EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/817852/2018
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lusutrombopag Shionogi

International non-proprietary name: lusutrombopag

Procedure No. EMEA/H/C/004720/0000

Note

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

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List of abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
APD30 (90)	action potential duration at 30% (90%) of repolarisation
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC0-8 (24, 48) hr	area under the plasma drug concentration-time curve between time 0 and 8 (24, 48) hours
AUC0-inf	area under the plasma concentration-time curve between time 0 and infinity
AV	atrioventricular
BA	bioavailability
Ba/F3 cell	murine IL-3-dependent Pro-B cell line
Ba/F3-hEPOR cell	human erythropoietin receptor-expressing Ba/F3 cells
Ba/F3-hMpl cell	human thrombopoietin receptor-expressing Ba/F3 cells
BCRP	breast cancer resistance protein
BLQ	below the lower limit of quantification
BMI	body mass index
BSEP	bile salt export pump
CHMP	Committee for Medicinal Products for Human use
CI	confidence interval
CK	creatine kinase
CLD	chronic liver disease
Cmax	maximum plasma concentration
CNS	central nervous system
CPP	Critical process parameter
CQA	Critical Quality Attribute
CSRs	clinical study reports
CT	computed tomography
CTD	Common Technical Document
CYP	cytochrome P450
DDI	drug-drug interaction
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DSC	Differential Scanning Calorimetry
DTA	Differential Thermal Analysis
EC	European Commission
EC50	50% effective concentration
ECG	electrocardiogram
ECHA	European Chemicals Agency
EMA	European Medicines Agency
Emax	maximum effect
EPO	erythropoietin
EU	European Union

EVL	endoscopic variceal ligation
FAS	Full Analysis Set
FDA	Food and Drug Administration
FOB	functional observational battery
G	gestation day
GC	Gas Chromatography
G-CSF	granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
HCT	hematocrit
HEK293 cell	human embryonic kidney cell
hERG	human ether-à-go-go related gene
HGB	hemoglobin concentration
HPLC	High performance liquid chromatography
HSA	human serum albumin
IC50	50% inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identifier
IL-3 (11)	interleukin 3 (11)
IPC	In-process control
IR	Infrared
ISS	Integrated Summary of Safety
ITP	idiopathic thrombocytopenic purpura
ITT	Intent-to-treat (population)
JAK2	Janus kinase 2
JP	Japanese Pharmacopoiea
KF	Karl Fischer titration
L	Lactation Day
LDH	lactate dehydrogenase
LDPE	Low density polyethylene
LoD	Limit of Detection
LUSU	lusutrombopag (S-888711)
MAH	Marketing Authorisation Holder
MAPK	mitogen-activated protein kinase
MATE	multidrug and toxin extrusion
MC	methylcellulose aqueous solution
MC/Tween 80	0.5% MC containing 0.1% Tween 80
MCT	microwave coagulation therapy
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NADPH	β-nicotinamide adenine dinucleotide phosphate
NAFLD	nonalcoholic fatty liver disease
ND	not detectable
NMR	Nuclear Magnetic Resonance
NMT	Not more than
No.	number
NOAEL	no observed adverse effect level
NOAEL	no observable adverse effect level

NOMO-1 cell	human G-CSF-dependent cell
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OPA	Oriented Polyamide
Papp	apparent membrane permeability coefficient
PAR	Proven Acceptable Range
PD	pharmacodynamics
PEG	polyethylene glycol 400
PEG/Tween 80	polyethylene glycol 400 containing 5% Tween 80
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	pharmacokinetics
PK	pharmacokinetic(s)
PND	postnatal day
PP	Per-protocol (population)
PT	prothrombin time
PVC	Polyvinyl chloride
Q1, Q3 25th percentile, 75th percentile	
QTPP	Quality target product profile
QWBA	quantitative whole body autoradiography
RBC	red blood cell
REACH	Registration, Evaluation, Authorisation & Restriction of Chemicals
RFA	radiofrequency ablation
RH	Relative Humidity
rhEPO	recombinant human EPO
rhG-CSF	recombinant human G-CSF
rhGM-CSF	recombinant human GM-CSF
rhIL-3	recombinant human IL-3
rhTPO	recombinant human TPO
rmIL-3	recombinant murine IL-3
rpm	Revolutions per Minute
SAE	serious adverse event
SLS	Sodium Lauryl Sulfate
SmPC	Summary of Product Characteristics
STAT	signal transducer and activator of transcription
SVHC	Substance of Very High Concern
t1/2, z	terminal elimination half-life
TACE	transcatheter arterial chemoembolization Tmax time to maximum plasma concentration
TAMC	Total Aerobic Microbial Count
TF-1 cell	human IL-3-dependent cell line
TGA	Thermogravimetric Analysis
TPO	thrombopoietin
TPO	thrombopoietin
TPOR-Ki/Shi mouse	mouse having chimeric TPO receptors with the human TPO receptor transmembrane domain knocked-in to the mouse TPO receptor
TYK2	tyrosine kinase 2
TYMC	Total Combined Yeasts/Moulds Count

UGT	uridine 5'-diphospho-glucuronosyltransferase
USP	United States Pharmacopoeia
UV	Ultraviolet
WHO	World Health Organization
XRD	X-ray Diffraction

× ULN times the upper limit of the reference range (ie, normal)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Shionogi B.V. submitted on 12 January 2018 an application for marketing authorisation to the European Medicines Agency (EMA) for Lusutrombopag Shionogi, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 December 2016.

The applicant applied for the following indication: Lusutrombopag Shionogi is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures (see section 5.1).

The legal basis for this application refers to:

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

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

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0224/2016 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

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

Scientific advice

The applicant received Scientific advice from the CHMP on 19 November 2015 (EMEA/H/SA/3196/1/2015/I). The Scientific advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Andrea Laslop Co-Rapporteur: Ewa Balkowiec Iskra

The application was received by the EMA on	12 January 2018
The procedure started on	1 February 2018
The Rapporteur's first Assessment Report was circulated to all CHMP members on	23 April 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	23 April 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	4 May 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	15 May 2018
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	31 May 2018
The applicant submitted the responses to the CHMP consolidated List of Questions on	15 August 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	24 September 2018
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	04 October 2018
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	18 October 2018
The applicant submitted the responses to the CHMP List of Outstanding Issues on	12 November 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	28 November 2018
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Lusutrombopag Shionogi on	13 December 2018

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Chronic liver disease (CLD), independent of aetiology, is commonly associated with thrombocytopenia due to a number of different causes. Contributing factors are, among others, decreased hepatic production of the haematopoietic growth factor thrombopoetin, sequestration of platelets in the spleen and suppression of the bone marrow.

Thrombocytopenia is defined as a platelet count below 150,000/µL. It can be further specified as moderate (50-100,000/µL) and severe (<50,000/µL). Low platelet counts in CLD increase the risk of bleeding during and after surgery and invasive procedures. Clinical practice guidelines vary with their recommendation of desirable platelet levels before attempting an elective procedure. However, it is generally agreed that many invasive procedures like liver biopsies can be done safely with platelet counts above 50-75,000/µL.

2.1.2. Epidemiology

CLD includes a number of long-term liver diseases of diverse aetiology. Some of these diseases may be viral in origin (e.g., hepatitis B and C); others may be caused by toxins (e.g., alcohol), metabolic disorders (e.g., non-alcoholic fatty liver disease [NAFLD]), autoimmune disorders (e.g., primary sclerosing cholangitis), or other factors. Regardless of the aetiology, CLD is generally characterized by gradual, irreversible destruction of the liver and many associated complications. The damage to the liver may be slowed, however, with lifestyle changes and/or appropriate medical and surgical management. Today a majority of patients are surviving their CLD [Newton JL *et al*, 2012], but live with many disease-related morbidities managed (with limited success) by drugs and surgical procedures.

Despite the high incidence of thrombocytopenia in patients with CLD, thrombocytopenia with a platelet count of < 50,000/µL is rare and, although literature on frequency is lacking, is thought to occur in only 1% to 2.6% of the CLD patient population [Afdhal *et al* 2008, Bashour FN, *et al* 2000,Giordano N, *et al* 2005].

The risk of bleeding varies depending on the procedure, the skills of the clinician performing the procedure, and the individual characteristics of the patient, but patients with CLD are generally considered at increased risk of this potentially serious event during or after the procedure if the platelet count is below 50,000/µL to 60,000/µL [Qureshi K, *et al* 2016].

