.0001
Homogeneity (Log-Rank)	<.0001	0.5201	0.1489	<.0001

#All Cum. % Cumulative Percentage except for Terminal sacrifice;
* = Significant at 5% level; ** = Significant at 1% level.

Table 5A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons – Male Rats

Organ Name	Tumor Name	0mg|kg|day Cont.(N=60) P – Trend	10mg|kg|day Low (N=60) P- C vs. L	25mg|kg|day Med (N=60) P – C vs. M	45mg|kg|day MHigh (N=60) P – C vs. MH
adrenal glands	ADENOMA, CORTICAL	1/60 (43) 0.9308	1/60 (45) 0.7641	0/60 (42) 1.0000	0/60 (32) 1.0000
	CARCINOMA, CORTICAL	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	C_cortical_A+C	**2/60 (44) 0.9813**	**1/60 (45) 0.8834**	**0/60 (42) 1.0000**	**0/60 (32) 1.0000**
	OSTEOSARCOMA [s]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	C_PHEOCHROMOCYTOMA Benign+Malignant	**8/60 (44) 0.6803**	**7/60 (47) 0.7595**	**12/60 (44) 0.2230**	**3/60 (32) 0.9234**
all sites	**C_fibrous histiocytoma**	**0/60 (43) 0.2515**	**1/60 (45) 0.5114**	**0/60 (42)**	**1/60 (32) 0.4267**
	C_hemangioma+sarcoma	**4/60 (44) 0.9968**	**3/60 (45) 0.7923**	**0/60 (42) 1.0000**	**0/60 (32) 1.0000**
	C_lipomas+carcomas	**1/60 (44) 0.9281**	**4/60 (47) 0.2017**	**0/60 (42) 1.0000**	**0/60 (32) 1.0000**
	C_lymphoma [m]	**2/60 (44) 0.8985**	**1/60 (46) 0.8873**	**1/60 (42) 0.8706**	**0/60 (32) 1.0000**
	C_sarcoma histiocytic [m]	**1/60 (44) 0.9215**	**3/60 (46) 0.3253**	**0/60 (42) 1.0000**	**0/60 (32) 1.0000**
bone	OSTEOSARCOMA	2/60 (44) 0.9817	1/60 (46) 0.8873	0/60 (42) 1.0000	0/60 (32) 1.0000
bone marrow, femur	HEMANGIOMA	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
	LYMPHOMA [m]	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
bone marrow, stern	HEMANGIOSARCOMA	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000

Organ Name	Tumor Name	0mg|kg|day Cont.(N=60) P – Trend	10mg|kg|day Low (N=60) P- C vs. L	25mg|kg|day Med (N=60) P – C vs. M	45mg|kg|day MHigh (N=60) P – C vs. MH
	LYMPHOMA [m]	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
	OSTEOSARCOMA [s]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
brain	ASTROCYTOMA	4/60 (44) 0.9440	5/60 (47) 0.5424	1/60 (43) 0.9706	1/60 (32) 0.9412
	CARCINOMA, PARS DISTALIS [s]	0/60 (43) 0.1975	0/60 (45)	0/60 (42)	1/60 (32) 0.4267
	GRANULAR CELL TUMOR	1/60 (43) 0.7065	0/60 (45) 1.0000	1/60 (42) 0.7471	0/60 (32) 1.0000
	LYMPHOMA [m]	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
cavity, abdominal	LIPOSARCOMA	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	OSTEOSARCOMA	1/60 (44) 0.7034	0/60 (45) 1.0000	1/60 (42) 0.7412	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
cavity, thoracic	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	OSTEOSARCOMA [s]	2/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
coagulating glands	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
epididymides	LYMPHOMA [m]	1/60 (44) 0.9292	1/60 (46) 0.7638	0/60 (42) 1.0000	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
eyes	LYMPHOMA [m]	1/60 (44) 0.9292	1/60 (46) 0.7638	0/60 (42) 1.0000	0/60 (32) 1.0000
hard palate	PAPILLOMA, SQUAMOUS CELL	0/60 (43) 0.4568	0/60 (45)	1/60 (42) 0.4941	0/60 (32)
harderian glands	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
head	CARCINOMA, SQUAMOUS CELL	0/60 (43) 0.4568	0/60 (45)	1/60 (42) 0.4941	0/60 (32)

Organ Name	Tumor Name	0mg|kg|day Cont.(N=60) P – Trend	10mg|kg|day Low (N=60) P- C vs. L	25mg|kg|day Med (N=60) P – C vs. M	45mg|kg|day MHigh (N=60) P – C vs. MH
heart	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	OSTEOSARCOMA [s]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	SCHWANNOMA	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
kidneys	ADENOMA, TUBULAR CELL	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
	CARCINOMA, TUBULAR CELL	0/60 (43) 0.4568	0/60 (45)	1/60 (42) 0.4941	0/60 (32)
	C_tubular_cell_A+C	**0/60 (43) 0.5680**	**1/60 (45) 0.5114**	**1/60 (42) 0.4941**	**0/60 (32)**
	LYMPHOMA [m]	1/60 (44) 0.9292	1/60 (46) 0.7638	0/60 (42) 1.0000	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
lacrimal glands, e	LYMPHOMA [m]	1/60 (44) 0.9292	1/60 (46) 0.7638	0/60 (42) 1.0000	0/60 (32) 1.0000
large intestine, c	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
larynx	LYMPHOMA [m]	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
liver	ADENOMA, HEPATOCELLULAR	1/60 (43) 0.0078	1/60 (45) 0.7641	1/60 (42) 0.7471	5/60 (32) 0.0475
	CARCINOMA, HEPATOCELLULAR	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
	CHOLANGIOCARCINOMA	1/60 (43) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	CHOLANGIOMA	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
	C_Hepatocellular_A+C	**1/60 (43) 0.0157**	**2/60 (46) 0.5256**	**1/60 (42) 0.7471**	**5/60 (32) 0.0475**
	C_cholangio_ma+carcinoma	**1/60 (43) 0.9308**	**1/60 (45) 0.7641**	**0/60 (42) 1.0000**	**0/60 (32) 1.0000**
	LYMPHOMA [m]	1/60 (44) 0.9292	1/60 (46) 0.7638	0/60 (42) 1.0000	0/60 (32) 1.0000
	OSTEOSARCOMA [s]	1/60 (44) 0.7034	0/60 (45) 1.0000	1/60 (42) 0.7412	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 0.9215	3/60 (46) 0.3253	0/60 (42) 1.0000	0/60 (32) 1.0000
lung	ADENOMA, BRONCHIOLAR ALVEOLAR	0/60 (43) 0.4568	0/60 (45)	1/60 (42) 0.4941	0/60 (32)
	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000

Organ Name	Tumor Name	0mg|kg|day Cont.(N=60) P – Trend	10mg|kg|day Low (N=60) P- C vs. L	25mg|kg|day Med (N=60) P – C vs. M	45mg|kg|day MHigh (N=60) P – C vs. MH
	OSTEOSARCOMA [s]	2/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 0.9214	2/60 (46) 0.5169	0/60 (42) 1.0000	0/60 (32) 1.0000
lymph node, axilla	LYMPHOMA [m]	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
lymph node, cervic	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
lymph node, iliac	LIPOSARCOMA [s]	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
lymph node, inguin	OSTEOSARCOMA [s]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
lymph node, mandib	ADENOCARCINOMA [s]	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
	CARCINOMA, SEBACEOUS CELL [s]	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
	LYMPHOMA [m]	1/60 (44) 0.9292	1/60 (46) 0.7638	0/60 (42) 1.0000	0/60 (32) 1.0000
	OSTEOSARCOMA [s]	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
lymph node, medias	LYMPHOMA [m]	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
lymph node, mesent	HEMANGIOSARCOMA	3/60 (44) 0.9920	2/60 (45) 0.8267	0/60 (42) 1.0000	0/60 (32) 1.0000
	LYMPHOMA [m]	1/60 (44) 0.7822	1/60 (46) 0.7638	1/60 (42) 0.7412	0/60 (32) 1.0000
mammary gland	FIBROADENOMA	1/60 (43) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
multicentric neopl	LYMPHOMA [m]	2/60 (44) 0.8985	1/60 (46) 0.8873	1/60 (42) 0.8706	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 0.9215	3/60 (46) 0.3253	0/60 (42) 1.0000	0/60 (32) 1.0000
nerve, sciatic	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
nose, level a	**C_adeno_ma+carcinoma**	**0/60 (43) 0.2509**	**1/60 (46) 0.5169**	**0/60 (42)**	**1/60 (32) 0.4267**
	ADENOCARCINOMA	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
	ADENOMA	0/60 (43) 0.1975	0/60 (45)	0/60 (42)	1/60 (32) 0.4267
nose, level c	CHONDROMA	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)

Organ Name	Tumor Name	0mg|kg|day Cont.(N=60) P – Trend	10mg|kg|day Low (N=60) P- C vs. L	25mg|kg|day Med (N=60) P – C vs. M	45mg|kg|day MHigh (N=60) P – C vs. MH
	LYMPHOMA [m]	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
nose, level d	ADENOMA, SEBACEOUS CELL	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	OSTEOMA	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
pancreas	ADENOMA, ACINAR CELL	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
	ADENOMA, ACINAR-ISLET CELL	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
	ADENOMA, ISLET CELL	5/60 (45) 0.8880	8/60 (47) 0.3047	3/60 (42) 0.8437	2/60 (32) 0.8727
	CARCINOMA, ACINAR CELL	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
	CARCINOMA, ISLET CELL	1/60 (43) 0.2724	2/60 (45) 0.5172	1/60 (42) 0.7471	2/60 (32) 0.3893
	C_acinar cell_A+C	**0/60 (43) 0.8081**	**3/60 (45) 0.1293**	**0/60 (42)**	**0/60 (32)**
	C_islet cell_A+C	**6/60 (45) 0.7853**	**11/60 (47) 0.1648**	**4/60 (43) 0.8237**	**4/60 (32) 0.6686**
	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	OSTEOSARCOMA [s]	0/60 (43) 0.4568	0/60 (45)	1/60 (42) 0.4941	0/60 (32)
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 0.9283	1/60 (45) 0.7584	0/60 (42) 1.0000	0/60 (32) 1.0000
parathyroid glands	ADENOMA	2/60 (43) 0.7806	2/60 (46) 0.7170	3/60 (42) 0.4887	0/60 (32) 1.0000
peyers patch	LYMPHOMA [m]	2/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
pituitary gland	ADENOMA, PARS DISTALIS	38/60 (52) 0.9670	34/60 (52) 0.8560	29/60 (49) 0.9545	21/60 (38) 0.9761
	ADENOMA, PARS INTERMEDIA	1/60 (43) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	CARCINOMA, PARS DISTALIS	0/60 (43) 0.1975	0/60 (45)	0/60 (42)	1/60 (32) 0.4267
	CRANIOPHARYNGIOMA	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
	C_pars distalis_A+C	**38/60 (52) 0.9447**	**34/60 (52) 0.8560**	**29/60 (49) 0.9545**	**22/60 (38) 0.9584**
preputial glands	CARCINOMA, SQUAMOUS CELL	1/60 (43) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000

Organ Name	Tumor Name	0mg|kg|day Cont.(N=60) P – Trend	10mg|kg|day Low (N=60) P- C vs. L	25mg|kg|day Med (N=60) P – C vs. M	45mg|kg|day MHigh (N=60) P – C vs. MH
	PAPILLOMA, SQUAMOUS CELL	0/60 (43) 0.4568	0/60 (45)	1/60 (42) 0.4941	0/60 (32)
prostate gland	ADENOMA	1/60 (43) 0.2639	0/60 (45) 1.0000	2/60 (42) 0.4911	1/60 (32) 0.6746
	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
salivary gland, ma	ADENOCARCINOMA	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
salivary gland, pa	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
seminal vesicles	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
skeletal muscle	HEMANGIOSARCOMA	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
	SARCOMA, HISTIOCYTIC [m]	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
skeletal muscle, b	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (43) 0.7818	2/60 (46) 0.2643	0/60 (42)	0/60 (32)
skin	ADENOMA, BASAL CELL	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	ADENOMA, SEBACEOUS CELL	1/60 (44) 0.3226	0/60 (45) 1.0000	1/60 (42) 0.7412	1/60 (32) 0.6681
	CARCINOMA, SEBACEOUS CELL	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	CARCINOMA, SQUAMOUS CELL	1/60 (44) 0.7034	0/60 (45) 1.0000	1/60 (42) 0.7412	0/60 (32) 1.0000
	C keratoacanthoma+papilloma+carcinoma squamous cell	**11/60 (46) 0.9858**	**6/60 (47) 0.9523**	**8/60 (44) 0.8221**	**1/60 (32) 0.9991**
	C_sebaceous cell_A+C	**1/60 (44) 0.3226**	**0/60 (45) 1.0000**	**1/60 (42) 0.7412**	**1/60 (32) 0.6681**
	HAIR FOLLICLE TUMOR	1/60 (44) 0.7034	0/60 (45) 1.0000	1/60 (42) 0.7412	0/60 (32) 1.0000
	KERATOACANTHOMA	6/60 (45) 0.8620	5/60 (47) 0.7636	7/60 (43) 0.4642	1/60 (32) 0.9811
	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	PAPILLOMA, SQUAMOUS CELL	4/60 (44) 0.9988	1/60 (45) 0.9738	0/60 (42) 1.0000	0/60 (32) 1.0000

Organ Name	Tumor Name	0mg|kg|day Cont.(N=60) P – Trend	10mg|kg|day Low (N=60) P- C vs. L	25mg|kg|day Med (N=60) P – C vs. M	45mg|kg|day MHigh (N=60) P – C vs. MH
skin, subcutis	**C_fibroma+fibrosarcoma**	**4/60 (44) 0.4753**	**2/60 (45) 0.9038**	**2/60 (42) 0.8880**	**3/60 (33) 0.6488**
	FIBROMA	2/60 (44) 0.8503	2/60 (45) 0.7003	2/60 (42) 0.6741	0/60 (32) 1.0000
	FIBROSARCOMA	2/60 (44) 0.1336	0/60 (45) 1.0000	0/60 (42) 1.0000	3/60 (33) 0.3644
	FIBROUS HISTIOCYTOMA	0/60 (43) 0.2515	1/60 (45) 0.5114	0/60 (42)	1/60 (32) 0.4267
	LIPOMA	1/60 (44) 0.9215	3/60 (47) 0.3337	0/60 (42) 1.0000	0/60 (32) 1.0000
	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 0.9214	2/60 (46) 0.5169	0/60 (42) 1.0000	0/60 (32) 1.0000
	SCHWANNOMA	0/60 (43) 0.4252	1/60 (46) 0.5169	2/60 (42) 0.2412	0/60 (32)
small intestine, i	SARCOMA, HISTIOCYTIC [m]	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
small intestine, j	ADENOCARCINOMA [s]	0/60 (43) 0.7362	1/60 (46) 0.5169	0/60 (42)	0/60 (32)
spinal cord, cervi	ASTROCYTOMA	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
spleen	LYMPHOMA [m]	1/60 (44) 0.9292	1/60 (46) 0.7638	0/60 (42) 1.0000	0/60 (32) 1.0000
	OSTEOSARCOMA [s]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
stomach, glandular	ADENOCARCINOMA	1/60 (43) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
stomach, nonglandu	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
testes	ADENOMA, INTERSTITIAL CELL	1/60 (44) 0.5218	2/60 (46) 0.5169	1/60 (42) 0.7412	1/60 (32) 0.6681
	LYMPHOMA [m]	1/60 (44) 0.9292	1/60 (46) 0.7638	0/60 (42) 1.0000	0/60 (32) 1.0000
thymus	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
thyroid gland	ADENOMA, C-CELL	11/60 (46) 0.9227	8/60 (46) 0.8485	6/60 (42) 0.9222	4/60 (33) 0.9491
	ADENOMA, FOLLICULAR CELL	3/60 (43) 0.9925	2/60 (45) 0.8337	0/60 (42) 1.0000	0/60 (32) 1.0000
	CARCINOMA, FOLLICULAR CELL	1/60 (43) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000

Organ Name	Tumor Name	0mg|kg|day Cont.(N=60) P – Trend	10mg|kg|day Low (N=60) P- C vs. L	25mg|kg|day Med (N=60) P – C vs. M	45mg|kg|day MHigh (N=60) P – C vs. MH
	C_follicular-cell_A+C	**4/60 (43) 0.9978**	**2/60 (45) 0.9088**	**0/60 (42) 1.0000**	**0/60 (32) 1.0000**
tongue	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
trachea	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
urinary bladder	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (42) 1.0000	0/60 (32) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (43) 0.7346	1/60 (45) 0.5114	0/60 (42)	0/60 (32)
zymbal`s gland	CARCINOMA, SEBACEOUS CELL	0/60 (43) 0.5687	1/60 (46) 0.5169	1/60 (43) 0.5000	0/60 (32)
	CARCINOMA, SQUAMOUS CELL	0/60 (43) 0.4601	0/60 (45)	1/60 (43) 0.5000	0/60 (32)

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed.
NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0 01 and 0 05 for a common tumor and a rare tumor, respectively.
Note: In all tumor tables, a tumor marked with "s" is a secondary tumor and marked with "m" is a multicentric tumor. The tumors without any mark are the primary tumors.