Consequently, diagnostic and therapeutic procedures essential to the care of this patient population may be delayed [Mitchell O *et al*, 2016, Hayashi H, *et al* 2014], thus exacerbating the patient's condition and directly or indirectly increasing morbidity and mortality. For example, a delay in administration of chemotherapy in a patient with hepatocellular cancer may impact the patient's survival, and a postponed endoscopy may put the patient at increased risk of a bleeding episode due to undiagnosed bleeding esophageal varices. In addition, the thrombocytopenia may also delay or prevent routine diagnostic and therapeutic procedures not related to the underlying liver disease, for example, routine dental care [Silva *et al* 2012].

2.1.3. Aetiology and pathogenesis

Thrombocytopenia commonly develops in patients with CLD regardless of the aetiology of the liver disease [Mitchell O *et al* 2016] and has been reported in up to 76% of patients with CLD [Afdhal *et al*

2008]. In clinical studies, its prevalence varies depending on such factors as the severity of the liver disease and the laboratory threshold value used to define this hematologic abnormality [Giannini EG. *et al* 2006]. The thrombocytopenia is multifactorial in origin in this patient population, with its causes including decreased platelet production due to decreased levels of the hematopoietic growth factor thrombopoietin (TPO), as well as suppression of platelet production in the bone marrow due to various causes; splenic sequestration of platelets in the presence of splenomegaly; and increased platelet destruction due to various causes [Mitchell O *et al* 2016, Giannini EG. *et al* 2006, Hayashi H, *et al* 2014].

2.1.4. Clinical presentation, diagnosis

A low platelet count is considered a major contributory factor to an increased risk of bleeding during and after invasive diagnostic and therapeutic procedures that are often required to optimally manage this patient population [Hayashi H, *et al* 2014, Qureshi K, *et al* 2016, Giannini EG, *et al* 2010]. In one study, 31% of patients with CLD undergoing a procedure and a platelet count < 75,000/µL had a procedure-related bleeding complication [Giannini EG, *et al* 2010].

2.1.5. Management

Currently, platelet transfusion is the only nonsurgical treatment available to correct clinically relevant thrombocytopenia in patients with CLD prior to invasive procedures [Qureshi K, *et al* 2016]. There are no international consensus guidelines that currently define the threshold platelet count below which platelet transfusion is needed prior to invasive procedures in this patient population [Maan R, *et al* 2015]. Thus, clinicians may rely on local guidelines, which recommend prophylactic administration of platelets to achieve a platelet count ≥ 50,000/µL prior to many invasive procedures [American Red Cross. A compendium of transfusion practice guidelines. Third edition. 2017].

About the product

Lusutrombopag (S-888711) is an orally active, small-molecule TPO receptor agonist. Lusutrombopag 3 mg once daily for 7 days is proposed for use in the treatment of patients with CLD who have thrombocytopenia and are at increased risk of bleeding associated with planned invasive procedures.

The applicant applied for the following indication:

“ Treatment of thrombocytopenia in patients with chronic liver disease who are at increased risk for bleeding associated with elective invasive procedures.”

The following indication was agreed by CHMP:

“ Treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures (see section 5.1).”

The recommended dose is 3 mg lusutrombopag once daily for 7 days. The procedure should be performed from day 9 after the start of lusutrombopag treatment. Platelet count should be measured prior to the procedure.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 3 mg of lusutrombopag as active substance.

Other ingredients are:

Tablet core: mannitol, microcrystalline cellulose, magnesium oxide, sodium lauryl sulfate, hydroxypropylcellulose, carmellose calcium and magnesium stearate.

Film-coating: hypromellose, titanium dioxide, triethyl citrate, talc and red ferric oxide (E172).

The product is available in OPA/Aluminium foil/PVC film blisters with push through aluminium lidding foil, as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of lusutrombopag is (2*E*)-3-{2,6-dichloro-4-[(4-{3-[(1*S*)-1-(hexyloxy)-ethyl]-2-methoxyphenyl}-1,3-thiazol-2-yl)carbamoyl]phenyl}-2-methylprop-2-enoic acid corresponding to the molecular formula $C_{29}H_{32}Cl_2N_2O_5S$. It has a relative molecular mass of 591.54 g/mol and the following structure:

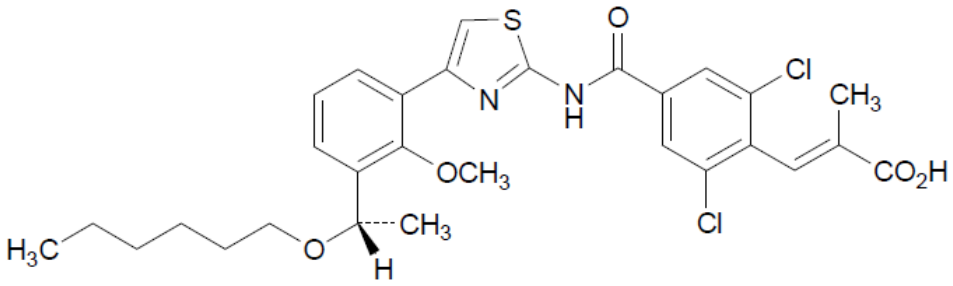


Figure 1: active substance structure

The chemical structure of lusutrombopag was elucidated by a combination of mass spectrometry, elemental analysis, infrared (IR) spectroscopy, ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, and ultraviolet (UV) spectroscopy. The solid state properties of the active substance were measured by x-ray diffraction (XRD), dynamic scanning calorimetry (DSC), thermogravimetric analysis (TGA), differential thermal analysis (DTA) and water adsorption/desorption.

The active substance is a white to slightly yellowish-white non-hygroscopic crystalline powder. It is practically insoluble in aqueous media between pH 1 and 9, slightly soluble in alcoholic solvents, and freely soluble in DMF. The active substance is milled to reduce particle size.

Studies showed that crystalline form 1, the proposed commercial form, is the most thermodynamically stable. The final crystallisation conditions have been developed to produce the desired form 1 – these conditions have also been shown to convert other forms to form 1. It was also demonstrated that the crystalline form is stable during milling, storage, and finished product formulation.

Lusutrombopag has 1 chiral centre and an olefin with two potential geometric isomers. The chiral centre has the (*S*)-configuration and is introduced during the synthetic process. The olefin has the (*E*)-configuration but is susceptible to isomerisation on exposure to light. Enantiomeric purity is controlled routinely in both an intermediate and active substance by chiral HPLC. The geometric isomer is tested in intermediates and the active substance by HPLC.

Manufacture, characterisation and process controls

Lusutrombopag is synthesized in four main steps, followed by milling, using well-defined starting materials with acceptable specifications. Data have been provided to demonstrate that the intermediates are stable for the proposed holding times in the defined packaging.

Target set-points have been set for relevant process parameters and critical process parameters (CPPs) have been defined. Detailed impurity fate and purge studies have been documented. Relevant impurities are monitored by in-process controls (IPCs) and controlled as appropriate in intermediate specifications. PARs have been established for the CPPs, based on univariate experiments and have been adequately justified. Target set-points are defined for each CPP and it is clarified that no design space is claimed.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials, solvents and reagents have been presented and are in-line with the impurity fate and purge studies.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. The control of mutagenic impurities has been adequately justified in line with ICH M7.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The route has stayed the same throughout development, and any changes to reagents, solvents and process parameters were intended to improve processing and reduce relevant impurities. All changes have been presented in sufficient detail and have been justified.

The active substance is packaged in double low density polyethylene (LDPE) bags and sealed with plastic ties. The LDPE bags are then placed into a secondary container, such as a fibre container for storage and shipping. The primary packaging complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for description, identity (IR, UV), assay (HPLC), related substances (HPLC), enantiomer (chiral HPLC), residual solvents (GC), water content (KF), residue on ignition (Ph. Eur.) and particle size (laser diffraction).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set. There is a test for particle size to ensure the performance of the active substance once formulated. Since no microbial growth was observed during stability studies, a microbial limit test is not deemed necessary. Relevant elemental and mutagenic impurities are controlled in intermediates in line with ICH Q3D and M7 respectively.

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

Batch analysis data on 12 batches of the active substance manufactured over the course of the development phase were provided. Of these, the last 3 were manufactured using the final commercial route and by the proposed commercial manufacturer on production scale and the results are within the specifications and consistent from batch to batch.

The active substance specifications and overall control strategy are based on the active substance critical quality attributes (CQAs).

Stability

Stability data from three production scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 36 months under long term conditions (30 ºC / 65% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. In addition, data on three batches of active substance manufactured using the commercial process but milled at a different site (using equivalent equipment) were provided, covering up

to 48 months under long term conditions and 6 months under accelerated conditions. The parameters tested were the same as for release with the exclusion of residual solvents and residue on ignition. The analytical methods used were the same as for release and are stability indicating as demonstrated by forced degradation studies. Under both long term and accelerated conditions, all related substances and total impurities remained less than the reporting thresholds at all time-points for all batches. No changes to water content or particle size distribution were observed.

Photostability testing following the ICH guideline Q1B was performed on one batch. There was an increase in one impurity over time although all other parameters remained constant. The active substance should be stored protected from light.

Results under stressed conditions indicate that lusutrombopag is susceptible to hydrolysis under acidic or basic conditions, is photosensitive in solution, but is stable to oxidation.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container to protect from light.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The finished product is presented as immediate release film-coated tablets containing 3 mg lusutrombopag. They are light red, round and debossed on 1 side with “551” and the MAA trademark and on the other with “3.”

The aim of development was to produce an immediate-release solid oral dosage form meeting the compendial requirements. Accordingly, the quality target product profile (QTPP) was defined and the associated CQAs were identified and justified.

Lusutrombopag is practically insoluble in aqueous media below pH 9, though is slightly soluble at pH 11. Therefore, excipients were investigated during formulation development that could enhance the active substance solubility and promote dissolution. The inclusion of the chosen excipients was adequately justified following a question from CHMP.

The compatibility of the active substance with the various excipients was tested using binary mixtures since it is known to be photosensitive. No incompatibilities were seen with the individual excipients. All excipients with the exception of MgO are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There is no Ph. Eur. monograph for the particular grade of MgO required for the product.. In addition to the compendial tests, MgO is tested for tapped bulk density which discriminates it from other grades. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

In order to establish a suitable dissolution medium, the applicant investigated aqueous media across a range of pHs. In addition the effects of different surfactants were examined. The compendial paddle apparatus was chosen, and the rotation speed optimised to give a robust profile. CHMP raised major objections about the composition of the dissolution medium and the proposed specification. The discriminatory power of the method had not been demonstrated. In response, the applicant was able to demonstrate that a surfactant is indeed required by comparing profiles with and without surfactant. The amount of surfactant used was reduced as an interim measure and a commitment was made to replace it with a different surfactant Furthermore, the specification was tightened to ensure that slower dissolving batches are rejected. The revised method was re-validated successfully. In order to assess the discriminatory power, three batches were manufactured with modified manufacturing process parameters. It was shown that these batches would not meet the revised specification, thereby,

demonstrating sufficient discriminatory power. . The major objections raised in relation to the dissolution method were therefore considered resolved and the post-approval commitment was noted.

A detailed description of the process development was given. Each unit operation was assessed for potential of process parameters to impact the CQAs of the finished product. Risk was assessed based on extensive prior experience of tablet manufacture in the same equipment. The definition of CPPs and non-CPPs has been adequately justified and the control of the relevant parameters for each unit operation is sufficient.

The pivotal phase 3 studies were conducted with tablets identical to those planned for commercialisation. Bridging to tablets of different strengths used in earlier trials was adequately demonstrated.

The primary packaging is OPA/Aluminium foil/PVC film blisters with push through aluminium lidding foil. The materials comply with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of 10 main steps: pre-mixing, screening, wet granulation, drying, screening and milling, blending with extra-granular excipients, lubrication, compression, film-coating and packaging. The process is considered to be a non-standard manufacturing process. The manufacturing process was described in detail, including target set-points and any allowed variability in each step. The control strategy has been explained and is deemed suitable.

Stability data for bulk intermediates has been provided for 1 batch, in the proposed container closure systems. Other than the bulk tablets, the proposed holding times are 30 days or less. For the bulk tablets, a holding time is proposed in LDPE bags. Data were generated from a batch stored under ambient conditions of the commercial warehouse. Data were provided for a second batch, which supports the conclusions from the first batch. The applicant committed to communicate any out of specification results from this second batch to the authorities. This was considered acceptable. The supplier of LDPE bags was unable to confirm compliance with regulation EC 10/2011. The applicant has provided a commitment to source a new supplier of LDPE bags, which was accepted by CHMP, given the low risk to patients.

Major steps of the manufacturing process have been validated by manufacture of six consecutive production scale batches, incorporating three different batches of active substance, according to the process description. The tablets sampled at the beginning and end of each run, after compression, met the acceptance criteria for all physical characteristics. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The IPCs are adequate for this type of manufacturing process and pharmaceutical form.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form including description, identification (HPLC/UV), assay (HPLC), degradation products (HPLC), uniformity of dosage units (HPLC), dissolution (HPLC), water content (KF), and microbiological examination (Ph. Eur.).

The proposed limits for degradation products, water content, and dissolution were tightened during the procedure at the request of CHMP and are now considered justified. A risk assessment was carried out in line with ICH Q3D to investigate the potential presence of class 1 and 2 elemental impurities. Data was provided to demonstrate that elemental impurity levels are consistently below the relevant control thresholds. Therefore, no testing for elemental impurities is mandated.

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

Batch analysis results are provided for 19 batches used for clinical, stability, and validation studies confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Stability data from 3 production batches of finished product stored for up to 24 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Mulpleta are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. In addition, supportive stability data from 3 batches was provided for up to 24 months under long term conditions. Samples were tested for description, assay, degradation products, water content, dissolution, and microbiological examination. With the exception of degradation products, none of the measured parameters changed significantly over the duration of the study.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No degradation was observed indicating that the film-coat provides sufficient protection from light. However, it was noted during the study that moisture content increased, indicating that the packaging is required to protect the product from moisture.

Forced degradation studies were carried out in the solid phase (different temperature and humidity conditions and in solution (acid, base and peroxide). The solid samples were stable whereas the most degradation was observed with aqueous base. This study demonstrates that the impurities and assay methods are stability indicating.

Based on available stability data, the proposed shelf-life of 36 months in the original package to protect from moisture as stated in the SmPC (section 6.3) is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used. The magnesium stearate is of vegetal origin.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. Adequate data and justifications were provided by the applicant in order to resolve the major objections on the product composition and dissolution method raised by CHMP during the procedure. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

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

- The applicant should replace the surfactant that is currently used in the dissolution medium, with an alternative before January 2021.
- The applicant should find an alternative source of LDPE bags used to store the bulk tablets who is able to confirm compliance with regulation EC 10/2011.

2.3. Non-clinical aspects

2.3.1. Introduction

Lusutrombopag is a novel small-molecule human TPO receptor agonist having orally-active pharmacological action. It is well known that TPO upregulates differentiation and growth of hematopoietic stem cells and megakaryocyte progenitor cells to upregulate maturation of megakaryocytes, leading to the release of platelets from matured megakaryocytes. Lusutrombopag acts on the transmembrane domain on TPO receptors expressed on megakaryocytes to induce proliferation and differentiation of megakaryocyte progenitor cells via 2 signaling pathways (the Janus kinase [JAK]−signal transducer and activator of transcription [STAT] pathway and the Ras−p44/42 mitogen-activated protein kinase [MAPK] pathway), leading to platelet production. This assumption was the basis for starting the conclusion about the usefulness of the lusutrombopag for the treatment of patients with thrombocytopenia.

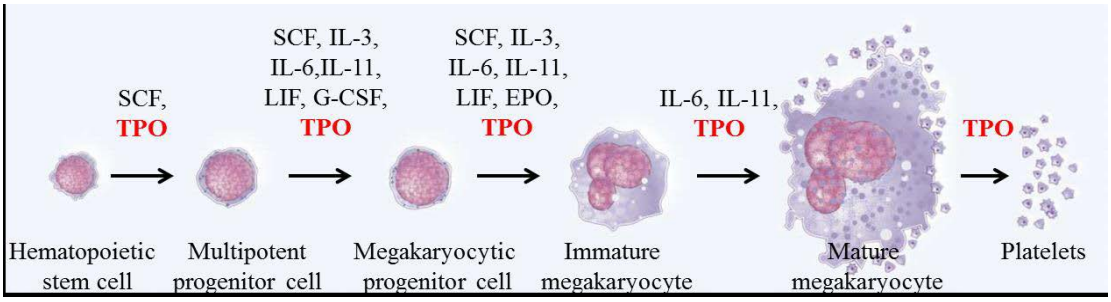


Figure 2. Proliferation of Hematopoietic Stem Cells and Cytokine

2.3.2. Pharmacology

Primary pharmacodynamic studies

Primary pharmacodynamic studies of lusutrombopag were conducted to investigate proliferative activity in human TPO receptor-expressing cells and cytokine-dependent cell lines, megakaryocyte colony-forming ability in human bone marrow-derived CD34 positive cells, and signaling pathways in human TPO receptor-expressing cells. Furthermore, thrombocytopoietic effect was investigated in knock-in mice (i.e. mice having chimeric TPO receptors with the human TPO receptor transmembrane domain knocked-in to the mouse TPO receptor [TPOR-Ki/Shi mouse]). Proliferative activity of lusutrombopag metabolites was investigated in Ba/F3-hMpl cells-expressing human TPO receptor (Mpl is the TPO receptor).