Table 5B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons – Female Rats

Organ Name	Tumor Name	0mg|kg|day Cont. (N=60) P - Trend	5mg|kg|day Low (N=60) P – C vs. L	12mg|kg|day Med (N=60) P – C vs. M	25mg|kg|day M-High (N=60) P – C vs. MH	40mg|kg|day High (N=60) P – C vs. H
adipose tissue, br	HIBERNOMA	1/60 (39) 0.7566	2/60 (50) 0.5933	3/60 (50) 0.4074	1/60 (32) 0.7018	0/60 (25) 1.0000
adrenal glands	ADENOMA, CORTICAL	1/60 (39) 0.5632	0/60 (49) 1.0000	1/60 (49) 0.8064	1/60 (32) 0.7018	0/60 (25) 1.0000
	LEUKEMIA, GRANULOCYTIC [m]	1/60 (39) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	LYMPHOMA [m]	1/60 (40) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	C_PHEOCHROMOCYTOMA _benign+malignant	**0/60 (39) 0.7008**	**3/60 (49) 0.1679**	**3/60 (49) 0.1679**	**1/60 (32) 0.4507**	**0/60 (25)**
all sites	**C_fibrous histiocytoma**	**1/60 (40) 0.8740**	**1/60 (50) 0.8052**	**1/60 (49) 0.8008**	**0/60 (32) 1.0000**	**0/60 (25) 1.0000**
	C_hemangioma+sarcoma	**0/60 (39) 0.7990**	**1/60 (49) 0.5568**	**0/60 (49)**	**0/60 (32)**	**0/60 (25)**
	C_lipomas+carcomas	**1/60 (39) 0.8781**	**1/60 (49) 0.8064**	**1/60 (49) 0.8064**	**0/60 (32) 1.0000**	**0/60 (25) 1.0000**

Organ Name	Tumor Name	0mg|kg|day Cont. (N=60) P - Trend	5mg|kg|day Low (N=60) P – C vs. L	12mg|kg|day Med (N=60) P – C vs. M	25mg|kg|day M-High (N=60) P – C vs. MH	40mg|kg|day High (N=60) P – C vs. H
	C_lymphoma [m]	**2/60 (40) 1.0000**	**0/60 (49) 1.0000**	**0/60 (49) 1.0000**	**0/60 (32) 1.0000**	**0/60 (25) 1.0000**
	C_sarcoma histiocytic [m]	**0/60 (39) 0.5464**	**0/60 (49)**	**1/60 (49) 0.5568**	**0/60 (32)**	**0/60 (25)**
bone	OSTEOSARCOMA	0/60 (39) 0.1289	0/60 (49)	0/60 (49)	0/60 (32)	1/60 (25) 0.3906
bone marrow, femur	LEUKEMIA, GRANULOCYTIC [m]	1/60 (39) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
bone marrow, stern	LEUKEMIA, GRANULOCYTIC [m]	1/60 (39) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
brain	ASTROCYTOMA	1/60 (39) 0.2757	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	1/60 (26) 0.6437
	CARCINOMA, PARS DISTALIS [s]	3/60 (40) 0.4103	5/60 (51) 0.5004	5/60 (49) 0.4762	2/60 (33) 0.7554	3/60 (26) 0.4426
	MIXED GLIOMA	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
cavity, abdominal	CARCINOMA, ACINAR CELL [s]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
	CARCINOMA, ISLET CELL [s]	1/60 (40) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	LIPOMA	0/60 (39) 0.7990	1/60 (49) 0.5568	0/60 (49)	0/60 (32)	0/60 (25)
	LYMPHOMA [m]	1/60 (40) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
clitoral glands	CARCINOMA, SQUAMOUS CELL	0/60 (39) 0.0588	0/60 (49)	0/60 (49)	1/60 (32) 0.4507	1/60 (25) 0.3906
hard palate	CARCINOMA, SQUAMOUS CELL	0/60 (39) 0.1289	0/60 (49)	0/60 (49)	0/60 (32)	1/60 (25) 0.3906
	PAPILLOMA, SQUAMOUS CELL	0/60 (39) 0.1333	0/60 (49)	0/60 (49)	0/60 (32)	1/60 (26) 0.4000
head	CARCINOMA, SQUAMOUS CELL	0/60 (39) 0.1333	0/60 (49)	0/60 (49)	0/60 (32)	1/60 (26) 0.4000
kidneys	ADENOMA, TUBULAR CELL	1/60 (39) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	CARCINOMA, ACINAR CELL [s]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)

Organ Name	Tumor Name	0mg|kg|day Cont. (N=60) P - Trend	5mg|kg|day Low (N=60) P – C vs. L	12mg|kg|day Med (N=60) P – C vs. M	25mg|kg|day M-High (N=60) P – C vs. MH	40mg|kg|day High (N=60) P – C vs. H
liver	ADENOMA, HEPATOCELLULAR	0/60 (39) 0.2938	0/60 (49)	0/60 (49)	1/60 (32) 0.4507	0/60 (25)
	CARCINOMA, ISLET CELL [s]	1/60 (40) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	CHOLANGIOMA	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
	LEUKEMIA, GRANULOCYTIC [m]	1/60 (39) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	LYMPHOMA [m]	1/60 (40) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
lung	ADENOCARCINOMA [s]	0/60 (39) 0.1289	0/60 (49)	0/60 (49)	0/60 (32)	1/60 (25) 0.3906
	ADENOMA, BRONCHIOLAR ALVEOLAR	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
	CARCINOMA, ACINAR CELL [s]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
	CHORDOMA, (PRIMARY SITE UNKNOWN)	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
	HIBERNOMA [s]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
	LEUKEMIA, GRANULOCYTIC [m]	1/60 (39) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	PHEOCHROMOCYTOMA [s]	0/60 (39) 0.7990	1/60 (49) 0.5568	0/60 (49)	0/60 (32)	0/60 (25)
	SARCOMA, HISTIOCYTIC [m]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
	SARCOMA, STROMAL [s]	0/60 (39) 0.2938	0/60 (49)	0/60 (49)	1/60 (32) 0.4507	0/60 (25)
lymph node, iliac	LYMPHOMA [m]	1/60 (40) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
lymph node, mandib	CARCINOMA, SQUAMOUS CELL [s]	0/60 (39) 0.1333	0/60 (49)	0/60 (49)	0/60 (32)	1/60 (26) 0.4000

Organ Name	Tumor Name	0mg|kg|day Cont. (N=60) P - Trend	5mg|kg|day Low (N=60) P – C vs. L	12mg|kg|day Med (N=60) P – C vs. M	25mg|kg|day M-High (N=60) P – C vs. MH	40mg|kg|day High (N=60) P – C vs. H
lymph node, medias	SARCOMA, HISTIOCYTIC [m]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
lymph node, mesent	HEMANGIOSARCOMA	0/60 (39) 0.7990	1/60 (49) 0.5568	0/60 (49)	0/60 (32)	0/60 (25)
	SARCOMA, HISTIOCYTIC [m]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
lymph node, renal	LYMPHOMA [m]	1/60 (40) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
mammary gland	ADENOCARCINOMA	14/60 (45) 0.9881	16/60 (52) 0.6018	16/60 (52) 0.6018	1/60 (32) 0.9999	5/60 (25) 0.9019
	ADENOMA	3/60 (40) 0.8939	1/60 (49) 0.9626	2/60 (49) 0.8763	1/60 (32) 0.9112	0/60 (25) 1.0000
	C_adenocarcinoma+adenoma	**17/60 (46) 0.9953**	**17/60 (52) 0.7439**	**17/60 (52) 0.7439**	**2/60 (32) 0.9999**	**5/60 (25) 0.9622**
	FIBROADENOMA	22/60 (44) 1.0000	21/60 (52) 0.8749	17/60 (50) 0.9627	0/60 (32) 1.0000	4/60 (25) 0.9993
multicentric neoplasm	LEUKEMIA, GRANULOCYTIC [m]	1/60 (39) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	LYMPHOMA [m]	2/60 (40) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
ovaries	GRANULOSA CELL TUMOR	0/60 (39) 0.3281	2/60 (50) 0.3128	0/60 (49)	0/60 (32)	1/60 (25) 0.3906
	LYMPHOMA [m]	1/60 (40) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	THECOMA	0/60 (39) 0.7990	1/60 (49) 0.5568	0/60 (49)	0/60 (32)	0/60 (25)
pancreas	ADENOMA, ISLET CELL	0/60 (39) 0.6093	2/60 (49) 0.3072	2/60 (49) 0.3072	1/60 (32) 0.4507	0/60 (25)
	CARCINOMA, ACINAR CELL	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
	CARCINOMA, ISLET CELL	2/60 (40) 0.5119	0/60 (49) 1.0000	1/60 (49) 0.9130	0/60 (32) 1.0000	1/60 (25) 0.7738
	C_islet_cell_A+C	**2/60 (40) 0.5975**	**2/60 (49) 0.7643**	**3/60 (49) 0.5963**	**1/60 (32) 0.8343**	**1/60 (25) 0.7738**

Organ Name	Tumor Name	0mg|kg|day Cont. (N=60) P - Trend	5mg|kg|day Low (N=60) P – C vs. L	12mg|kg|day Med (N=60) P – C vs. M	25mg|kg|day M-High (N=60) P – C vs. MH	40mg|kg|day High (N=60) P – C vs. H
parathyroid glands	ADENOMA	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
pituitary gland	ADENOMA, PARS DISTALIS	45/60 (53) 0.9943	45/60 (57) 0.8548	47/60 (58) 0.7855	27/60 (39) 0.9798	16/60 (26) 0.9947
	CARCINOMA, PARS DISTALIS	3/60 (40) 0.4103	5/60 (51) 0.5004	5/60 (49) 0.4762	2/60 (33) 0.7554	3/60 (26) 0.4426
	C_pars distalis_A+C	**48/60 (54) 0.9961**	**50/60 (58) 0.7616**	**52/60 (58) 0.5678**	**29/60 (40) 0.9895**	**19/60 (27) 0.9902**
	LYMPHOMA [m]	1/60 (40) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
salivary gland, pa	ADENOCARCINOMA	0/60 (39) 0.2974	0/60 (49)	0/60 (49)	1/60 (33) 0.4583	0/60 (25)
skin	ADENOMA, BASAL CELL	0/60 (39) 0.8000	1/60 (50) 0.5618	0/60 (49)	0/60 (32)	0/60 (25)
	C_carcinoma squamous cell+keratoacanthoma	**0/60 (39) 0.6934**	**1/60 (49) 0.5568**	**1/60 (49) 0.5568**	**0/60 (32)**	**0/60 (25)**
	KERATOACANTHOMA	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
	PAPILLOMA, SQUAMOUS CELL	0/60 (39) 0.7990	1/60 (49) 0.5568	0/60 (49)	0/60 (32)	0/60 (25)
skin, subcutis	**C_fibro_ma+sarcoma**	**3/60 (39) 0.9755**	**0/60 (49) 1.0000**	**1/60 (49) 0.9647**	**0/60 (32) 1.0000**	**0/60 (25) 1.0000**
	FIBROMA	2/60 (39) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	FIBROSARCOMA	1/60 (39) 0.7955	0/60 (49) 1.0000	1/60 (49) 0.8064	0/60 (32) 1.0000	0/60 (25) 1.0000
	FIBROUS HISTIOCYTOMA	1/60 (40) 0.8740	1/60 (50) 0.8052	1/60 (49) 0.8008	0/60 (32) 1.0000	0/60 (25) 1.0000
	LIPOMA	1/60 (39) 0.7955	0/60 (49) 1.0000	1/60 (49) 0.8064	0/60 (32) 1.0000	0/60 (25) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
	SCHWANNOMA	1/60 (39) 0.9604	1/60 (49) 0.8064	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
small intestine, j	LEIOMYOMA	0/60 (39) 0.2974	0/60 (49)	0/60 (49)	1/60 (33) 0.4583	0/60 (25)