Primary pharmacodynamic studies of lusutrombopag were conducted to investigate proliferative activity in human TPO receptor-expressing cells and cytokine-dependent cell lines, megakaryocyte colony-forming ability in human bone marrow-derived CD34 positive cells, and signaling pathways in human TPO receptor-expressing cells. In order to investigate the thrombocytopoietic effect of lusutrombopag *in vivo*, TPOR-Ki/Shi mice were produced, which have chimeric TPO receptors where the human TPO receptor transmembrane domain knocked-in to the mouse TPO receptor. Proliferative activity of lusutrombopag metabolites was investigated in Ba/F3-hMpl cells-expressing human TPO receptor. As a secondary pharmacology study, crossing of lusutrombopag and erythropoietin (EPO) or the granulocyte colony-stimulating factor (G-CSF) was investigated in human bone marrow-derived CD34 positive cells.

In vitro

Lusutrombopag presents the S-enantiomer of an orally administered, novel small-molecule human TPO receptor agonist. The (+)-lusutrombopag form is specified as an impurity and shows pharmacological activity and lusutrombopag is not chirally transformed *in vivo*.

The choice of the S-enantiomer of lusutrombopag instead of (+)-lusutrombopag with the observation of a higher increase in platelets in rats was explained, the absence of inducing any hepatic metabolising enzyme in rats up to 100 mg/kg/day and the absence of any chiral inversion. A preliminary 2-week toxicity study in rats showed no differences in toxic findings between both enantiomers.

Pharmacological activity of lusutrombopag was evaluated non-clinically in direct comparison to eltrombopag and/or recombinant hTPO:

Proliferative activity of lusutrombopag was shown on the *in vitro* level in Ba/F3-hMpl cells (murine, mIL-3 dependent Pro-B cell line) expressing the human TPO receptor with EC50 of 84 nmol/L (rhTPO: 0.08 nmol/L), but no proliferation was observed in non-transfected (TPO receptor negative) Ba/F3 cells.

The absence of receptor promiscuity of lusutrombopag against human EPO, G-CSF, GM-CSF, and IL-3 receptors was confirmed by measuring proliferative effect on the respective cytokine-dependent cell lines (Ba/F3-hEPOR cells, NOMO-1 cells, and TF-1 cell). The effects of lusutrombopag on IFN-alfa and IFN-gamma receptors were not investigated. However, sufficient evidence can be built by extrapolation from data with other TPO-receptor agonists such as eltrombopag, where no effect on IFN-alfa and IFN-gamma receptors were observed (Erickson-Miller et al 2009).

The signal transduction pathway of lusutrombopag in comparison to TPO was investigated on Ba/F3-hMpl cells, and showed phosphorylation of JAK2, STAT3, STAT5, and p44/42 MAPK for both. The outcome of *in vitro* studies by stimulation of Ba/F3-hMpl cells indicates a comparable mechanism of action. Lusutrombopag acts additively with TPO: Although no *in vitro* combination studies with TPO and lusutrombopag were conducted, evidence for additivity is provided based on data from proliferation and activation assays in N2C-Tpo cells with eltrombopag and TPO. Above that it is shown that TPO binds to the extracellular domain of the TPO receptor while eltrombopag binds to the transmembrane domain – thus no binding competition with TPO is expected. For lusutrombopag a study report (EB-317-N) was provided showing that H499 in the transmembrane domain of TPO receptor is essential for lusutrombopag to exert its action. This was measured by proliferation activities and JAK2, STAT3, STAT5 and p44/42 MAPK phosphorylation on respective cell lines, i.e. with or without Histidine 499 substitution on the TPO receptor. Importantly, the relevance of the 499th amino acid histidine on the TPO receptor is known for eltrombopag. As such appropriate evidence is provided to cover this aspect.

In signal transduction studies of washed human platelets eltrombopag stimulates platelet signal transduction with little or no effect on overall platelet function, in contrast to TPO, which significantly primes platelet activation via phosphorylation of AKT as well as STAT1, 3, and 5 (Erhardt *et al.* 2009).

Phosphorylation status of some downstream signalling proteins for lusutrombopag was provided in comparison to hTPO. TPO acts mainly via the three signaling pathways of JAK2, MAPK, and AKT phosphorylation [1]. Lusutrombopag has been demonstrated to activate two main pathways, MAPK and JAK2 (including STAT3/5 which are downstream signaling molecules of JAK2). Based on the evidence that binding sites and mechanism of action of eltrombopag and lusutrombopag are the same, AKT phosphorylation by lusutrombopag was not investigated. Eltrombopag induced AKT phosphorylation in human platelets, albeit to a lesser degree compared to rhTPO (Jeong et al. 2015). Although this aspect remains an interesting matter of research, the impact on a final benefit risk assessment is considered neglectable.

Deshexyl and 5-keto lusutrombopag were detected as metabolites in human plasma after oral administration, showing proliferative activity far below the parent molecule (EC50: deshexyl = 34861.0 nmol/L and 5-keto = 555.7 nmol/L).

Lusutrombopag confirmed its thrombopoietic activity in human bone marrow derived CD34+ cells by cell differentiation to megakaryocytes with an EC50 of 0.31 µmol/L (defining the maximum signal derived from rhTPO stimulation as 100%).

In vivo

Due to species specific activity of lusutrombopag TPOR-Ki/Shi mice (having chimeric TPO receptors with the human TPO receptor transmembrane domain knocked-in to the mouse TPO receptor) were used to examine thrombocytopoietic activities *in vivo*: H499 in the human transmembrane domain of humans and chimpanzees the TPOR was published to be essential for exerting pharmacological action of eltrombopag (Erickson-Miller et al. 2004). This molecular feature was confirmed with butyzamide, a compound with high structural similarity to lusutrombicopag in cell lines transfected with the respective amino acid substitutions of the human or murine TPOR: Ba/F3-hMplH499L (His substituted by Leu) and Ba/F3-mMplL499H (Leu substituted with His) (Nogami *et al.* 2008).

Daily oral treatment of TPOR-Ki/Shi mice with lusutrombopag for 21-days showed dose-dependent increase in platelet count at ≥ 0.3 mg/kg/d from day 7 to day 22 if compared to the control group. PK/PD analysis showed correlation for platelet increase with AUC0-inf and Cmax in the model.

Regarding extrapolation of data, Cmax and AUC0-inf values (at the time when platelet counts increased by 50%) in humans and TPOR-Ki/Shi mice were largely comparable with 0.062 µg/ml Cmax and 0.639 µg.hr/ml in TPOR-Ki/Shi mice and 0.0389 µg/mL Cmax and 0.703 µg.hr/mL AUC0-inf in healthy adults (0.5 mg dose group).

A 6 weeks study showed consistent platelet counts after d29 at the highest (3 mg/kg/d) dose group, which is taken as an indicator that also clinically a continued increase in platelet count unlikely occurs with prolonged administration.

Another *in vivo* PD study in the same model (oral, daily, 21-days) showed megakaryocytopoiesis in the bone marrow and the spleen, consistent with increasing platelet counts – thus indicating TPOR driven upregulation and proliferation of megakaryocytic cells, responsible for increased platelet counts. Comparable PD effects were observed in a parallel, eltrombopag exposed study group. Both high dose groups showed small decreases in RBC count, HGB concentration and HCT – not affecting any changes in the coagulation tests.

As thrombocytopenia is one of the manifestations in MDS, lusutrombopag was investigated in combination with EPO or G-CSF. The compound showed in a CFU assay in human bone marrow-derived CD34 positive cells no effect on the EPO or G-CSF induced hematopoietic colony formation.