Organ Name	Tumor Name	0mg|kg|day Cont. (N=60) P - Trend	5mg|kg|day Low (N=60) P – C vs. L	12mg|kg|day Med (N=60) P – C vs. M	25mg|kg|day M-High (N=60) P – C vs. MH	40mg|kg|day High (N=60) P – C vs. H
spinal cord, cervi	MIXED GLIOMA [s]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
spinal cord, lumba	MIXED GLIOMA	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
spinal cord, thora	MIXED GLIOMA [s]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
spleen	CARCINOMA, ISLET CELL [s]	1/60 (40) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	LEUKEMIA, GRANULOCYTIC [m]	1/60 (39) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	LYMPHOMA [m]	1/60 (40) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	SARCOMA, HISTIOCYTIC [m]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
thymus	LYMPHOMA [m]	1/60 (39) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
thyroid gland	ADENOMA, C-CELL	10/60 (41) 0.9980	9/60 (51) 0.8538	6/60 (49) 0.9624	4/60 (32) 0.9454	0/60 (25) 1.0000
	CARCINOMA, C-CELL	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
	CARCINOMA, FOLLICULAR CELL	1/60 (39) 0.8781	1/60 (49) 0.8064	1/60 (49) 0.8064	0/60 (32) 1.0000	0/60 (25) 1.0000
	C_c-cell_A+C	**10/60 (41) 0.9978**	**9/60 (51) 0.8538**	**7/60 (50) 0.9375**	**4/60 (32) 0.9454**	**0/60 (25) 1.0000**
uterus with cervix	ADENOCARCINOMA	0/60 (39) 0.1289	0/60 (49)	0/60 (49)	0/60 (32)	1/60 (25) 0.3906
	ADENOMA	0/60 (39) 0.7990	1/60 (49) 0.5568	0/60 (49)	0/60 (32)	0/60 (25)
	GRANULAR CELL TUMOR	4/60 (39) 0.9574	1/60 (49) 0.9853	1/60 (49) 0.9853	1/60 (32) 0.9558	0/60 (25) 1.0000
	LEIOMYOMA	1/60 (39) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
	POLYP, STROMAL	8/60 (41) 0.9987	10/60 (50) 0.5835	2/60 (49) 0.9968	1/60 (32) 0.9964	1/60 (25) 0.9905
	SARCOMA, HISTIOCYTIC [m]	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)

Organ Name	Tumor Name	0mg|kg|day Cont. (N=60) P - Trend	5mg|kg|day Low (N=60) P – C vs. L	12mg|kg|day Med (N=60) P – C vs. M	25mg|kg|day M-High (N=60) P – C vs. MH	40mg|kg|day High (N=60) P – C vs. H
	SARCOMA, STROMAL	1/60 (40) 0.5600	0/60 (49) 1.0000	1/60 (49) 0.8008	1/60 (32) 0.6948	0/60 (25) 1.0000
vagina	**C_leiomyo_ma+sarcoma**	**0/60 (39) 0.4380**	**1/60 (50) 0.5618**	**0/60 (49)**	**1/60 (33) 0.4583**	**0/60 (25)**
	GRANULAR CELL TUMOR	2/60 (39) 0.6813	1/60 (50) 0.9195	0/60 (49) 1.0000	2/60 (32) 0.6144	0/60 (25) 1.0000
	LEIOMYOMA	0/60 (39) 0.8000	1/60 (50) 0.5618	0/60 (49)	0/60 (32)	0/60 (25)
	LEIOMYOSARCOMA	0/60 (39) 0.2974	0/60 (49)	0/60 (49)	1/60 (33) 0.4583	0/60 (25)
	POLYP	0/60 (39) 0.5464	0/60 (49)	1/60 (49) 0.5568	0/60 (32)	0/60 (25)
	SARCOMA, STROMAL [s]	1/60 (40) 1.0000	0/60 (49) 1.0000	0/60 (49) 1.0000	0/60 (32) 1.0000	0/60 (25) 1.0000
zymbal`s gland	CARCINOMA, SEBACEOUS CELL	0/60 (39) 0.2974	0/60 (49)	0/60 (49)	1/60 (33) 0.4583	0/60 (25)

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed.
NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0 01 and 0 05 for a common tumor and a rare tumor, respectively.
Note: In all tumor tables, a tumor marked with "s" is a secondary tumor and marked with "m" is a multicentric tumor. The tumors without any mark are the primary tumors.

Table 6A: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Water Control in Male mice

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
adrenal glands	ADENOMA, CORTICAL	1/60 (46) 0.8700	2/60 (44) 0.4831	0/60 (39) 1.0000	0/60 (13) 1.0000
	ADENOMA, SUBCAPSULAR CELL	2/60 (47) 0.8273	2/60 (44) 0.6663	1/60 (39) 0.8416	0/60 (13) 1.0000
	LYMPHOMA [m]	1/60 (47) 0.3903	0/60 (44) 1.0000	2/60 (41) 0.4483	0/60 (13) 1.0000
all sites	**C_hemangioma+sarcoma [m]**	**8/60 (49) 0.9657**	**1/60 (44) 0.9979**	**3/60 (39) 0.9415**	**0/60 (13) 1.0000**
	C_leukemia_granulocytic [m]	**1/60 (47) 1.0000**	**0/60 (44) 1.0000**	**0/60 (39) 1.0000**	**0/60 (13) 1.0000**
	C_lymphoma [m]	**9/60 (50) 0.1602**	**4/60 (45) 0.9460**	**9/60 (43) 0.4613**	**4/60 (16) 0.3871**
	C_sarcoma histiocytic [m]	**1/60 (46) 1.0000**	**0/60 (44) 1.0000**	**0/60 (39) 1.0000**	**0/60 (13) 1.0000**
aorta	LYMPHOMA [m]	0/60 (46) 0.6761	1/60 (44) 0.4889	0/60 (39)	0/60 (13)

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
bone marrow, femur	HEMANGIOSARCOMA [m]	2/60 (48) 0.9645	1/60 (44) 0.8623	0/60 (39) 1.0000	0/60 (13) 1.0000
	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	7/60 (49) 0.8576	3/60 (45) 0.9395	5/60 (42) 0.7387	0/60 (13) 1.0000
bone marrow, stern	CARCINOMA, BRONCHIOLAR ALVEOL [s]	0/60 (46) 0.3662	0/60 (44)	1/60 (39) 0.4588	0/60 (13)
	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	7/60 (49) 0.6927	3/60 (45) 0.9395	5/60 (42) 0.7387	1/60 (14) 0.8836
	MAST CELL TUMOR	0/60 (46) 0.0979	0/60 (44)	0/60 (39)	1/60 (14) 0.2333
bone, femur	LYMPHOMA [m]	0/60 (46) 0.3706	0/60 (44)	1/60 (40) 0.4651	0/60 (13)
bone, femur (proxi	LYMPHOMA [m]	0/60 (46) 0.3706	0/60 (44)	1/60 (40) 0.4651	0/60 (13)
bone, sternum	CARCINOMA, BRONCHIOLAR ALVEOL [s]	0/60 (46) 0.3662	0/60 (44)	1/60 (39) 0.4588	0/60 (13)
	LYMPHOMA [m]	1/60 (47) 0.1103	0/60 (44) 1.0000	2/60 (40) 0.4391	1/60 (14) 0.4093
brain	LYMPHOMA [m]	1/60 (47) 0.1103	0/60 (44) 1.0000	2/60 (40) 0.4391	1/60 (14) 0.4093
cavity, abdominal	HEMANGIOSARCOMA [m]	2/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	4/60 (48) 0.5711	2/60 (44) 0.8771	5/60 (42) 0.4146	0/60 (13) 1.0000
cavity, thoracic	CARCINOMA, BRONCHIOLAR ALVEOL [s]	0/60 (46) 0.1713	2/60 (44) 0.2362	1/60 (39) 0.4588	1/60 (14) 0.2333
	LYMPHOMA [m]	4/60 (49) 0.4281	2/60 (44) 0.8716	4/60 (42) 0.5530	1/60 (14) 0.7287
coagulating glands	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	3/60 (48) 0.0824	0/60 (44) 1.0000	4/60 (41) 0.4115	2/60 (15) 0.3411
epididymides	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	4/60 (48) 0.0464	0/60 (44) 1.0000	5/60 (42) 0.4146	3/60 (16) 0.2346
esophagus	LYMPHOMA [m]	2/60 (48) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
eyes	LYMPHOMA [m]	1/60 (47) 0.6023	0/60 (44) 1.0000	1/60 (40) 0.7110	0/60 (13) 1.0000

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
gallbladder	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	3/60 (47) 0.3693	3/60 (45) 0.6405	4/60 (42) 0.4366	1/60 (14) 0.6582
harderian glands	ADENOMA	11/60 (48) 0.3612	8/60 (45) 0.8079	8/60 (41) 0.7410	5/60 (17) 0.4083
	LYMPHOMA [m]	3/60 (48) 0.1132	1/60 (44) 0.9304	4/60 (41) 0.4115	2/60 (15) 0.3411
heart	CARCINOMA, BRONCHIOLAR ALVEOL [s]	0/60 (46) 0.1166	1/60 (44) 0.4889	1/60 (39) 0.4588	1/60 (14) 0.2333
	LYMPHOMA [m]	6/60 (49) 0.2040	2/60 (44) 0.9585	5/60 (41) 0.6261	3/60 (16) 0.3875
joint, tibiofemora	LYMPHOMA [m]	1/60 (47) 0.3903	0/60 (44) 1.0000	2/60 (41) 0.4483	0/60 (13) 1.0000
kidneys	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	8/60 (50) 0.3420	3/60 (45) 0.9618	6/60 (42) 0.6960	3/60 (16) 0.5323
lacrimal glands, e	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	5/60 (49) 0.1065	1/60 (44) 0.9817	5/60 (41) 0.5116	3/60 (16) 0.3059
large intestine, c	LYMPHOMA [m]	3/60 (47) 0.5384 3/60 (47) 0.5384	0/60 (44) 1.0000 0/60 (44) 1.0000	1/60 (40) 0.9199 1/60 (40) 0.9199	1/60 (14) 0.6582 1/60 (14) 0.6582
large intestine, r	LYMPHOMA [m]	2/60 (47) 0.7779	0/60 (44) 1.0000	1/60 (40) 0.8470	0/60 (13) 1.0000
larynx	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	3/60 (48) 0.7390	0/60 (44) 1.0000	2/60 (41) 0.7665	0/60 (13) 1.0000
liver	ADENOMA, HEPATOCELLULAR	11/60 (48) 0.9538	3/60 (44) 0.9941	4/60 (39) 0.9696	1/60 (14) 0.9677
	CARCINOMA, HEPATOCELLULAR	3/60 (47) 0.8854	0/60 (44) 1.0000	1/60 (39) 0.9160	0/60 (13) 1.0000
	C_Hepatocellular_A+C	**14/60 (49) 0.9784**	**3/60 (44) 0.9990**	**5/60 (39) 0.9814**	**1/60 (14) 0.9871**
	HEMANGIOSARCOMA [m]	3/60 (47) 0.8854	0/60 (44) 1.0000	1/60 (39) 0.9160	0/60 (13) 1.0000
	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	7/60 (50) 0.0793	3/60 (45) 0.9352	8/60 (43) 0.3736	4/60 (16) 0.2524

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	SARCOMA, HISTIOCYTIC [m]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
lung	ADENOMA, BRONCHIOLAR ALVEOLAR	18/60 (49) 0.9920	9/60 (44) 0.9756	6/60 (39) 0.9942	2/60 (15) 0.9841
	CARCINOMA, BRONCHIOLAR ALVEOL	5/60 (48) 0.8728	8/60 (45) 0.2349	2/60 (39) 0.9055	1/60 (14) 0.8004
	C_bronchiolar alveolar_A+C	**22/60 (51) 0.9946**	**16/60 (45) 0.8332**	**8/60 (40) 0.9953**	**3/60 (15) 0.9768**
	HEMANGIOSARCOMA [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	8/60 (50) 0.3704	2/60 (44) 0.9867	5/60 (41) 0.7918	3/60 (16) 0.5323
lymph node, hepati	LYMPHOMA [m]	2/60 (47) 0.3446	0/60 (44) 1.0000	1/60 (39) 0.8416	1/60 (14) 0.5495
lymph node, iliac	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
lymph node, inguin	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
lymph node, mandib	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	7/60 (49) 0.1747	3/60 (45) 0.9395	5/60 (41) 0.7240	4/60 (16) 0.2630
	SARCOMA, HISTIOCYTIC [m]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
lymph node, medias	CARCINOMA, BRONCHIOLAR ALVEOL [s]	1/60 (47) 0.8935	1/60 (44) 0.7360	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	1/60 (47) 0.6620	1/60 (44) 0.7360	1/60 (40) 0.7110	0/60 (13) 1.0000
lymph node, mesent	CARCINOMA, ISLET CELL [s]	0/60 (46) 0.3662	0/60 (44)	1/60 (39) 0.4588	0/60 (13)
	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	8/60 (50) 0.1437	4/60 (45) 0.9131	8/60 (43) 0.4758	4/60 (16) 0.3185
	SARCOMA, HISTIOCYTIC [m]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
lymph node, renal	LYMPHOMA [m]	2/60 (47) 0.2480	1/60 (44) 0.8665	0/60 (39) 1.0000	2/60 (15) 0.2443

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
mammary gland	LYMPHOMA [m]	2/60 (47) 0.7779	0/60 (44) 1.0000	1/60 (40) 0.8470	0/60 (13) 1.0000
mesentery/peritone	LYMPHOMA [m]	0/60 (46) 0.0979	0/60 (44)	0/60 (39)	1/60 (14) 0.2333
multicentric neoplasm	**C_hemangioma_A+C [m]**	**8/60 (49) 0.9657**	**1/60 (44) 0.9979**	**3/60 (39) 0.9415**	**0/60 (13) 1.0000**
	HEMANGIOMA [m]	0/60 (46) 0.3662	0/60 (44)	1/60 (39) 0.4588	0/60 (13)
	HEMANGIOSARCOMA [m]	8/60 (49) 0.9885	1/60 (44) 0.9979	2/60 (39) 0.9804	0/60 (13) 1.0000
	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	9/60 (50) 0.1602	4/60 (45) 0.9460	9/60 (43) 0.4613	4/60 (16) 0.3871
	SARCOMA, HISTIOCYTIC [m]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
nerve, sciatic	LYMPHOMA [m]	3/60 (47) 0.8854	0/60 (44) 1.0000	1/60 (39) 0.9160	0/60 (13) 1.0000
nose, level a	LYMPHOMA [m]	2/60 (48) 0.4192	0/60 (44) 1.0000	3/60 (41) 0.4249	0/60 (13) 1.0000
nose, level b	ADENOMA	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	2/60 (48) 0.4192	0/60 (44) 1.0000	3/60 (41) 0.4249	0/60 (13) 1.0000
nose, level c	LYMPHOMA [m]	3/60 (48) 0.5849	0/60 (44) 1.0000	3/60 (41) 0.5835	0/60 (13) 1.0000
nose, level d	LYMPHOMA [m]	3/60 (48) 0.5849	0/60 (44) 1.0000	3/60 (41) 0.5835	0/60 (13) 1.0000
pancreas	CARCINOMA, ISLET CELL	0/60 (46) 0.3662	0/60 (44)	1/60 (39) 0.4588	0/60 (13)
	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	5/60 (48) 0.2116	2/60 (45) 0.9339	6/60 (43) 0.4216	2/60 (15) 0.5342
parathyroid glands	LYMPHOMA [m]	1/60 (47) 0.8935	1/60 (44) 0.7360	0/60 (39) 1.0000	0/60 (13) 1.0000
penis	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
peyers patch	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	5/60 (48) 0.2581	1/60 (44) 0.9828	2/60 (40) 0.9111	3/60 (16) 0.3159
pharynx	LYMPHOMA [m]	1/60 (47) 0.6023	0/60 (44) 1.0000	1/60 (40) 0.7110	0/60 (13) 1.0000

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
pituitary gland	ADENOMA, PARS DISTALIS	0/60 (46) 0.6761	1/60 (44) 0.4889	0/60 (39)	0/60 (13)
	LYMPHOMA [m]	0/60 (46) 0.0393	0/60 (44)	2/60 (41) 0.2192	1/60 (14) 0.2333
preputial glands	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	5/60 (48) 0.8476	1/60 (44) 0.9828	3/60 (41) 0.8094	0/60 (13) 1.0000
prostate gland	ADENOMA	0/60 (46) 0.6761	1/60 (44) 0.4889	0/60 (39)	0/60 (13)
	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	5/60 (49) 0.3676	1/60 (44) 0.9817	3/60 (41) 0.8008	2/60 (15) 0.5241
salivary gland, ma	LYMPHOMA [m]	3/60 (48) 0.4622	1/60 (44) 0.9304	2/60 (41) 0.7665	1/60 (14) 0.6512
salivary gland, pa	LYMPHOMA [m]	2/60 (47) 0.2434	0/60 (44) 1.0000	2/60 (41) 0.6384	1/60 (14) 0.5495
salivary gland, su	LYMPHOMA [m]	2/60 (47) 0.7779	0/60 (44) 1.0000	1/60 (40) 0.8470	0/60 (13) 1.0000
seminal vesicles	LEUKEMIA, GRANULOCYTIC	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	2/60 (47) 0.0384	0/60 (44) 1.0000	4/60 (42) 0.2860	2/60 (15) 0.2443
skeletal muscle, b	LYMPHOMA [m]	2/60 (47) 0.7732	0/60 (44) 1.0000	1/60 (39) 0.8416	0/60 (13) 1.0000
skin	LYMPHOMA [m]	2/60 (48) 0.5748	0/60 (44) 1.0000	2/60 (40) 0.6199	0/60 (13) 1.0000
skin, subcutis	HEMANGIOSARCOMA [m]	2/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	1/60 (47) 0.1119	0/60 (44) 1.0000	2/60 (41) 0.4483	1/60 (14) 0.4093
	SARCOMA, UNDIFFERENTIATED	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
small intestine, d	LYMPHOMA [m]	3/60 (47) 0.0853	0/60 (44) 1.0000	4/60 (41) 0.4231	2/60 (15) 0.3495
small intestine, i	LYMPHOMA [m]	2/60 (47) 0.0079	0/60 (44) 1.0000	5/60 (42) 0.1732	3/60 (16) 0.0989
small intestine, j	LYMPHOMA [m]	1/60 (47) 0.0183	0/60 (44) 1.0000	3/60 (41) 0.2583	2/60 (15) 0.1425

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
spinal cord, cervi	LYMPHOMA [m]	0/60 (46) 0.3662	0/60 (44)	1/60 (39) 0.4588	0/60 (13)
spinal cord, lumba	LYMPHOMA [m]	1/60 (47) 0.5967	0/60 (44) 1.0000	1/60 (39) 0.7042	0/60 (13) 1.0000
spleen	HEMANGIOSARCOMA [m]	2/60 (48) 0.7695	0/60 (44) 1.0000	1/60 (39) 0.8368	0/60 (13) 1.0000
	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	7/60 (49) 0.0839	3/60 (45) 0.9395	8/60 (43) 0.3899	4/60 (16) 0.2630
stomach, glandular	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	6/60 (48) 0.4438	2/60 (45) 0.9638	4/60 (41) 0.7700	2/60 (15) 0.6174
stomach, nonglandu	LYMPHOMA [m]	0/60 (46) 0.3706	0/60 (44)	1/60 (40) 0.4651	0/60 (13)
tail	FIBROMA	0/60 (46) 0.6783	1/60 (45) 0.4945	0/60 (39)	0/60 (13)
testes	ADENOMA, INTERSTITIAL CELL	2/60 (47) 0.9660	1/60 (44) 0.8665	0/60 (39) 1.0000	0/60 (13) 1.0000
	HEMANGIOMA [m]	0/60 (46) 0.3662	0/60 (44)	1/60 (39) 0.4588	0/60 (13)
	HEMANGIOSARCOMA [m]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	2/60 (47) 0.7779	0/60 (44) 1.0000	1/60 (40) 0.8470	0/60 (13) 1.0000
thymus	CARCINOMA, BRONCHIOLAR ALVEOL [s]	0/60 (46) 0.3662	0/60 (44)	1/60 (39) 0.4588	0/60 (13)
	LYMPHOMA [m]	7/60 (49) 0.1396	3/60 (45) 0.9395	6/60 (42) 0.6155	4/60 (16) 0.2630
thyroid gland	LYMPHOMA [m]	5/60 (48) 0.6919	0/60 (44) 1.0000	2/60 (41) 0.9163	1/60 (14) 0.8004
tongue	LYMPHOMA [m]	4/60 (48) 0.9446	0/60 (44) 1.0000	1/60 (39) 0.9537	0/60 (13) 1.0000
trachea	LYMPHOMA [m]	2/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
ureters	LYMPHOMA [m]	0/60 (46) 0.0632	0/60 (44)	1/60 (40) 0.4651	1/60 (14) 0.2333
urinary bladder	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	5/60 (48) 0.3250	1/60 (44) 0.9828	6/60 (42) 0.4050	1/60 (14) 0.8004
zymbal`s gland	LEUKEMIA, GRANULOCYTIC [m]	1/60 (47) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	LYMPHOMA [m]	1/60 (47) 0.3858	0/60 (44) 1.0000	2/60 (40) 0.4391	0/60 (13) 1.0000

Note: X/ (YY): X=number of tumor bearing animals; YY=unweighted total number of animals observed; NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0 01 and 0 05 for a common tumor and a rare tumor, respectively.
Note: In all tumor tables, a tumor marked with "s" is a secondary tumor and marked with "m" is a multicentric tumor. The tumors without any mark are the primary tumors.

Table 6B: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Water Control in Female mice

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
adrenal glands	ADENOMA, SUBCAPSULAR CELL	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	2/60 (44) 0.4947	4/60 (47) 0.3705	2/60 (46) 0.7084	1/60 (11) 0.4952
all sites	**C_hemangioma+sarcoma [m]**	**7/60 (45) 0.7656**	**8/60 (46) 0.5188**	**4/60 (46) 0.9082**	**2/60 (12) 0.6140**
	C_lipomas+carcomas	**0/60 (44) 0.6966**	**1/60 (45) 0.5056**	**0/60 (46)**	**0/60 (10)**
	C_lymphoma [m]	**16/60 (49) 0.7543**	**8/60 (47) 0.9783**	**9/60 (48) 0.9645**	**4/60 (13) 0.6705**
	C_sarcoma histiocytic [m]	**3/60 (44) 0.9923**	**1/60 (45) 0.9444**	**0/60 (46) 1.0000**	**0/60 (10) 1.0000**
bone marrow, femur	HEMANGIOSARCOMA [m]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	10/60 (48) 0.7736	3/60 (46) 0.9911	5/60 (48) 0.9553	2/60 (12) 0.7565
bone marrow, stern	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	10/60 (47) 0.9040	3/60 (46) 0.9921	5/60 (48) 0.9595	1/60 (11) 0.9235
bone marrow, tibia	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
bone, femur	LYMPHOMA [m]	2/60 (45) 0.8009	0/60 (45) 1.0000	1/60 (47) 0.8870	0/60 (10) 1.0000
bone, femur (proxi	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
bone, rib	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
bone, sternum	LYMPHOMA [m]	3/60 (46) 0.7907	1/60 (46) 0.9416	2/60 (47) 0.8260	0/60 (10) 1.0000
brain	ASTROCYTOMA	0/60 (44) 0.3862	0/60 (45)	1/60 (46) 0.5111	0/60 (10)
	LYMPHOMA [m]	3/60 (45) 0.7978	1/60 (45) 0.9417	2/60 (47) 0.8328	0/60 (10) 1.0000
cavity, abdominal	ADENOCARCINOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	HEMANGIOMA [m]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	HEMANGIOSARCOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LIPOSARCOMA	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	7/60 (47) 0.3870	3/60 (46) 0.9513	4/60 (46) 0.8944	3/60 (13) 0.3710
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
cavity, thoracic	ADENOCARCINOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	HEMANGIOSARCOMA [m]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	6/60 (46) 0.3093	3/60 (45) 0.9160	4/60 (47) 0.8508	3/60 (13) 0.3101
clitoral glands	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	6/60 (46) 0.9924	3/60 (45) 0.9160	1/60 (46) 0.9939	0/60 (10) 1.0000
esophagus	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LYMPHOMA [m]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
eyes	LYMPHOMA [m]	0/60 (44) 0.7194	2/60 (46) 0.2584	0/60 (46)	0/60 (10)
eyes, optic nerves	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
gallbladder	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	8/60 (45) 0.9340	4/60 (46) 0.9453	5/60 (47) 0.9005	0/60 (10) 1.0000
harderian glands	ADENOMA	6/60 (44) 0.4743	2/60 (45) 0.9731	4/60 (47) 0.8679	2/60 (12) 0.5515
	LYMPHOMA [m]	6/60 (46) 0.7985	3/60 (45) 0.9160	3/60 (47) 0.9259	1/60 (11) 0.7976
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
heart	ADENOCARCINOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	HEMANGIOSARCOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	7/60 (46) 0.3834	6/60 (47) 0.7383	6/60 (48) 0.7514	3/60 (13) 0.3832
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
joint, tibiofemora	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
kidneys	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (44) 0.9106	1/60 (46) 0.7638	0/60 (46) 1.0000	0/60 (10) 1.0000
	LYMPHOMA [m]	14/60 (48) 0.8253	6/60 (46) 0.9856	5/60 (48) 0.9954	4/60 (13) 0.5801
	SARCOMA, HISTIOCYTIC [m]	2/60 (44) 0.9734	1/60 (45) 0.8834	0/60 (46) 1.0000	0/60 (10) 1.0000
lacrimal glands, e	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	11/60 (47) 0.7245	5/60 (45) 0.9678	3/60 (46) 0.9959	4/60 (13) 0.4152
large intestine, c	LYMPHOMA [m]	4/60 (46) 0.7937	6/60 (47) 0.3837	2/60 (47) 0.9032	1/60 (11) 0.6726
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
large intestine, r	LYMPHOMA [m]	2/60 (44) 0.9592	3/60 (46) 0.5213	0/60 (46) 1.0000	0/60 (10) 1.0000
larynx	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	LYMPHOMA [m]	3/60 (46) 0.6265	4/60 (45) 0.4876	2/60 (47) 0.8260	1/60 (11) 0.5869
	PAPILLOMA	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
liver	ADENOMA, HEPATOCELLULAR	2/60 (44) 0.9734	1/60 (45) 0.8834	0/60 (46) 1.0000	0/60 (10) 1.0000
	CARCINOMA, HEPATOCELLULAR	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	C_Hepatocellular_A+C	**2/60 (44) 0.9586**	**2/60 (45) 0.7003**	**0/60 (46) 1.0000**	**0/60 (10) 1.0000**
	HEMANGIOSARCOMA [m]	2/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (44) 0.6831	1/60 (46) 0.7638	1/60 (46) 0.7638	0/60 (10) 1.0000
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	14/60 (48) 0.8391	7/60 (47) 0.9737	7/60 (48) 0.9767	3/60 (12) 0.7328
	SARCOMA, HISTIOCYTIC [m]	2/60 (44) 0.9734	1/60 (45) 0.8834	0/60 (46) 1.0000	0/60 (10) 1.0000
lung	ADENOCARCINOMA	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	ADENOMA, BRONCHIOLAR ALVEOLAR	6/60 (45) 0.7930	9/60 (46) 0.3028	5/60 (46) 0.7517	1/60 (11) 0.8043
	CARCINOMA, BRONCHIOLAR ALVEOL	0/60 (44) 0.2595	1/60 (45) 0.5056	2/60 (46) 0.2584	0/60 (10)
	C_bronchiolar alveolar_A+C	**6/60 (45) 0.6756**	**10/60 (46) 0.2189**	**7/60 (46) 0.5173**	**1/60 (11) 0.8043**
	HEMANGIOSARCOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEIOMYOSARCOMA	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (44) 0.9106	1/60 (46) 0.7638	0/60 (46) 1.0000	0/60 (10) 1.0000
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	13/60 (48) 0.7501	8/60 (47) 0.9241	6/60 (48) 0.9807	4/60 (13) 0.5217
	SARCOMA, HISTIOCYTIC [m]	2/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
lymph node, axilla	LYMPHOMA [m]	2/60 (45) 0.5061	0/60 (45) 1.0000	0/60 (46) 1.0000	1/60 (11) 0.4881
	SARCOMA, UNDIFFERENTIATED [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
lymph node, hepati	LYMPHOMA [m]	0/60 (44) 0.4347	1/60 (45) 0.5056	1/60 (47) 0.5165	0/60 (10)
lymph node, iliac	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	2/60 (44) 0.9586	2/60 (45) 0.7003	0/60 (46) 1.0000	0/60 (10) 1.0000
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
lymph node, inguin	LYMPHOMA [m]	3/60 (44) 0.9925	1/60 (46) 0.9469	0/60 (46) 1.0000	0/60 (10) 1.0000
lymph node, mandib	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (44) 0.9106	1/60 (46) 0.7638	0/60 (46) 1.0000	0/60 (10) 1.0000
	LYMPHOMA [m]	12/60 (49) 0.6654	8/60 (47) 0.8756	6/60 (48) 0.9635	4/60 (13) 0.4454
lymph node, medias	LYMPHOMA [m]	2/60 (44) 0.5121	2/60 (46) 0.7084	1/60 (46) 0.8873	1/60 (11) 0.4952
	SARCOMA, UNDIFFERENTIATED [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
lymph node, mesent	HEMANGIOSARCOMA [m]	1/60 (44) 0.6249	0/60 (45) 1.0000	1/60 (46) 0.7638	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (44) 0.9106	1/60 (46) 0.7638	0/60 (46) 1.0000	0/60 (10) 1.0000
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	14/60 (49) 0.6820	8/60 (47) 0.9447	8/60 (48) 0.9505	4/60 (13) 0.5631
	SARCOMA, HISTIOCYTIC [m]	2/60 (44) 0.9734	1/60 (45) 0.8834	0/60 (46) 1.0000	0/60 (10) 1.0000
lymph node, renal	LYMPHOMA [m]	2/60 (44) 0.6628	1/60 (45) 0.8834	2/60 (46) 0.7084	0/60 (10) 1.0000
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
mammary gland	ADENOACANTHOMA	0/60 (44) 0.3862	0/60 (45)	1/60 (46) 0.5111	0/60 (10)
	ADENOCARCINOMA	1/60 (44) 0.6844	1/60 (45) 0.7584	1/60 (46) 0.7638	0/60 (10) 1.0000
	C_adenoacanthoma+adenocarcinoma	**1/60 (44) 0.4847**	**1/60 (45) 0.7584**	**2/60 (47) 0.5250**	**0/60 (10) 1.0000**
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	6/60 (47) 0.7670	3/60 (46) 0.9159	1/60 (46) 0.9934	2/60 (12) 0.5178