A panel of 11 enzymes and 30 receptors was used to evaluate for inhibitory activities of lusutrombopag, identifying COX-1, COX-2, PDE1, adrenergic α2C and BLT (LTB4). IC50 values for these interactions were

far above clinical Cmax values, providing a margin around 5100 to the plasma concentration of unbound unchanged lusutrombopag. Thus no or little effect on enzymes, ion channels and other receptors than TPOR can be expected.

Secondary pharmacodynamic studies

The effect of lusutrombopag (concentration: 0.25 and 1 µmol/L) on recombinant human EPO (rhEPO)- and human G-CSF (rhG-CSF)-induced hematopoietic colony formation was evaluated. Human bone marrow-derived CD34 positive cells were incubated with lusutrombopag only or together with rhEPO (concentration: 0.05 and 3 U/mL). In addition, human bone marrow-derived CD34 positive cells were incubated with lusutrombopag alone or together with rhG-CSF (concentration: 1 and 10 ng/mL). Lusutrombopag did not induce differentiation of hematopoietic stem cells to erythroid cells and granulocytic/macrophage cells, except for megakaryocytes. Therefore, it was demonstrated that lusutrombopag has no effect on hematopoietic colony-forming activities of EPO and G-CSF (Report S-888711-EB-159-N).

A total of 11 enzyme assays and 30 receptor binding assays were evaluated at 10 µmol/L. When inhibitory activities (≥ 50% inhibition) were noted, 50% inhibition concentration (IC50) values were determined. The IC50 of adrenergic α2C, leukotriene B4, cyclooxygenase (COX)-1, COX-2, and phosphodiesterase 1 were calculated as 2.75, 2.78, 16.2, 4.08, and 1.36 µmol/L, respectively. Lusutrombopag had no effect on other receptors and enzymes at a concentration of 10 µmol/L.

Safety pharmacology programme

Core battery safety pharmacology studies of lusutrombopag were performed to investigate effects on the central nervous system (CNS) and respiratory system in rats and the cardiovascular system *in vitro* and in dogs. Two follow-up studies were performed to further investigate effects on the cardiovascular system in dogs.

Lusutrombopag had no significant effects on general physical behaviour and neurobehavioral function at any doses, suggesting that lusutrombopag at a dose up to 1000 mg/kg had no effect on the CNS system in rats. No lusutrombopag-related changes were noted on ECG parameter. It was concluded that the second-degree AV block and PR prolongation observed in the 1-month oral repeat-dose toxicity study were due to vehicle (PEG/Tween 80), and lusutrombopag had no effect on the cardiovascular system in dogs. There was no effect of lusutrombopag on blood pressure, heart rate, and ECG parameters at any doses, suggesting that lusutrombopag at doses up to 500 mg/kg had no effect on the cardiovascular system. There was no effect of lusutrombopag on respiration rate, tidal volume, and minute ventilation volume at any dose, suggesting that lusutrombopag at a dose up to 1000 mg/kg had no effect on the respiratory system in rat.

Pharmacodynamic drug interactions

With the exception of studies which assessed the effect of lusutrombopag on rhEPO- and rhG-CSF-induced hematopoietic colony formation, no studies investigating pharmacodynamic drug interactions were conducted.

2.3.3. Pharmacokinetics

The pharmacokinetic (PK) and toxicokinetic studies of lusutrombopag were conducted with mice, rats, rabbits, and dogs, which were used for the pharmacology studies and/or the toxicity studies. The distribution of radioactivity in melanin-containing tissues in pigmented rats was investigated by quantitative whole body autoradiography (QWBA). The excretion of radioactivity into milk in nursing rats

was investigated. The 14C-radiolabeled lusutrombopag ([14C]-lusutrombopag) was used in the PK studies where radioactivity was used. *In vitro* studies were performed to investigate the inhibition/induction of cytochrome P450 (CYP) enzymes and inhibition of transporters by lusutrombopag, as well as to identify responsible metabolising enzymes and transporters for the pharmacokinetics of lusutrombopag.

After oral administration of lusutrombopag to non-fasting rats and dogs, plasma concentrations increased in a dose-dependent manner. Fasting before administration did not impact absorption. Bioavailability in fasting rats was between 45-52%. Using 0.5% methylcellulose suspension as a vehicle instead of PEG400, both Cmax and AUC did not increase in a dose proportional manner at high dose (10 mg/kg), suggesting earlier saturation when using methylcellulose as vehicle.

Since the ratio of (+)-S-888711 to S-888711 in plasma sample was similar to that in the test substance in all tested species, it was demonstrated that chiral inversion from S-888711 to (+)-S-888711 does not occur *in vivo* in mice, rats and dogs.

For both RSC-888711 and (+)-RSC-888711 in both sexes, the Cmax and AUC0-24hr values increased dose proportionally between the lower and medium dose groups, and increased less than dose proportionally or even decreased in medium and high dose groups, respectively. In contrast to mice, repeated-dosing of lusutrombopag resulted in increases in Cmax and AUC0-24hr in the toxicokinetic studies conducted in rats and rabbits.

Quantitative whole body autoradiography after single oral administration of 3 mg/kg to male and female albino rats revealed similar tissue distribution of lusutrombopag to almost all tissues in both sexes. Most of the tissue reached the peak levels between 8 (males) and 8-12 hours (females) with the liver and the adrenal cortex showing highest radioactivity. Studies in male pigmented rats resulted in similar findings indicating no evidence for drug-binding to melanin-containing tissues.

After oral administration of radiolabelled-lusutrombopag to pregnant rats, highest tissue concentrations of radioactivity were detected in adrenal gland and liver 8 hours after administration. Moreover, radioactivity was also detected in fetus indicating placental transfer of lusutrombopag.

Protein binding was found to be very high (>99%) within *in vitro* assays conducted with plasma from mice, rats, rabbits, dogs and male human volunteers. Distribution of radioactivity to blood cells was found to be low in all species tested. These findings suggest that there are no species differences in plasma protein binding and distribution to blood cells.

The major component of radioactivity in plasma of mice, rat and rabbit was unchanged lusutrombopag. Deshexyl, β-oxidated carboxylic acid, and 5-keto were identified to be major metabolites. These results indicate that major metabolites detected in human plasma exist also in plasma of the tested animals. Other metabolites occurred at lower concentrations. The results suggest that lusutrombopag is mainly metabolised via oxidation of the hexyl group of the RSC-888711 side chain.

The major metabolites occurring in urine, faeces and bile were also investigated in rats, mice and dogs, with unchanged lusutrombopag again representing the major amount of radioactivity measured.

Approximately 98% of the administered dose was excreted in the faeces after oral administration of [14C]-lusutrombopag. 23.7% of the radioactivity detected was excreted via bile into faeces. After repeated oral dosing for 14 days a main excretion route was the faeces and similar amount of excreted cumulative radioactivity (98.2%) was detected as after single administration. Some of the reabsorbed radioactive components were excreted into the bile again, indicating enterohepatic circulation.

After single oral administration of [14C]-S-888711 at 3 mg/kg to nursing rats, the radioactivity was excreted into milk. Forty-eight hours after administration, the milk concentration of radioactivity decreased to about 10% of the maximum concentration.

To evaluate the effects of lusutrombopag on hepatic drug metabolising enzymes two GLP compliant studies were conducted in rat and dog, respectively. Dose-related increases in microsomal protein content were associated with lusutrombopag treatment in male rats without complete recovery. In dogs, the only significant finding was a slight, dose-dependent increase of the T16α-OHase activity, a marker activity for CYP2B11/2C21. All of the alterations found in dogs were fully reversible.

Lusutrombopag was shown to be a substrate of P-gp and BCRP. This signal was followed up on the clinical level.

Further, specific marker activities and the binding site of lusutrombopag on human serum albumin were investigated using human hepatocytes.

2.3.4. Toxicology

Key toxicology studies, which include single-dose and repeat-dose toxicity studies, *in vitro* and *in vivo* genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, local tolerance studies, a skin phototoxicity study, were conducted for lusutrombopag, and *in vitro* reverse mutation assays were also conducted for possible impurities of lusutrombopag. Standard species for nonclinical safety evaluation of pharmaceuticals (mice, rats, rabbits and dogs) were used for these studies. As lusutrombopag does not stimulate platelet production in normal (non-genetically engineered) laboratory animals because of its human TPO receptor specificity, the data from these animals do not fully model the effects of lusutrombopag in humans derived from its pharmacological effects. Accordingly, to assess on-target effects of lusutrombopag on the bone marrow, especially the potential risk of fibrosis in humans, a potential to evoke bone marrow fibrosis was assessed using TPOR-Ki/Shi mice. Long-term repeat-dose toxicity studies and carcinogenicity studies were conducted to address possible indications requiring long-term treatment of thrombocytopenia with lusutrombopag.

Single dose toxicity

A single oral dose toxicity study was conducted in rats (5 animals/sex/group) and dogs (1 animal/sex/group) with up to 2000 mg/kg. As no deaths occurred throughout the study period the lethal dose was determined to be >2000 mg/kg for rats and dogs.

Repeat dose toxicity

All relevant repeated dose toxicity studies were conducted in compliance with current GLP guidance.

The principal toxicity findings associated with lusutrombopag treatment included prolongation of PT and APTT (rats), increased activities of plasma ALT, AST and ALP (rats and dogs), adrenal toxicity (rats and dogs), skin and forestomach lesions (rats), renal toxicity (rats) and minor findings in the gallbladder of dogs. Changes in the adrenal or gallbladder completely or at least partially recovered at the end of the withdrawal period.

Lusutrombopag showed no toxicity in rats at a dose up to 8 mg/kg/day or in dogs at a dose up to 3 mg/kg/day after 1-month of dosing. There were no significant sex differences in the incidence of lusutrombopag-related lesions, and no exacerbation or significant increase in the incidence of effects with treatment for longer than 1 month. All changes showed reversibility or a tendency towards reversibility after 1-month drug-withdrawal.

Within the three month dog study 0.5% methylcellulose was used as the vehicle instead of polyethylene glycol 400 with 5 w/w% polyoxyethylene sorbitan monooleate (PEG/Tw 80) which was used in the previous 1-month study. Compared to the one-month study, second-degree AV block was not detected in any of the treated groups up to 600 mg/kg/day. The effects on ECG parameters seem to be associated to

PEG/Tw 80 rather than the drug substance itself. With regard to the three-month study the NOAEL was considered to be 10 mg/kg/day for males and 80 mg/kg/day for females.

Genotoxicity

Three GLP compliant genotoxicity studies were conducted in bacteria and mammalian cells. Negative results were observed in the reverse mutation test with bacteria as well as in the chromosomal aberration test in cultured mammalian cells and the micronucleus test with mouse bone marrow cells.

Carcinogenicity

Two GLP compliant long-term carcinogenicity studies (104 weeks) in mice and rats, respectively, were conducted. Neither in mice nor in rats were any neoplastic changes or evidence for carcinogenic potential of lusutrombopag observed.

Reproduction Toxicity

Four GLP compliant studies in rats and rabbits were conducted to assess the potential of lusutrombopag for reproductive and developmental toxicity. Additional four studies (two of them in compliance with GLP) were conducted for dose range finding purposes.

In the rat study on fertility and early embryonic development no effects on male or female fertility was found up to the highest dose (100mg/kg/day) tested. Exfoliation of the limbs was found in all studies conducted in rats. In F1 rat pups, adverse effects were found in the high dose group. These findings included low viability index, low body weight, low score of negative geotaxis, delayed eyelid opening, prominent annular rings, slightly low fertility index in F1 females and slightly low numbers of corpora lutea and implantations, and a tendency to high pre-implantation loss rate. Moreover, transient test substance-related increase in frequency of short supernumerary rib, which was classified as skeletal variation of isolated nature, was observed in culled pups after birth from the 12.5 mg/kg group upwards in the rat EFD study. Thus, the NOAEL in this study was determined to be 12.5 mg/kg/day.

In rats, treatment-related non-neoplastic changes were confined to the ovaries of S-888711 treated females consisting of granulosa cell hyperplasia. Other changes consisted of marginally lower α2 globulin for males at 6 mg/kg/day and above and an increased incidence of dark adrenals noted macroscopically for males at 6 mg/kg/day and above and females at 1 mg/kg/day and above. No histopathological findings could be correlated with the increased incidence of dark adrenals and neither histopathological nor clinical findings were associated with decreased α2 globulin concentrations in male rats.

Lusutrombopag up to 80 or 1000 mg/kg/day showed no teratogenicity in rats or rabbits, respectively. However, adverse effects were detected on fetal intrauterine growth and skeletal morphology in rats. No effects of lusutrombopag on viability, intrauterine growth, and skeletal morphology were noted in rabbits treated up to 1000 mg/kg/day.

Local Tolerance

Lusutrombopag (0.5 g/site) was applied to the skin of New Zealand White rabbits by occlusive application to investigate its potential of dermal irritation. The skin reaction was evaluated in accordance with Draize's criteria. Lusutrombopag has no potential of dermal irritation on rabbit skin.

Lusutrombopag (0.1 g/left eye) was applied to the conjunctival sac of New Zealand White rabbits to investigate its potential of ocular irritation. The ocular reaction in the eye was evaluated in accordance with Draize's criteria. Lusutrombopag has no potential of ocular irritation on rabbit eye.

Other toxicity studies

Studies on impurities

Five impurities, were shown to be positive in the Ames test. All of these potentially mutagenic impurities were shown to be present at levels below the acceptable limit of either not more than 0.5% (respectively the TTC) according to ICH M7 or were not detectable at all. The assessment of these impurities is acceptable with regard to current guidance and thus, the need for setting specification limits is not given for these five potentially mutagenic impurities.

2.3.5. Ecotoxicity / environmental risk assessment

Summary of main study results

Substance (INN / Invented Name): Lusutrombopag			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD TG 123 (2006)	log D_{ow} at pH 7 = 6.9	Potential PBT: Yes
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log D_{ow} at pH 7 = 6.9	B
	BCF	138038	vB
Persistence	DT50	390	vP
Toxicity	NOEC	0.027 µg/L	T
	The compound is considered as vPvBT.		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.00564	µg/L	> 0.01 threshold: No
Other concerns (e.g. chemical class)			No
Phase II Physical-chemical properties and			

fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 84300, 30, 500, and 9680 L/kg Average: 41493 L/kg			List all values
Ready Biodegradability Test	OECD 301	No data available			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT50, water = 0.5 DT50, sediment = 390 DT50, whole system = 78 % shifting to sediment = 28-32.7% after 100 days			Not required if readily biodegradable
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/Species	OECD 201	NOEC	0.027	µg/ L	*Pseudokirchneriella subcapita*
Daphnia sp. Reproduction Test	OECD 211	NOEC	2.8 (at saturation)	µg/ L	*Daphnia*
Fish, Early Life Stage Toxicity Test/Species	OECD 210	NOEC	1.95 (at saturation)	µg/ L	*Pimephales promelas*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	No data	µg/ L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF		L/k g	%lipids:
Aerobic and anaerobic transformation in soil	OECD 307	DT50 %CO_2			for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect		mg/ kg	
Terrestrial Plants, Growth Test/Species	OECD 208	NOEC		mg/ kg	

Earthworm, Acute Toxicity Tests	OECD 207	NOEC		mg/ kg	
Collembola, Reproduction Test	ISO 11267	NOEC		mg/ kg	
Sediment dwelling organism		NOEC		mg/ kg	species

Lusutrombopag's PEC surfacewater value is below the action limit of 0.01 µg/L. As the log_{Dow} exceeds the action limit of 4.5, formal PBT testing is needed.

The active ingredient lusutrombopag has to be classified as very persistent (vP, DT_{50}sediment $\geq$180d) in the environment according to the half-lives in sediment derived in the present study on transformation in water/sediment systems (OECD 308). Results from bioaccumulation studies in rainbow trout revealed a BCF of >5000. Accordingly, lusutrombopag was categorised to be very bioaccumulative (vB) (OECD 305). Subsequent aquatic toxicity testing showed a NOEC for algae above 0.01 mg/L.

Thus, lusutrombopag has to be categorised as very persistent, very bioaccumulative and toxic (vPvBT).

2.3.6. Discussion on non-clinical aspects

Lusutrombopag presents the S-enantiomer of an orally administered, novel small-molecule human TPO receptor agonist, inducing platelet production by triggering proliferation and differentiation of megakaryocyte progenitor cells via 2 signalling pathways (JAK-STAT pathway and Ras-p44/42 MAPK pathway).