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
mesentery/peritone	LYMPHOMA [m]	0/60 (44) 0.3904	0/60 (45)	1/60 (47) 0.5165	0/60 (10)
multicentric neoplasm	**C_hemangioma_A+C [m]**	**7/60 (45) 0.7656**	**8/60 (46) 0.5188**	**4/60 (46) 0.9082**	**2/60 (12) 0.6140**
	HEMANGIOMA [m]	1/60 (44) 0.2448	3/60 (45) 0.3167	0/60 (46) 1.0000	2/60 (12) 0.1127
	HEMANGIOSARCOMA [m]	6/60 (45) 0.9108	5/60 (45) 0.7392	4/60 (46) 0.8513	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (44) 0.6831	1/60 (46) 0.7638	1/60 (46) 0.7638	0/60 (10) 1.0000
	LYMPHOMA [m]	16/60 (49) 0.7543	8/60 (47) 0.9783	9/60 (48) 0.9645	4/60 (13) 0.6705
	SARCOMA, HISTIOCYTIC [m]	3/60 (44) 0.9923	1/60 (45) 0.9444	0/60 (46) 1.0000	0/60 (10) 1.0000
nerve, sciatic	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (44) 0.9106	1/60 (46) 0.7638	0/60 (46) 1.0000	0/60 (10) 1.0000
	LYMPHOMA [m]	5/60 (46) 0.9842	4/60 (45) 0.7464	1/60 (46) 0.9869	0/60 (10) 1.0000
nose, level a	LYMPHOMA [m]	2/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
nose, level b	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	3/60 (46) 0.8998	0/60 (45) 1.0000	1/60 (46) 0.9416	0/60 (10) 1.0000
nose, level c	LYMPHOMA [m]	2/60 (45) 0.3458	0/60 (45) 1.0000	1/60 (46) 0.8832	1/60 (11) 0.4881
nose, level d	LYMPHOMA [m]	2/60 (45) 0.7967	0/60 (45) 1.0000	1/60 (46) 0.8832	0/60 (10) 1.0000
ovaries	CYSTADENOCARCINOMA	0/60 (44) 0.3904	0/60 (45)	1/60 (47) 0.5165	0/60 (10)
	CYSTADENOMA	1/60 (44) 0.9051	3/60 (46) 0.3253	0/60 (46) 1.0000	0/60 (10) 1.0000
	C_cystadenoma+carcinoma	**1/60 (44) 0.7634**	**3/60 (46) 0.3253**	**1/60 (47) 0.7690**	**0/60 (10) 1.0000**
	HEMANGIOMA [m]	0/60 (44) 0.0062	0/60 (45)	0/60 (46)	2/60 (12) 0.0429
	HEMANGIOSARCOMA [m]	1/60 (44) 0.9094	1/60 (45) 0.7584	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	LYMPHOMA [m]	11/60 (48) 0.7777	6/60 (47) 0.9414	7/60 (48) 0.9049	2/60 (12) 0.8009
	SARCOMA, HISTIOCYTIC [m]	2/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	SEX-CORD/STROMAL TUMOR	0/60 (44) 0.4310	1/60 (45) 0.5056	1/60 (46) 0.5111	0/60 (10)
oviducts	ADENOCARCINOMA	0/60 (44) 0.3862	0/60 (45)	1/60 (46) 0.5111	0/60 (10)
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	7/60 (47) 0.9654	4/60 (46) 0.8944	3/60 (46) 0.9513	0/60 (10) 1.0000
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
pancreas	HEMANGIOSARCOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (44) 0.9106	1/60 (46) 0.7638	0/60 (46) 1.0000	0/60 (10) 1.0000
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	9/60 (46) 0.5711	7/60 (46) 0.7950	6/60 (47) 0.8799	3/60 (12) 0.4752
	SARCOMA, HISTIOCYTIC [m]	2/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
parathyroid glands	LYMPHOMA [m]	1/60 (44) 0.9094	1/60 (45) 0.7584	0/60 (46) 1.0000	0/60 (10) 1.0000
peyers patch	LYMPHOMA [m]	5/60 (45) 0.4045	5/60 (46) 0.6445	5/60 (48) 0.6709	2/60 (12) 0.4587
pharynx	LYMPHOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
pituitary gland	ADENOMA, PARS DISTALIS	0/60 (44) 0.8003	3/60 (45) 0.1250	0/60 (46)	0/60 (10)
	ADENOMA, PARS INTERMEDIA	1/60 (44) 0.6249	0/60 (45) 1.0000	1/60 (46) 0.7638	0/60 (10) 1.0000
	LYMPHOMA [m]	2/60 (44) 0.6664	1/60 (46) 0.8873	2/60 (47) 0.7163	0/60 (10) 1.0000
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
salivary gland, ma	LYMPHOMA [m]	8/60 (47) 0.9570	4/60 (45) 0.9303	2/60 (46) 0.9916	1/60 (11) 0.8720

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
salivary gland, pa	LYMPHOMA [m]	4/60 (45) 0.5633	3/60 (45) 0.7830	1/60 (46) 0.9737	2/60 (12) 0.3715
salivary gland, su	LYMPHOMA [m]	3/60 (46) 0.7127	0/60 (45) 1.0000	0/60 (46) 1.0000	1/60 (11) 0.5869
skeletal muscle, b	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	3/60 (46) 0.9913	1/60 (45) 0.9389	0/60 (46) 1.0000	0/60 (10) 1.0000
skin	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	4/60 (46) 0.7434	1/60 (45) 0.9705	1/60 (46) 0.9721	1/60 (11) 0.6726
skin, subcutis	FIBROSARCOMA	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	HEMANGIOMA [m]	0/60 (44) 0.0753	0/60 (45)	0/60 (46)	1/60 (11) 0.2000
	LYMPHOMA [m]	2/60 (45) 0.5061	0/60 (45) 1.0000	0/60 (46) 1.0000	1/60 (11) 0.4881
	SARCOMA, UNDIFFERENTIATED	1/60 (44) 0.9094	1/60 (45) 0.7584	0/60 (46) 1.0000	0/60 (10) 1.0000
small intestine, d	LYMPHOMA [m]	4/60 (45) 0.9232	4/60 (47) 0.6673	2/60 (47) 0.9080	0/60 (10) 1.0000
small intestine, i	ADENOCARCINOMA	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	5/60 (46) 0.6738	3/60 (46) 0.8666	1/60 (46) 0.9869	2/60 (12) 0.4482
small intestine, j	LYMPHOMA [m]	1/60 (44) 0.6831	1/60 (46) 0.7638	1/60 (46) 0.7638	0/60 (10) 1.0000
spinal cord, cervi	LYMPHOMA [m]	1/60 (44) 0.9094	1/60 (45) 0.7584	0/60 (46) 1.0000	0/60 (10) 1.0000
spinal cord, lumba	LYMPHOMA [m]	1/60 (44) 0.6249	0/60 (45) 1.0000	1/60 (46) 0.7638	0/60 (10) 1.0000
spinal cord, thora	LYMPHOMA [m]	3/60 (45) 0.9918	1/60 (45) 0.9417	0/60 (46) 1.0000	0/60 (10) 1.0000
spleen	ADENOCARCINOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	HEMANGIOSARCOMA [m]	0/60 (44) 0.3862	0/60 (45)	1/60 (46) 0.5111	0/60 (10)
	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (44) 0.6831	1/60 (46) 0.7638	1/60 (46) 0.7638	0/60 (10) 1.0000
	LYMPHOMA [m]	15/60 (49) 0.7484	8/60 (47) 0.9648	8/60 (48) 0.9689	4/60 (13) 0.6185
	SARCOMA, HISTIOCYTIC [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
stomach, glandular	LYMPHOMA [m]	7/60 (47) 0.8598	3/60 (46) 0.9513	3/60 (47) 0.9547	1/60 (11) 0.8359
stomach, nonglandu	LYMPHOMA [m]	1/60 (44) 0.2433	0/60 (45) 1.0000	0/60 (46) 1.0000	1/60 (11) 0.3630
thymus	HEMANGIOSARCOMA [m]	1/60 (44) 0.6249	0/60 (45) 1.0000	1/60 (46) 0.7638	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LIPOSARCOMA [m]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	10/60 (48) 0.3795	6/60 (47) 0.9080	7/60 (48) 0.8576	4/60 (13) 0.3387
thyroid gland	LYMPHOMA [m]	8/60 (46) 0.9332	5/60 (45) 0.8764	3/60 (46) 0.9750	1/60 (11) 0.8775
tongue	LYMPHOMA [m]	3/60 (45) 0.8506	4/60 (45) 0.5000	0/60 (46) 1.0000	1/60 (11) 0.5943
trachea	LYMPHOMA [m]	1/60 (44) 0.8878	2/60 (45) 0.5085	0/60 (46) 1.0000	0/60 (10) 1.0000
urinary bladder	HEMANGIOSARCOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	12/60 (48) 0.9280	7/60 (46) 0.9255	5/60 (47) 0.9830	2/60 (12) 0.8387
	SARCOMA, HISTIOCYTIC [m]	2/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
uterus with cervix	**C_leiomyo_ma+sarcoma**	**3/60 (44) 0.6281**	**3/60 (45) 0.6725**	**4/60 (47) 0.5373**	**0/60 (10) 1.0000**
	C_polyp_glandular+stromal	**6/60 (46) 0.7119**	**7/60 (46) 0.5000**	**3/60 (47) 0.9259**	**2/60 (11) 0.4858**
	GRANULAR CELL TUMOR	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	HEMANGIOMA [m]	1/60 (44) 0.8878	2/60 (45) 0.5085	0/60 (46) 1.0000	0/60 (10) 1.0000
	HEMANGIOSARCOMA [m]	3/60 (44) 0.8262	2/60 (45) 0.8267	2/60 (46) 0.8332	0/60 (10) 1.0000
	LEIOMYOMA	1/60 (44) 0.3312	1/60 (45) 0.7584	3/60 (47) 0.3337	0/60 (10) 1.0000
	LEIOMYOSARCOMA	2/60 (44) 0.8516	2/60 (45) 0.7003	1/60 (46) 0.8873	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)

Organ Name	Tumor Name	Water Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	10/60 (48) 0.8303	6/60 (46) 0.9002	5/60 (47) 0.9511	2/60 (12) 0.7565
	POLYP, GLANDULAR	3/60 (45) 0.9918	1/60 (45) 0.9417	0/60 (46) 1.0000	0/60 (10) 1.0000
	POLYP, STROMAL	3/60 (44) 0.3773	6/60 (46) 0.2652	3/60 (47) 0.6927	2/60 (11) 0.2586
	SARCOMA, HISTIOCYTIC [m]	3/60 (44) 0.9923	1/60 (45) 0.9444	0/60 (46) 1.0000	0/60 (10) 1.0000
	SARCOMA, STROMAL	4/60 (44) 0.7910	2/60 (45) 0.9038	1/60 (46) 0.9753	1/60 (11) 0.6878
vagina	HEMANGIOSARCOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	4/60 (46) 0.6396	4/60 (46) 0.6430	3/60 (48) 0.7998	1/60 (11) 0.6726
	POLYP	2/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	SARCOMA, HISTIOCYTIC [m]	2/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	SARCOMA, STROMAL [s]	0/60 (44) 0.1975	1/60 (45) 0.5056	0/60 (46)	1/60 (11) 0.2000
zymbal`s gland	LYMPHOMA [m]	3/60 (45) 0.9918	1/60 (45) 0.9417	0/60 (46) 1.0000	0/60 (10) 1.0000

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed.
NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0 01 and 0 05 for a common tumor and a rare tumor, respectively.
Note: In all tumor tables, a tumor marked with "s" is a secondary tumor and marked with "m" is a multicentric tumor. The tumors without any mark are the primary tumors.

Table 6C: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Vehicle Control in Male Mice

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
adrenal glands	ADENOMA, CORTICAL	0/60 (45) 0.6991	2/60 (44) 0.2416	0/60 (39)	0/60 (13)
	ADENOMA, SUBCAPSULAR CELL	3/60 (46) 0.9121	2/60 (44) 0.8054	1/60 (39) 0.9194	0/60 (13) 1.0000
	LYMPHOMA [m]	3/60 (47) 0.7444	0/60 (44) 1.0000	2/60 (41) 0.7742	0/60 (13) 1.0000

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
all sites	**C_hemangioma+sarcoma [m]**	**3/60 (46)** **0.6374**	**1/60 (44)** **0.9361**	**3/60 (39)** **0.5799**	**0/60 (13)** **1.0000**
	C_lymphoma [m]	**7/60 (49)** **0.0776**	**4/60 (45)** **0.8721**	**9/60 (43)** **0.2862**	**4/60 (16)** **0.2630**
aorta	LYMPHOMA [m]	0/60 (45) 0.6809	1/60 (44) 0.4944	0/60 (39)	0/60 (13)
bone marrow, femur	HEMANGIOSARCOMA [m]	0/60 (45) 0.6809	1/60 (44) 0.4944	0/60 (39)	0/60 (13)
	LYMPHOMA [m]	5/60 (49) 0.7044	3/60 (45) 0.8369	5/60 (42) 0.5279	0/60 (13) 1.0000
bone marrow, stern	CARCINOMA, BRONCHIOLAR ALVEOL [a]	0/60 (45) 0.3688	0/60 (44)	1/60 (39) 0.4643	0/60 (13)
	HEMANGIOSARCOMA [m]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	5/60 (49) 0.4884	3/60 (45) 0.8369	5/60 (42) 0.5279	1/60 (14) 0.7942
	MAST CELL TUMOR	0/60 (45) 0.0986	0/60 (44)	0/60 (39)	1/60 (14) 0.2373
bone marrow, tibia	HEMANGIOSARCOMA [m]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
bone, femur	LYMPHOMA [m]	1/60 (46) 0.6055	0/60 (44) 1.0000	1/60 (40) 0.7168	0/60 (13) 1.0000
bone, femur (proxi	LYMPHOMA [m]	1/60 (46) 0.6055	0/60 (44) 1.0000	1/60 (40) 0.7168	0/60 (13) 1.0000
bone, sternum	CARCINOMA, BRONCHIOLAR ALVEOL [s]	1/60 (46) 0.5999	0/60 (44) 1.0000	1/60 (39) 0.7101	0/60 (13) 1.0000
	LYMPHOMA [m]	4/60 (48) 0.5496	0/60 (44) 1.0000	2/60 (40) 0.8510	1/60 (14) 0.7354
brain	LYMPHOMA [m]	3/60 (47) 0.3995	0/60 (44) 1.0000	2/60 (40) 0.7654	1/60 (14) 0.6582
cavity, abdominal	LYMPHOMA [m]	2/60 (47) 0.3238	2/60 (44) 0.6663	5/60 (42) 0.1732	0/60 (13) 1.0000
cavity, thoracic	CARCINOMA, BRONCHIOLAR ALVEOL [s]	2/60 (47) 0.4947	2/60 (44) 0.6663	1/60 (39) 0.8416	1/60 (14) 0.5495
	LYMPHOMA [m]	1/60 (46) 0.1189	2/60 (44) 0.4831	4/60 (42) 0.1531	1/60 (14) 0.4153
coagulating glands	LYMPHOMA [m]	3/60 (48) 0.0824	0/60 (44) 1.0000	4/60 (41) 0.4115	2/60 (15) 0.3411
epididymides	LYMPHOMA [m]	4/60 (48) 0.0464	0/60 (44) 1.0000	5/60 (42) 0.4146	3/60 (16) 0.2346
eyes	LYMPHOMA [m]	3/60 (47) 0.8886	0/60 (44) 1.0000	1/60 (40) 0.9199	0/60 (13) 1.0000
gallbladder	LYMPHOMA [m]	3/60 (48) 0.3607	3/60 (45) 0.6301	4/60 (42) 0.4249	1/60 (14) 0.6512