The (+)-lusutrombopag form is specified as an impurity and shows pharmacological activity and lusutrombopag is not chirally transformed *in vivo*. The applicant clarified that the selected S-enantiomer showed a higher increase in platelets in rats and absence of inducing any hepatic metabolizing enzyme in rats. A preliminary 2-week toxicity study in rats showed no differences in toxic findings between both enantiomers.

Pharmacological activity of lusutrombopag was evaluated non-clinically in direct comparison to eltrombopag and/or recombinant hTPO: Proliferative activity of lusutrombopag was shown on the *in vitro* level in Ba/F3-hMpl cells expressing the human TPO receptor, but no proliferation was observed in non-transfected (TPO receptor negative) Ba/F3 cells.

The absence of receptor binding of lusutrombopag against human EPO, G-CSF, GM-CSF, and IL-3 receptors was confirmed by measuring proliferative effect on the respective cytokine-dependent cell lines (Ba/F3-hEPOR cells, NOMO-1 cells, and TF-1 cell). No data on the evaluation of lusutrombopag for receptor binding to IFN-alfa and IFN-gamma receptors were provided. This was justified based on data showing that the binding site and mechanism of action of lusutrombopag and eltrombopag are the same, hence there is sufficient evidence that both products can bind to the receptors. This is considered acceptable.

The signal transduction pathway of lusutrombopag in comparison to TPO was investigated on Ba/F3-hMpl cells, and showed phosphorylation of JAK2, STAT3, STAT5, and p44/42 MAPK for both. The outcome of *in vitro* studies by stimulation of Ba/F3-hMpl cells indicates a comparable mechanism of action. Lusutrombopag acts additively with TPO: although no *in vitro* combination studies with TPO and lusutrombopag were conducted, evidence for additivity is provided based on data from proliferation and activation assays in N2C-Tpo cells with eltrombopag and TPO. Above that different binding sites for TPO and eltrombopag indicate the absence of binding competition.

Overall, the *in vitro* and *in vivo* safety pharmacology studies performed in rats and dogs indicated no adverse effects on CNS and respiratory system. Cardiovascular effects (AV block) were observed in a few animals of an initial CV study in dogs, but later on confirmed to be unrelated to lusutrombopag but caused by PEG/Tween 80 used as a vehicle. Thus in summary, no findings from safety pharmacology studies were detected with animal to human exposure ratios ranging from 48 to 222 for the *in vivo* studies.

The Applicant performed an extensive set of non-clinical studies in relevant rodent and non-rodent species and in agreement with recent guidelines to evaluate the toxicological profile of lusutrombopag. No findings on the genotoxic and carcinogenic potential of lusutrombopag were observed. Treatment-related non-neoplastic granulosa cell hyperplasia in the ovaries of female rats was observed histopathologically, however, not considered to be adverse because there were no effects found in other hormone-related tissues. Macroscopic findings of dark adrenals in male and female rats could not be correlated with any histopathological findings. The observed increase in the mortality rate of treated female rats was not considered significant and occurred only after long-term treatment and at much higher doses than the proposed human dose.

Treatment-related toxicity findings in single and repeat-dose toxicity studies in rats and dogs were all reversible and NOAELs showed sufficient safety margins when compared to the proposed human dose of 3 mg/day.

Lusutrombopag up to 80 or 1000 mg/kg/day showed no teratogenicity in rats or rabbits, respectively. No effects of lusutrombopag on viability, intrauterine growth, and skeletal morphology were noted in rabbits treated up to 1000 mg/kg/day.

However, adverse effects were detected on fetal intrauterine growth and skeletal morphology in rats. Exfoliation of the limbs was found in all studies conducted in rats. In F1 rat pups, adverse effects were found in the high dose group. These findings included low viability index, low body weight, low score of negative geotaxis, delayed eyelid opening, prominent annular rings, slightly low fertility index in F1 females and slightly low number of corpora lutea and implantations, and a tendency to high pre-implantation loss rate. Moreover, transient test substance-related increase in frequency of short supernumerary rib, which was classified as skeletal variation of isolated nature, was observed in culled pups after birth from the 12.5 mg/kg group upwards in the rat EFD study. These findings are reflected in the sections 4.6 and 5.3 of the SmPC, where it is stated that lusutrombopag should not be used during pregnancy unless the expected benefit outweighs the expected risk.

Fibrosis of the bone marrow may occur as an exaggerated on-target effect of lusutrombopag at high dose long-term treatment. This is accordingly mentioned in section 5.3 of the SmPC.

Lusutrombopag was shown to be very persistent (vP), very bioaccumulative (vB) and toxic (T). Appropriate statements have been included in the SmPC.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical data submitted for lusutrombopag support the approval of lusutrombopag.

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points to be addressed:

Lusutrombopag has shown to be vP and vB. The applicant is asked to provide chronic aquatic studies for T assessment, to allow a final conclusion on PBT evaluation.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Description of Study	Study No. Country	Study Objectives	Study Design, Including Type of Control	Test Product(s) Route of Administration	Number of Subjects Exposed	Healthy Subjects or Diagnosis of Patients	Dosage Regimen Duration of Treatment	Study Status Type of Report
Phase 1 BA and food effect	0801M0612 Japan	Evaluate relative BA (2-mg tablet and 2-mg solution), food effect, safety, and tolerability	Single-center, randomized, open-label, 3-sequence crossover	Lusutrombopag 2 mg and 10 mg Oral tablet Lusutrombopag 2 mg Oral solution	Lusutrombopag, N = 26	Healthy male subjects	Single dose	Complete Full
Phase 1 Food effect	0924M0618 United States	Evaluate food effect, effect of calcium, and safety	Single-center, randomized, open-label, 3-period crossover	Lusutrombopag 0.75 mg Oral tablet	Lusutrombopag, N = 15	Healthy subjects	Single dose	Complete Full
Phase 1 BA and food effect	1218M061A Japan	Evaluate relative BA, food effect, safety, and tolerability	Single-center, randomized, open-label, 3-way crossover	Lusutrombopag 1 mg (× 4 tablets) and 4 mg (1 tablet) Oral tablet	Lusutrombopag, N = 15	Healthy male subjects	Single dose	Complete Full
Phase 1 PK	0820M0614 Japan	Evaluate PK and safety	Single-center, randomized, open-label crossover	Lusutrombopag 0.1 mg, 0.25 mg, and 2 mg Oral tablet Lusutrombopag 0.1 mg and 0.25 mg Oral solution	Lusutrombopag, N = 28	Healthy white male subjects	Single dose	Complete Full

CTD Section Description of Study	Study No. Country	Study Objectives	Study Design, Including Type of Control	Test Product(s) Route of Administration	Number of Subjects Exposed	Healthy Subjects or Diagnosis of Patients	Dosage Regimen Duration of Treatment	Study Status Type of Report
Phase 1 Dose escalation, PK	0713M0611 Japan	Evaluate PK, safety, and tolerability	Single-center, randomized, double-blind, placebo-controlled, dose escalation	Lusutrombopag 1 mg, 2 mg, 4 mg, 10 mg, 25 mg, and 50 mg and placebo Oral solution	Lusutrombopag, N = 36 Placebo, N = 11	Healthy male subjects	Single dose	Complete Full
Phase 1 Mass balance, PK	1012M0619 United States	Evaluate PK, mass balance, safety, and tolerability	Single-center, open-label, non-randomized	Lusutrombopag 2 mg Oral solution	Lusutrombopag, N = 7	Healthy male subjects	Single dose	Complete Full
Phase 1 Ascending dose, PK	0806M0613 Japan	Evaluate PK, safety, and tolerability	Single-center, randomized, double-blind, placebo-controlled	Lusutrombopag 2 mg and placebo Oral tablet Lusutrombopag 0.25 mg and 0.5 mg and placebo Oral solution	Lusutrombopag, N = 18 Placebo, N = 6	Healthy male subjects	Once daily 14 days	Complete Full
Phase 1 Ascending dose, PK	0823M0615 United States	Evaluate PK, safety, and tolerability	Single-center, randomized, double-blind, placebo-controlled	Lusutrombopag 0.25 mg, 0.5 mg, 0.75 mg, and 1 mg and placebo Oral tablet	Lusutrombopag, N = 24 Placebo, N = 8	Healthy subjects	Once daily 14 days	Complete Full