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
harderian glands	ADENOMA	5/60 (47) 0.0533	8/60 (45) 0.2476	8/60 (41) 0.1924	5/60 (17) 0.0795
	LYMPHOMA [m]	3/60 (48) 0.1132	1/60 (44) 0.9304	4/60 (41) 0.4115	2/60 (15) 0.3411
heart	CARCINOMA, BRONCHIOLAR ALVEOL [s]	2/60 (46) 0.4336	1/60 (44) 0.8708	1/60 (39) 0.8463	1/60 (14) 0.5564
	HEMANGIOSARCOMA [m]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	4/60 (48) 0.0836	2/60 (44) 0.8771	5/60 (41) 0.3994	3/60 (16) 0.2346
joint, tibiofemora	LYMPHOMA [m]	0/60 (45) 0.1973	0/60 (44)	2/60 (41) 0.2244	0/60 (13)
kidneys	CARCINOMA, BRONCHIOLAR ALVEOL [s]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	7/60 (49) 0.2663	3/60 (45) 0.9395	6/60 (42) 0.6155	3/60 (16) 0.4682
lacrimal glands, e	LYMPHOMA [m]	5/60 (49) 0.1065	1/60 (44) 0.9817	5/60 (41) 0.5116	3/60 (16) 0.3059
large intestine, c	LYMPHOMA [m]	4/60 (48) 0.6902 4/60 (48) 0.6902	0/60 (44) 1.0000 0/60 (44) 1.0000	1/60 (40) 0.9563 1/60 (40) 0.9563	1/60 (14) 0.7354 1/60 (14) 0.7354
large intestine, r	LYMPHOMA [m]	0/60 (45) 0.3732	0/60 (44)	1/60 (40) 0.4706	0/60 (13)
larynx	LYMPHOMA [m]	2/60 (47) 0.5856	0/60 (44) 1.0000	2/60 (41) 0.6384	0/60 (13) 1.0000
liver	ADENOMA, HEPATOCELLULAR	4/60 (45) 0.4892	3/60 (44) 0.7737	4/60 (39) 0.5599	1/60 (14) 0.7560
	CARCINOMA, HEPATOCELLULAR	2/60 (46) 0.7769	0/60 (44) 1.0000	1/60 (39) 0.8463	0/60 (13) 1.0000
	C_Hepatocellular_A+C	6/60 (46) 0.6040	3/60 (44) 0.9105	5/60 (39) 0.6355	1/60 (14) 0.8614
	HEMANGIOSARCOMA [m]	3/60 (46) 0.8885	0/60 (44) 1.0000	1/60 (39) 0.9194	0/60 (13) 1.0000
	LYMPHOMA [m]	5/60 (49) 0.0292	3/60 (45) 0.8369	8/60 (43) 0.1966	4/60 (16) 0.1426
lung	ADENOMA, BRONCHIOLAR ALVEOLAR	12/60 (46) 0.9212	9/60 (44) 0.8105	6/60 (39) 0.9305	2/60 (15) 0.9215
	CARCINOMA, BRONCHIOLAR ALVEOL	6/60 (47) 0.9214	8/60 (45) 0.3526	2/60 (39) 0.9478	1/60 (14) 0.8558
	C_bronchiolar alveolar_A+C	17/60 (47) 0.9740	16/60 (45) 0.6095	8/60 (40) 0.9723	3/60 (15) 0.9355
	FIBROSARCOMA [s]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	LYMPHOMA [m]	2/60 (47) 0.0220	2/60 (44) 0.6663	5/60 (41) 0.1644	3/60 (16) 0.0989
	OSTEOSARCOMA [s]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
lymph node, hepati	LYMPHOMA [m]	0/60 (45) 0.0636	0/60 (44)	1/60 (39) 0.4643	1/60 (14) 0.2373
lymph node, iliac	LYMPHOMA [m]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
lymph node, inguin	LYMPHOMA	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
lymph node, mandib	LYMPHOMA [m]	6/60 (49) 0.1159	3/60 (45) 0.8990	5/60 (41) 0.6261	4/60 (16) 0.1994
lymph node, medias	CARCINOMA, BRONCHIOLAR ALVEOL [s]	1/60 (46) 0.8966	1/60 (44) 0.7416	0/60 (39) 1.0000	0/60 (13) 1.0000
	HEMANGIOSARCOMA [m]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	0/60 (45) 0.4290	1/60 (44) 0.4944	1/60 (40) 0.4706	0/60 (13)
lymph node, mesent	CARCINOMA, ISLET CELL [s]	0/60 (45) 0.3688	0/60 (44)	1/60 (39) 0.4643	0/60 (13)
	HEMANGIOSARCOMA [m]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	5/60 (49) 0.0386	4/60 (45) 0.7125	8/60 (43) 0.1966	4/60 (16) 0.1426
lymph node, renal	LYMPHOMA [m]	1/60 (46) 0.1186	1/60 (44) 0.7416	0/60 (39) 1.0000	2/60 (15) 0.1468
mammary gland	LYMPHOMA [m]	0/60 (45) 0.3732	0/60 (44)	1/60 (40) 0.4706	0/60 (13)
mesentery/peritone	LYMPHOMA [m]	0/60 (45) 0.0986	0/60 (44)	0/60 (39)	1/60 (14) 0.2373
multicentric neoplasm	**C_hemangioma_A+C [m]**	**3/60 (46) 0.6374**	**1/60 (44) 0.9361**	**3/60 (39) 0.5799**	**0/60 (13) 1.0000**
	HEMANGIOMA [m]	0/60 (45) 0.3688	0/60 (44)	1/60 (39) 0.4643	0/60 (13)
	HEMANGIOSARCOMA [m]	3/60 (46) 0.7769	1/60 (44) 0.9361	2/60 (39) 0.7642	0/60 (13) 1.0000
	LYMPHOMA [m]	7/60 (49) 0.0776	4/60 (45) 0.8721	9/60 (43) 0.2862	4/60 (16) 0.2630
nerve, sciatic	LYMPHOMA [m]	2/60 (46) 0.7769	0/60 (44) 1.0000	1/60 (39) 0.8463	0/60 (13) 1.0000
nose, level a	LYMPHOMA [m]	3/60 (48) 0.5849	0/60 (44) 1.0000	3/60 (41) 0.5835	0/60 (13) 1.0000

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
nose, level b	LYMPHOMA [m]	3/60 (48) 0.5849	0/60 (44) 1.0000	3/60 (41) 0.5835	0/60 (13) 1.0000
nose, level c	LYMPHOMA [m]	4/60 (48) 0.7238	0/60 (44) 1.0000	3/60 (41) 0.7125	0/60 (13) 1.0000
nose, level d	LYMPHOMA [m]	3/60 (48) 0.5849	0/60 (44) 1.0000	3/60 (41) 0.5835	0/60 (13) 1.0000
pancreas	CARCINOMA, ISLET CELL	0/60 (45) 0.3688	0/60 (44)	1/60 (39) 0.4643	0/60 (13)
	LYMPHOMA [m]	5/60 (49) 0.2042	2/60 (45) 0.9301	6/60 (43) 0.4072	2/60 (15) 0.5241
parathyroid glands	LYMPHOMA [m]	0/60 (45) 0.6809	1/60 (44) 0.4944	0/60 (39)	0/60 (13)
peyers patch	LYMPHOMA [m]	5/60 (49) 0.2511	1/60 (44) 0.9817	2/60 (40) 0.9064	3/60 (16) 0.3059
pharynx	LYMPHOMA [m]	1/60 (46) 0.6055	0/60 (44) 1.0000	1/60 (40) 0.7168	0/60 (13) 1.0000
pituitary gland	ADENOMA, PARS DISTALIS	0/60 (45) 0.6809	1/60 (44) 0.4944	0/60 (39)	0/60 (13)
	ADENOMA, PARS INTERMEDIA	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	3/60 (47) 0.4052	0/60 (44) 1.0000	2/60 (41) 0.7742	1/60 (14) 0.6582
preputial glands	LYMPHOMA [m]	3/60 (48) 0.6365	1/60 (44) 0.9304	3/60 (41) 0.5835	0/60 (13) 1.0000
prostate gland	ADENOMA	0/60 (45) 0.6809	1/60 (44) 0.4944	0/60 (39)	0/60 (13)
	LYMPHOMA [m]	2/60 (47) 0.0855	1/60 (44) 0.8665	3/60 (41) 0.4348	2/60 (15) 0.2443
salivary gland, ma	LYMPHOMA [m]	3/60 (48) 0.4622	1/60 (44) 0.9304	2/60 (41) 0.7665	1/60 (14) 0.6512
salivary gland, pa	LYMPHOMA [m]	2/60 (47) 0.2434	0/60 (44) 1.0000	2/60 (41) 0.6384	1/60 (14) 0.5495
salivary gland, su	LYMPHOMA [m]	2/60 (47) 0.7779	0/60 (44) 1.0000	1/60 (40) 0.8470	0/60 (13) 1.0000
seminal vesicles	LYMPHOMA [m]	1/60 (46) 0.0132	0/60 (44) 1.0000	4/60 (42) 0.1531	2/60 (15) 0.1468
skeletal muscle, b	LYMPHOMA [m]	2/60 (47) 0.7732	0/60 (44) 1.0000	1/60 (39) 0.8416	0/60 (13) 1.0000
skin	LYMPHOMA [m]	1/60 (46) 0.3899	0/60 (44) 1.0000	2/60 (40) 0.4471	0/60 (13) 1.0000
skin, subcutis	FIBROSARCOMA	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	1/60 (46) 0.1140	0/60 (44) 1.0000	2/60 (41) 0.4564	1/60 (14) 0.4153

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	OSTEOSARCOMA	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
small intestine, d	LYMPHOMA [m]	4/60 (48) 0.1536	0/60 (44) 1.0000	4/60 (41) 0.5510	2/60 (15) 0.4414
small intestine, i	LYMPHOMA [m]	3/60 (48) 0.0208	0/60 (44) 1.0000	5/60 (42) 0.2844	3/60 (16) 0.1595
small intestine, j	LYMPHOMA [m]	2/60 (47) 0.0554	0/60 (44) 1.0000	3/60 (41) 0.4348	2/60 (15) 0.2443
spinal cord, cervi	LYMPHOMA [m]	1/60 (46) 0.5999	0/60 (44) 1.0000	1/60 (39) 0.7101	0/60 (13) 1.0000
spinal cord, lumba	LYMPHOMA [m]	2/60 (47) 0.7732	0/60 (44) 1.0000	1/60 (39) 0.8416	0/60 (13) 1.0000
spinal cord, thora	LYMPHOMA [m]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
spleen	HEMANGIOSARCOMA [m]	1/60 (46) 0.5999	0/60 (44) 1.0000	1/60 (39) 0.7101	0/60 (13) 1.0000
	LYMPHOMA [m]	6/60 (49) 0.0514	3/60 (45) 0.8990	8/60 (43) 0.2885	4/60 (16) 0.1994
stomach, glandular	ADENOMA	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA [m]	5/60 (49) 0.3250	2/60 (45) 0.9301	4/60 (41) 0.6601	2/60 (15) 0.5241
stomach, nonglandu	LYMPHOMA [m]	2/60 (47) 0.7779	0/60 (44) 1.0000	1/60 (40) 0.8470	0/60 (13) 1.0000
tail	FIBROMA	0/60 (45) 0.6831	1/60 (45) 0.5000	0/60 (39)	0/60 (13)
testes	ADENOMA, INTERSTITIAL CELL	2/60 (45) 0.9690	1/60 (44) 0.8750	0/60 (39) 1.0000	0/60 (13) 1.0000
	HEMANGIOMA [m]	0/60 (45) 0.3688	0/60 (44)	1/60 (39) 0.4643	0/60 (13)
	LYMPHOMA [m]	1/60 (46) 0.6055	0/60 (44) 1.0000	1/60 (40) 0.7168	0/60 (13) 1.0000
thymus	CARCINOMA, BRONCHIOLAR ALVEOL [s]	2/60 (47) 0.7732	0/60 (44) 1.0000	1/60 (39) 0.8416	0/60 (13) 1.0000
	LYMPHOMA [m]	5/60 (48) 0.0569	3/60 (45) 0.8445	6/60 (42) 0.4050	4/60 (16) 0.1495
thyroid gland	LYMPHOMA [m]	1/60 (46) 0.1140	0/60 (44) 1.0000	2/60 (41) 0.4564	1/60 (14) 0.4153
tongue	LYMPHOMA [m]	2/60 (47) 0.7732	0/60 (44) 1.0000	1/60 (39) 0.8416	0/60 (13) 1.0000
trachea	LYMPHOMA [m]	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
ureters	LYMPHOMA m	0/60 (45) 0.0641	0/60 (44)	1/60 (40) 0.4706	1/60 (14) 0.2373
urinary bladder	LYMPHOMA m	4/60 (48) 0.2237	1/60 (44) 0.9652	6/60 (42) 0.2873	1/60 (14) 0.7354
zymbal`s gland	CARCINOMA, ZYMBALS GLAND	1/60 (46) 1.0000	0/60 (44) 1.0000	0/60 (39) 1.0000	0/60 (13) 1.0000
	LYMPHOMA m	4/60 (48) 0.8457	0/60 (44) 1.0000	2/60 (40) 0.8510	0/60 (13) 1.0000

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed.
NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0 01 and 0 05 for a common tumor and a rare tumor, respectively.
Note: In all tumor tables, a tumor marked with "s" is a secondary tumor and marked with "m" is a multicentric tumor. The tumors without any mark are the primary tumors.

Table 6D: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons with Vehicle Control in Female Mice

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
adrenal glands	ADENOMA, SUBCAPSULAR CELL	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP m	1/60 (45) 0.9077	1/60 (46) 0.7582	0/60 (46) 1.0000	0/60 (10) 1.0000
	LYMPHOMA m	0/60 (44) 0.2122	4/60 (47) 0.0667	2/60 (46) 0.2584	1/60 (11) 0.2000
all sites	**C_hemangioma+sarcoma m**	**9/60 (46) 0.8751**	**8/60 (46) 0.7039**	**4/60 (46) 0.9653**	**2/60 (12) 0.7266**
	C_lipomas+carcomas	**0/60 (44) 0.6966**	**1/60 (45) 0.5056**	**0/60 (46)**	**0/60 (10)**
	C_lymphoma m	**12/60 (48) 0.4780**	**8/60 (47) 0.8862**	**9/60 (48) 0.8382**	**4/60 (13) 0.4612**
	C_sarcoma histiocytic m	**2/60 (45) 0.9721**	**1/60 (45) 0.8792**	**0/60 (46) 1.0000**	**0/60 (10) 1.0000**
bone marrow, femur	HEMANGIOSARCOMA m	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LEUKEMIA, LARGE GRANULAR LYMP m	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA m	2/60 (45) 0.0747	3/60 (46) 0.5105	5/60 (48) 0.2450	2/60 (12) 0.1917
	SARCOMA, STROMAL	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
bone marrow, stern	LEUKEMIA, LARGE GRANULAR LYMP m	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	LYMPHOMA [m]	3/60 (46) 0.2731	3/60 (46) 0.6616	5/60 (48) 0.3814	1/60 (11) 0.5869
bone, femur	LYMPHOMA [m]	0/60 (44) 0.3904	0/60 (45)	1/60 (47) 0.5165	0/60 (10)
bone, sternum	LYMPHOMA [m]	0/60 (44) 0.2616	1/60 (46) 0.5111	2/60 (47) 0.2640	0/60 (10)
brain	ASTROCYTOMA	0/60 (44) 0.3862	0/60 (45)	1/60 (46) 0.5111	0/60 (10)
	LYMPHOMA [m]	0/60 (44) 0.2630	1/60 (45) 0.5056	2/60 (47) 0.2640	0/60 (10)
cavity, abdominal	ADENOCARCINOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	HEMANGIOMA [m]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	HEMANGIOSARCOMA [m]	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LIPOSARCOMA	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	7/60 (47) 0.3870	3/60 (46) 0.9513	4/60 (46) 0.8944	3/60 (13) 0.3710
	SARCOMA, HISTIOCYTIC [m]	2/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	SARCOMA, STROMAL [s]	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
cavity, thoracic	ADENOCARCINOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	HEMANGIOSARCOMA [m]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	6/60 (47) 0.2994	3/60 (45) 0.9105	4/60 (47) 0.8420	3/60 (13) 0.2995
	SARCOMA, HISTIOCYTIC [m]	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
clitoral glands	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	4/60 (45) 0.9662	3/60 (45) 0.7830	1/60 (46) 0.9737	0/60 (10) 1.0000
esophagus	LYMPHOMA [m]	1/60 (45) 0.9065	1/60 (45) 0.7528	0/60 (46) 1.0000	0/60 (10) 1.0000
eyes	LYMPHOMA [m]	1/60 (45) 0.8848	2/60 (46) 0.5083	0/60 (46) 1.0000	0/60 (10) 1.0000

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
gallbladder	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LIPOSARCOMA [S]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	6/60 (46) 0.8294	4/60 (46) 0.8423	5/60 (47) 0.7511	0/60 (10) 1.0000
harderian glands	ADENOMA	7/60 (46) 0.5663	2/60 (45) 0.9836	4/60 (47) 0.9077	2/60 (12) 0.6025
	LYMPHOMA [m]	1/60 (45) 0.2059	3/60 (45) 0.3082	3/60 (47) 0.3250	1/60 (11) 0.3571
heart	ADENOCARCINOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (45) 0.9077	1/60 (46) 0.7582	0/60 (46) 1.0000	0/60 (10) 1.0000
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	5/60 (45) 0.2202	6/60 (47) 0.5312	6/60 (48) 0.5462	3/60 (13) 0.2483
	SARCOMA, HISTIOCYTIC [m]	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
kidneys	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (45) 0.9077	1/60 (46) 0.7582	0/60 (46) 1.0000	0/60 (10) 1.0000
	LYMPHOMA [m]	9/60 (47) 0.4513	6/60 (46) 0.8605	5/60 (48) 0.9327	4/60 (13) 0.2918
	SARCOMA, HISTIOCYTIC [m]	2/60 (45) 0.9721	1/60 (45) 0.8792	0/60 (46) 1.0000	0/60 (10) 1.0000
lacrimal glands, e	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	6/60 (45) 0.2837	5/60 (45) 0.7392	3/60 (46) 0.9263	4/60 (13) 0.1471
large intestine, c	LYMPHOMA [m]	4/60 (46) 0.7937 4/60 (46) 0.7937	6/60 (47) 0.3837 6/60 (47) 0.3837	2/60 (47) 0.9032 2/60 (47) 0.9032	1/60 (11) 0.6726 1/60 (11) 0.6726
large intestine, r	LYMPHOMA [m]	2/60 (44) 0.9592	3/60 (46) 0.5213	0/60 (46) 1.0000	0/60 (10) 1.0000
larynx	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	4/60 (45) 0.7485	4/60 (45) 0.6432	2/60 (47) 0.9080	1/60 (11) 0.6802
	PAPILLOMA	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
liver	ADENOMA, HEPATOCELLULAR	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	CARCINOMA, HEPATOCELLULAR	1/60 (45) 0.9065	1/60 (45) 0.7528	0/60 (46) 1.0000	0/60 (10) 1.0000
	C_Hepatocellular_A+C	**1/60 (45) 0.8844**	**2/60 (45) 0.5000**	**0/60 (46) 1.0000**	**0/60 (10) 1.0000**
	HEMANGIOSARCOMA [m]	3/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (45) 0.6780	1/60 (46) 0.7582	1/60 (46) 0.7582	0/60 (10) 1.0000
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	7/60 (47) 0.3109	7/60 (47) 0.6135	7/60 (48) 0.6298	3/60 (12) 0.3270
	SARCOMA, HISTIOCYTIC [m]	2/60 (45) 0.9721	1/60 (45) 0.8792	0/60 (46) 1.0000	0/60 (10) 1.0000
lung	ADENOCARCINOMA	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	ADENOMA, BRONCHIOLAR ALVEOLAR	7/60 (45) 0.8535	9/60 (46) 0.4108	5/60 (46) 0.8338	1/60 (11) 0.8483
	CARCINOMA, BRONCHIOLAR ALVEOL	1/60 (44) 0.4791	1/60 (45) 0.7584	2/60 (46) 0.5169	0/60 (10) 1.0000
	C_bronchiolar alveolar_A+C	**8/60 (45) 0.8167**	**10/60 (46) 0.4169**	**7/60 (46) 0.7292**	**1/60 (11) 0.8830**
	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (45) 0.9077	1/60 (46) 0.7582	0/60 (46) 1.0000	0/60 (10) 1.0000
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	7/60 (47) 0.2770	8/60 (47) 0.5000	6/60 (48) 0.7377	4/60 (13) 0.1802
	SARCOMA, HISTIOCYTIC [m]	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
lymph node, axilla	LYMPHOMA [m]	1/60 (45) 0.2410	0/60 (45) 1.0000	0/60 (46) 1.0000	1/60 (11) 0.3571
	SARCOMA, UNDIFFERENTIATED [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
lymph node, hepati	LYMPHOMA [m]	2/60 (44) 0.8395	1/60 (45) 0.8834	1/60 (47) 0.8910	0/60 (10) 1.0000
lymph node, iliac	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	0/60 (44) 0.7197	2/60 (45) 0.2528	0/60 (46)	0/60 (10)
	SARCOMA, HISTIOCYTIC [m]	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
lymph node, inguin	LYMPHOMA [m]	2/60 (45) 0.9726	1/60 (46) 0.8832	0/60 (46) 1.0000	0/60 (10) 1.0000
lymph node, mandib	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	7/60 (46) 0.2892	8/60 (47) 0.5183	6/60 (48) 0.7514	4/60 (13) 0.1893
lymph node, medias	LYMPHOMA [m]	3/60 (45) 0.6603	2/60 (46) 0.8263	1/60 (46) 0.9443	1/60 (11) 0.5943
	SARCOMA, UNDIFFERENTIATED [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
lymph node, mesent	HEMANGIOSARCOMA [m]	2/60 (45) 0.7967	0/60 (45) 1.0000	1/60 (46) 0.8832	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (45) 0.9077	1/60 (46) 0.7582	0/60 (46) 1.0000	0/60 (10) 1.0000
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	9/60 (47) 0.3156	8/60 (47) 0.7035	8/60 (48) 0.7198	4/60 (13) 0.2918
	SARCOMA, HISTIOCYTIC [m]	1/60 (45) 0.9065	1/60 (45) 0.7528	0/60 (46) 1.0000	0/60 (10) 1.0000
lymph node, renal	LYMPHOMA [m]	1/60 (45) 0.4731	1/60 (45) 0.7528	2/60 (46) 0.5083	0/60 (10) 1.0000
	SARCOMA, HISTIOCYTIC [m]	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
mammary gland	ADENOACANTHOMA	0/60 (44) 0.3862	0/60 (45)	1/60 (46) 0.5111	0/60 (10)
	ADENOCARCINOMA	1/60 (45) 0.6791	1/60 (45) 0.7528	1/60 (46) 0.7582	0/60 (10) 1.0000
	C adenoacanthoma+adenocarcinoma	**1/60 (45) 0.4787**	**1/60 (45) 0.7528**	**2/60 (47) 0.5165**	**0/60 (10) 1.0000**
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	6/60 (46) 0.7751	3/60 (46) 0.9211	1/60 (46) 0.9939	2/60 (12) 0.5288
mesentery/peritone	LYMPHOMA [m]	0/60 (44) 0.3904	0/60 (45)	1/60 (47) 0.5165	0/60 (10)
multicentric neoplasm	**C_hemangioma_A+C [m]**	**9/60 (46) 0.8751**	**8/60 (46) 0.7039**	**4/60 (46) 0.9653**	**2/60 (12) 0.7266**
	HEMANGIOMA [m]	1/60 (44) 0.2448	3/60 (45) 0.3167	0/60 (46) 1.0000	2/60 (12) 0.1127
	HEMANGIOSARCOMA [m]	9/60 (46) 0.9806	5/60 (45) 0.9214	4/60 (46) 0.9653	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (45) 0.6780	1/60 (46) 0.7582	1/60 (46) 0.7582	0/60 (10) 1.0000

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	LYMPHOMA [m]	12/60 (48) 0.4780	8/60 (47) 0.8862	9/60 (48) 0.8382	4/60 (13) 0.4612
	SARCOMA, HISTIOCYTIC [m]	2/60 (45) 0.9721	1/60 (45) 0.8792	0/60 (46) 1.0000	0/60 (10) 1.0000
nerve, sciatic	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	4/60 (45) 0.9692	4/60 (45) 0.6432	1/60 (46) 0.9737	0/60 (10) 1.0000
nose, level b	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	0/60 (44) 0.3862	0/60 (45)	1/60 (46) 0.5111	0/60 (10)
nose, level c	LYMPHOMA [m]	1/60 (45) 0.1538	0/60 (45) 1.0000	1/60 (46) 0.7582	1/60 (11) 0.3571
nose, level d	LYMPHOMA [m]	0/60 (44) 0.3862	0/60 (45)	1/60 (46) 0.5111	0/60 (10)
ovaries	CYSTADENOCARCINOMA	0/60 (44) 0.3904	0/60 (45)	1/60 (47) 0.5165	0/60 (10)
	CYSTADENOMA	1/60 (44) 0.9051	3/60 (46) 0.3253	0/60 (46) 1.0000	0/60 (10) 1.0000
	C_cystadenoma+carcinoma	**1/60 (44) 0.7634**	**3/60 (46) 0.3253**	**1/60 (47) 0.7690**	**0/60 (10) 1.0000**
	HEMANGIOMA [m]	0/60 (44) 0.0062	0/60 (45)	0/60 (46)	2/60 (12) 0.0429
	HEMANGIOSARCOMA [m]	1/60 (45) 0.9065	1/60 (45) 0.7528	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEIOMYOSARCOMA	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (45) 0.9077	1/60 (46) 0.7582	0/60 (46) 1.0000	0/60 (10) 1.0000
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	8/60 (47) 0.5500	6/60 (47) 0.8072	7/60 (48) 0.7277	2/60 (12) 0.6573
	SARCOMA, HISTIOCYTIC [m]	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	SEX-CORD/STROMAL TUMOR	1/60 (45) 0.6791	1/60 (45) 0.7528	1/60 (46) 0.7582	0/60 (10) 1.0000
oviducts	ADENOCARCINOMA	0/60 (44) 0.3862	0/60 (45)	1/60 (46) 0.5111	0/60 (10)
	LEUKEMIA, LARGE GRANULAR LYMP	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	4/60 (46) 0.8414	4/60 (46) 0.6430	3/60 (46) 0.7828	0/60 (10) 1.0000
	SARCOMA, HISTIOCYTIC [m]	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
pancreas	ADENOMA, ISLET CELL	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP	1/60 (45) 0.9077	1/60 (46) 0.7582	0/60 (46) 1.0000	0/60 (10) 1.0000
	LIPOSARCOMA	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	7/60 (47) 0.3738	7/60 (46) 0.5966	6/60 (47) 0.7242	3/60 (12) 0.3270
	SARCOMA, HISTIOCYTIC [m]	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
parathyroid glands	LYMPHOMA [m]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
peyers patch	LYMPHOMA [m]	5/60 (46) 0.3929	5/60 (46) 0.6303	5/60 (48) 0.6572	2/60 (12) 0.4482
pharynx	LYMPHOMA [m]	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
pituitary gland	ADENOMA, PARS DISTALIS	4/60 (45) 0.9933	3/60 (45) 0.7830	0/60 (46) 1.0000	0/60 (10) 1.0000
	ADENOMA, PARS INTERMEDIA	0/60 (44) 0.3862	0/60 (45)	1/60 (46) 0.5111	0/60 (10)
	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LYMPHOMA [m]	1/60 (45) 0.4763	1/60 (46) 0.7582	2/60 (47) 0.5165	0/60 (10) 1.0000
salivary gland, ma	LYMPHOMA [m]	5/60 (46) 0.8221	4/60 (45) 0.7464	2/60 (46) 0.9447	1/60 (11) 0.7419
salivary gland, pa	LYMPHOMA [m]	5/60 (45) 0.6859	3/60 (45) 0.8668	1/60 (46) 0.9878	2/60 (12) 0.4587
salivary gland, su	LYMPHOMA [m]	0/60 (44) 0.0753	0/60 (45)	0/60 (46)	1/60 (11) 0.2000
skeletal muscle, b	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	2/60 (45) 0.9721	1/60 (45) 0.8792	0/60 (46) 1.0000	0/60 (10) 1.0000
skeletal muscle, d	SARCOMA, HISTIOCYTIC [m]	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
skin	FIBROMA	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	0/60 (44) 0.1120	1/60 (45) 0.5056	1/60 (46) 0.5111	1/60 (11) 0.2000
skin, subcutis	FIBROSARCOMA	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	HEMANGIOMA [m]	0/60 (44) 0.0753	0/60 (45)	0/60 (46)	1/60 (11) 0.2000
	HEMANGIOSARCOMA [m]	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LYMPHOMA [m]	1/60 (45) 0.2410	0/60 (45) 1.0000	0/60 (46) 1.0000	1/60 (11) 0.3571
	SARCOMA, UNDIFFERENTIATED	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
small intestine, d	LYMPHOMA	4/60 (45) 0.9232	4/60 (47) 0.6673	2/60 (47) 0.9080	0/60 (10) 1.0000
small intestine, i	ADENOCARCINOMA	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	HEMANGIOSARCOMA	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LYMPHOMA [m]	3/60 (46) 0.4135	3/60 (46) 0.6616	1/60 (46) 0.9416	2/60 (12) 0.2735
small intestine, j	LYMPHOMA [m]	3/60 (45) 0.9164	1/60 (46) 0.9443	1/60 (46) 0.9443	0/60 (10) 1.0000
spinal cord, cervi	LYMPHOMA [m]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
spinal cord, lumba	LYMPHOMA [m]	0/60 (44) 0.3862	0/60 (45)	1/60 (46) 0.5111	0/60 (10)
spinal cord, thora	LYMPHOMA [m]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
spleen	ADENOCARCINOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	HEMANGIOSARCOMA [m]	1/60 (45) 0.6216	0/60 (45) 1.0000	1/60 (46) 0.7582	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	1/60 (45) 0.6780	1/60 (46) 0.7582	1/60 (46) 0.7582	0/60 (10) 1.0000
	LYMPHOMA [m]	11/60 (47) 0.4796	8/60 (47) 0.8478	8/60 (48) 0.8594	4/60 (13) 0.4152
stomach, glandular	LYMPHOMA [m]	5/60 (46) 0.7030	3/60 (46) 0.8666	3/60 (47) 0.8733	1/60 (11) 0.7419
stomach, nonglandu	LYMPHOMA [m]	2/60 (45) 0.5061	0/60 (45) 1.0000	0/60 (46) 1.0000	1/60 (11) 0.4881

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
thymus	HEMANGIOSARCOMA [m]	0/60 (44) 0.3862	0/60 (45)	1/60 (46) 0.5111	0/60 (10)
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	9/60 (48) 0.2974	6/60 (47) 0.8602	7/60 (48) 0.7940	4/60 (13) 0.2794
	SARCOMA, HISTIOCYTIC [m]	2/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
thyroid gland	LYMPHOMA [m]	5/60 (45) 0.7704	5/60 (45) 0.6305	3/60 (46) 0.8737	1/60 (11) 0.7491
tongue	CARCINOMA, SQUAMOUS CELL	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	LYMPHOMA [m]	3/60 (45) 0.8506	4/60 (45) 0.5000	0/60 (46) 1.0000	1/60 (11) 0.5943
trachea	LYMPHOMA [m]	2/60 (45) 0.9566	2/60 (45) 0.6918	0/60 (46) 1.0000	0/60 (10) 1.0000
ureters	LYMPHOMA [m]	2/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
urinary bladder	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	7/60 (47) 0.6468	7/60 (46) 0.5966	5/60 (47) 0.8227	2/60 (12) 0.5913
	SARCOMA, HISTIOCYTIC [m]	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
uterus with cervix	ADENOCARCINOMA	1/60 (44) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	C_leiomyo_ma+sarcoma	**2/60 (45) 0.4823**	**3/60 (45) 0.5000**	**4/60 (47) 0.3595**	**0/60 (10) 1.0000**
	C_polyp_glandular+stromal	**4/60 (46) 0.5122**	**7/60 (46) 0.2611**	**3/60 (47) 0.7915**	**2/60 (11) 0.3264**
	GRANULAR CELL TUMOR	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	HEMANGIOMA [m]	1/60 (44) 0.8878	2/60 (45) 0.5085	0/60 (46) 1.0000	0/60 (10) 1.0000
	HEMANGIOSARCOMA [m]	2/60 (45) 0.7011	2/60 (45) 0.6918	2/60 (46) 0.7000	0/60 (10) 1.0000
	LEIOMYOMA [m]	0/60 (44) 0.1612	1/60 (45) 0.5056	3/60 (47) 0.1335	0/60 (10)
	LEIOMYOSARCOMA	2/60 (45) 0.8469	2/60 (45) 0.6918	1/60 (46) 0.8832	0/60 (10) 1.0000
	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)

Organ Name	Tumor Name	Vehicle Control 0mg|kg|day (N=60) P - Trend	Low Dose 50mg|kg|day (N=60) P – C vs. L	Mid Dose 150mg|kg|day (N=60) P – C vs. M	M-High Dose 500/250mg|kg|day (N=60) P – C vs. MH
	LIPOSARCOMA [s]	0/60 (44) 0.6966	1/60 (45) 0.5056	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	9/60 (47) 0.7776	6/60 (46) 0.8605	5/60 (47) 0.9272	2/60 (12) 0.7157
	POLYP, GLANDULAR	2/60 (45) 0.9721	1/60 (45) 0.8792	0/60 (46) 1.0000	0/60 (10) 1.0000
	POLYP, STROMAL	2/60 (46) 0.2504	6/60 (46) 0.1334	3/60 (47) 0.5103	2/60 (11) 0.1642
	SARCOMA, HISTIOCYTIC [m]	2/60 (45) 0.9721	1/60 (45) 0.8792	0/60 (46) 1.0000	0/60 (10) 1.0000
	SARCOMA, STROMAL	4/60 (45) 0.7844	2/60 (45) 0.8986	1/60 (46) 0.9737	1/60 (11) 0.6802
vagina	LEUKEMIA, LARGE GRANULAR LYMP [m]	0/60 (44) 0.6986	1/60 (46) 0.5111	0/60 (46)	0/60 (10)
	LYMPHOMA [m]	4/60 (46) 0.6396	4/60 (46) 0.6430	3/60 (48) 0.7998	1/60 (11) 0.6726
	POLYP	1/60 (45) 1.0000	0/60 (45) 1.0000	0/60 (46) 1.0000	0/60 (10) 1.0000
	SARCOMA, STROMAL [s]	0/60 (44) 0.1975	1/60 (45) 0.5056	0/60 (46)	1/60 (11) 0.2000
zymbal`s gland	LYMPHOMA [m]	2/60 (45) 0.9721	1/60 (45) 0.8792	0/60 (46) 1.0000	0/60 (10) 1.0000

Note: X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed.
NC = Not calculable.
Note: The p-values marked with an asterisk * indicate statistically significant dose responses at 0.005 and 0.025 for a common tumor and a rare tumor, respectively. The p-values marked with an asterisk ** indicate statistically significant pairwise comparison at 0 01 and 0 05 for a common tumor and a rare tumor, respectively.
Note: In all tumor tables, a tumor marked with “s” is a secondary tumor and marked with “m” is a multicentric tumor. The tumors without any mark are the primary tumors.

Figure 1A: Kaplan-Meier Survival Functions for Male Rats

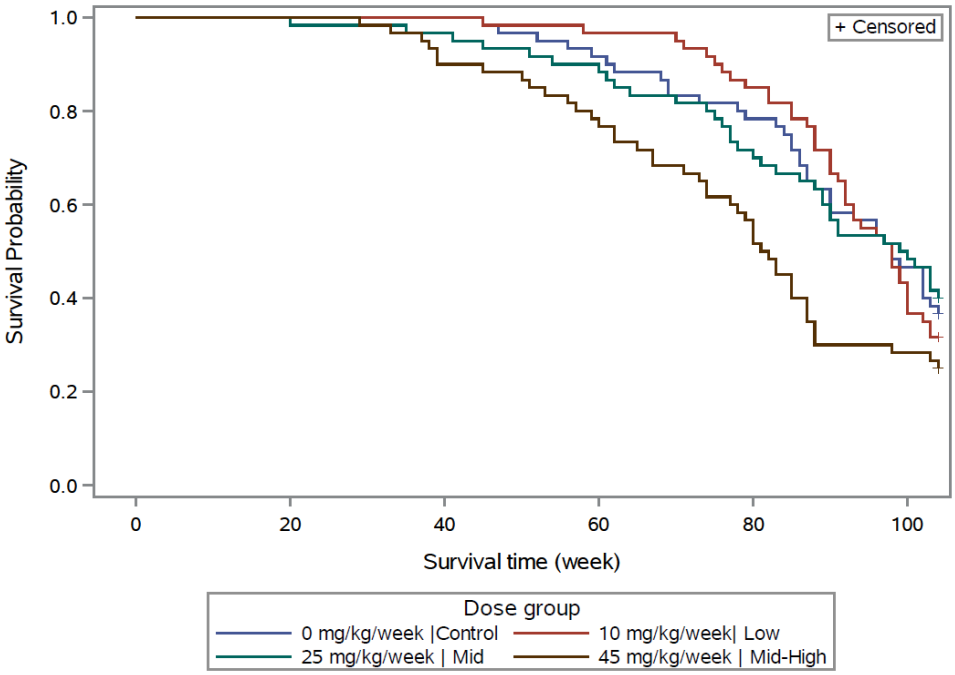


Figure 1B: Kaplan-Meier Survival Functions for Female Rats

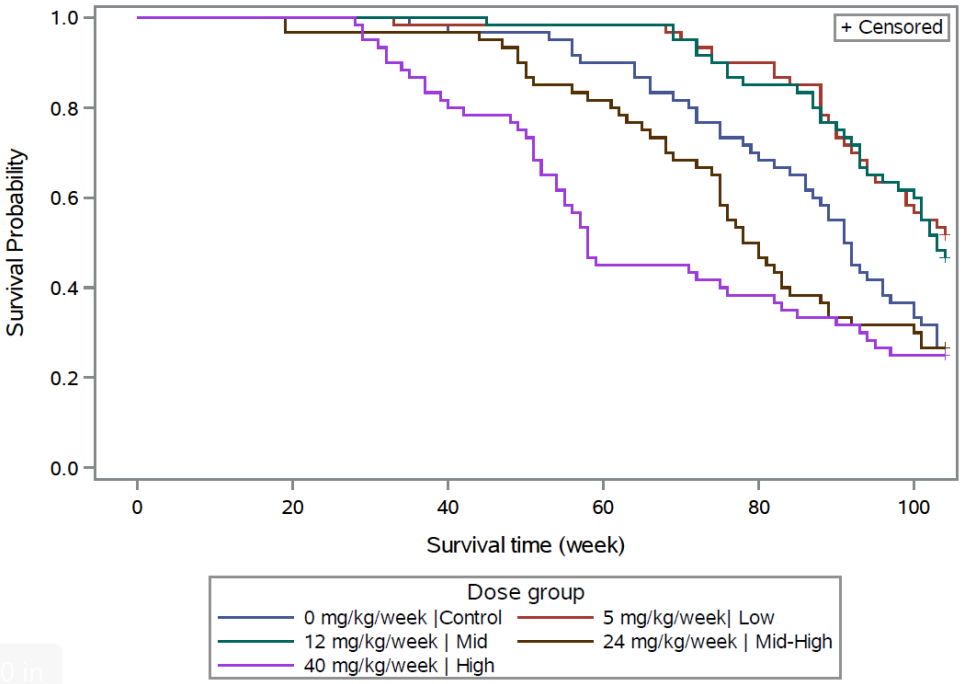


Figure 2A: Kaplan-Meier Survival Functions for Male Mice

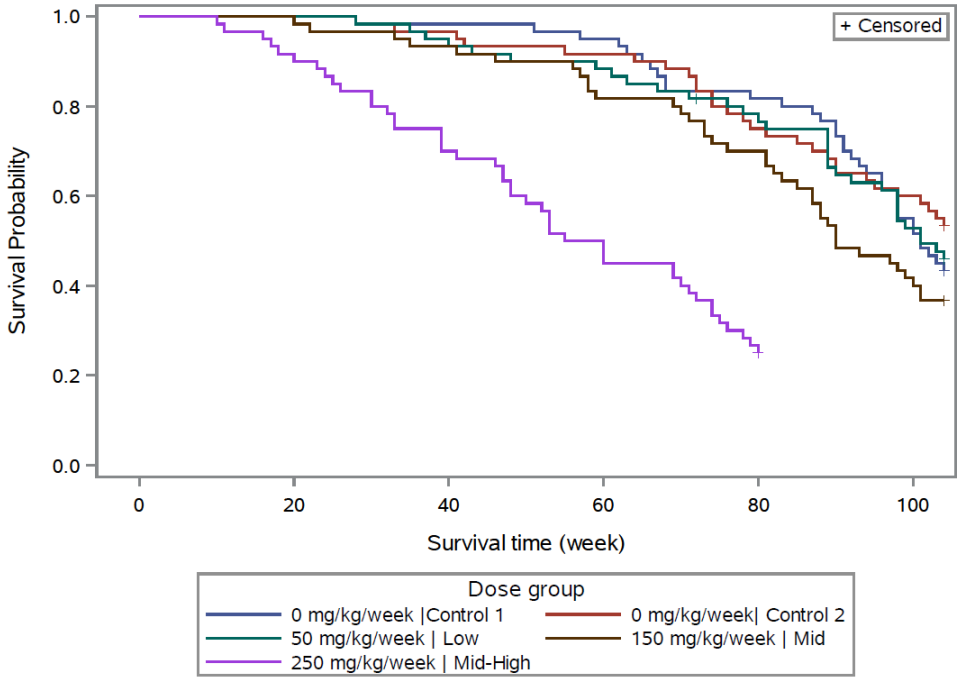
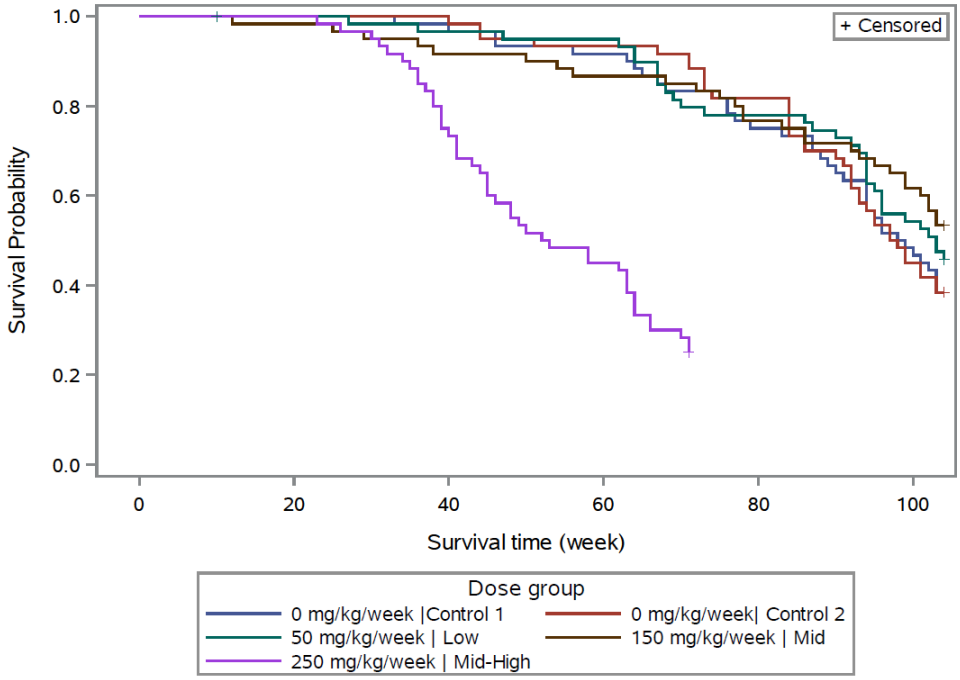


Figure 2B: Kaplan-Meier Survival Functions for Female Mice



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/s/

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12/05/2017

KARL K LIN
12/06/2017
Concur with review.