Description of Study	Study No. Country	Study Objectives	Study Design, Including Type of Control	Test Product(s) Route of Administration	Number of Subjects Exposed	Healthy Subjects or Diagnosis of Patients	Dosage Regimen Duration of Treatment	Study Status Type of Report
Phase 1 Intrinsic factor PK (hepatic impairment)	0911M0616 United States	Evaluate effect of impaired hepatic function on PK, safety, and tolerability	Single-center, open-label, non-randomized, case-matched	Lusutrombopag 0.75 mg Oral tablet	Lusutrombopag, N = 24 (8 per cohort)	Subjects with mild hepatic impairment (Child-Pugh class A), moderate hepatic impairment (Child-Pugh class B), and healthy subjects	Single dose	Complete Full
Phase 1 Extrinsic factor PK (DDI)	0912M0617 United States	Evaluate effect on midazolam PK and safety	Single-center, open-label, 1-sequence crossover	Lusutrombopag 0.75 mg with loading dose of 1.5 mg Oral tablet	Lusutrombopag, N = 15	Healthy subjects	Once daily 7 days	Complete Full
Phase 1 Extrinsic factor PK (DDI)	1514M061E Japan	Evaluate effect of cyclosporine and/or quinidine sulfate [a] on PK, safety, and tolerability	Single-center, open-label, randomized, 3-period [a] crossover	Lusutrombopag 3 mg Oral tablet	Lusutrombopag, N = 24	Healthy subjects	Single dose Up to 2 non-consecutive days of single doses	Complete Full

Description of Study	Study No. Country	Study Objectives	Study Design, Including Type of Control	Test Product(s) Route of Administration	Number of Subjects Exposed	Healthy Subjects or Diagnosis of Patients	Dosage Regimen Duration of Treatment	Study Status Type of Report
Phase 1 PK/PD (TQTc)	1303M061D Japan	Evaluate effect on QT interval and other ECG parameters, PK, and safety	Single-center, randomized, double-blind, placebo- and positive-controlled, 4-period, crossover	Lusutrombopag 6 mg and 24 mg, moxifloxacin 400 mg, and placebo Oral tablet	Lusutrombopag, N = 59 Moxifloxacin, N = 57 Placebo, N = 59	Healthy subjects	Single dose 4 non-consecutive days of single doses	Complete Full
Phase 1 PK/PD Child-Pugh class A and class B liver disease	1301M061B Japan	Evaluate platelet function, efficacy, PK, and safety	Multicenter, open-label	Lusutrombopag 3 mg Oral tablet	Lusutrombopag, N = 8	Thrombocytopenic patients [b] with CLD	Once daily 7 days	Complete Full

Description of Study	Study No. Country	Study Objectives	Study Design, Including Type of Control	Test Product(s) Route of Administration	Number of Subjects Exposed	Healthy Subjects or Diagnosis of Patients	Dosage Regimen Duration of Treatment	Study Status Type of Report
Phase 2b Efficacy (Controlled clinical study pertinent to the claimed indication) Child-Pugh class A and class B liver disease	1208M0626 Japan	Evaluate efficacy, PK, and safety	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	Lusutrombopag 2 mg, 3 mg, and 4 mg and placebo Oral tablet	Lusutrombopag, N = 46 (2 mg, N = 15, 3 mg, N = 16, 4 mg, N = 15) Placebo, N = 15	Thrombo-cytopenic subjects [b] with CLD undergoing percutaneous liver ablation for primary hepatic cancer	Once daily Up to 7 days [c]	Complete Full
Phase 3 Child-Pugh class A and class B liver disease	1304M0631 Japan	Evaluate efficacy, PK, and safety	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	Lusutrombopag 3 mg and placebo Oral tablet	Lusutrombopag, N = 48 Placebo, N = 48	Thrombo-cytopenic subjects [b] with CLD undergoing an invasive procedure	Once daily Up to 7 days [c]	Complete Full

Description of Study	Study No. Country	Study Objectives	Study Design, Including Type of Control	Test Product(s) Route of Administration	Number of Subjects Exposed	Healthy Subjects or Diagnosis of Patients	Dosage Regimen Duration of Treatment	Study Status Type of Report
Phase 3 Child-Pugh class A and class B liver disease	1423M0634 Argentina, Australia, Austria, Belgium, Canada, Czech Republic, France, Germany, Hungary, Israel, Italy, Poland, Republic of Korea, Romania, Russian Federation, Spain, Taiwan, Thailand, Turkey, Ukraine, United Kingdom, United States	Evaluate efficacy, PK, and safety	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	Lusutrombopag 3 mg and placebo Oral tablet	Lusutrombopag, N = 108 Placebo, N = 107	Thrombo-cytopenic subjects [b] with CLD undergoing an elective invasive procedure	Once daily Up to 7 days [c]	Complete Full

Description of Study	Study No. Country	Study Objectives	Study Design, Including Type of Control	Test Product(s) Route of Administration	Number of Subjects Exposed	Healthy Subjects or Diagnosis of Patients	Dosage Regimen Duration of Treatment	Study Status Type of Report
Phase 2 Ascending dose, PK Child-Pugh class A and class B liver disease	1017M0623 Japan	Evaluate efficacy, PK, and safety	Multicenter, randomized, open-label, parallel-group	Lusutrombopag 0.25 mg, 0.5 mg, 1 mg, 1.5 mg, and 2 mg Oral tablet	Lusutrombopag, N = 34 (0.25 mg, N = 5, 0.5 mg, N = 6, 1 mg, N = 5, 1.5 mg, N = 6, 2 mg, N = 12)	Thrombo-cytopenic subjects [b] with CLD undergoing percutaneous liver ablation for primary hepatic cancer	Once daily Up to 7 days [c]	Complete Full
Phase 2 Ascending dose, PK Child-Pugh class A and class B liver disease	1112M0625 Japan	Evaluate efficacy, PK, and safety	Multicenter, open-label	Lusutrombopag 2.5 mg, 3 mg, and 4 mg Oral tablet	Lusutrombopag, N = 21 (2.5 mg, N = 6, 3 mg, N = 7, 4 mg, N = 8)	Thrombo-cytopenic subjects [b] with CLD undergoing percutaneous liver ablation for primary hepatic cancer	Once daily Up to 7 days [d]	Complete Full
Phase 3b Child-Pugh class A and class B liver disease, including subjects previously treated with lusutrom-bopag	1338M0633 Japan	Evaluate efficacy, PK, and safety with effect of removing stopping criterion for study drug evaluated in a stepwise manner in 2 sequentially treated cohorts	Multicenter, open-label	Lusutrombopag 3 mg Oral tablet	Lusutrombopag, N = 101 [e] (Group A/B-1, N = 47; Group A/B-2, N = 47; Non-naive Group A/B, N = 8 [e])	Thrombo-cytopenic subjects [b] with CLD undergoing an elective invasive procedure	Once daily Up to 7 days [f]	Complete Full

Description of Study	Study No. Country	Study Objectives	Study Design, Including Type of Control	Test Product(s) Route of Administration	Number of Subjects Exposed	Healthy Subjects or Diagnosis of Patients	Dosage Regimen Duration of Treatment	Study Status Type of Report
Phase 1/2 Child-Pugh class C liver disease	1525M0627 Japan	Evaluate platelet count, PK, and safety	Multicenter, open-label	Lusutrombopag 3 mg Oral tablet	Lusutrombopag, N = 5	Thrombo-cytopenic subjects [b]	Once daily Up to 7 days [d]	Complete Full
Phase 2 PK/PD	0913M0621 United States	Evaluate efficacy, PK, and safety	Multicenter, randomized, double-blind, placebo-controlled, parallel-group	Lusutrombopag 0.5 mg, 0.75 mg, and 1 mg and placebo Oral tablet	Lusutrombopag, N = 15 (0.5 mg, N = 5, 0.75 mg, N = 5, 1 mg, N = 5) Placebo, N = 5	Subjects with relapsed persistent or chronic ITP with or without splenectomy	Once daily 42 days	Terminated Full
Phase 2 Long-term safety	0914M0622 United States	Evaluate efficacy and safety	Multicenter, open-label	Lusutrombopag 0.5 mg, 1 mg, 1.5 mg, and 2 mg Oral tablet	Lusutrombopag, N = 19 [g]	Subjects with relapsed persistent or chronic ITP with or without splenectomy who participated in Study 0913M0621	Once daily 10 to 387 days	Terminated Full

BA = bioavailability; CLD = chronic liver disease; DDI = drug-drug interaction; ECG = electrocardiogram; ITP = immune thrombocytopenia; PD = pharmacodynamics; PK = pharmacokinetics; TQTc = thorough QTc

[a] Administration of quinidine sulfate in the third period was dependent on the magnitude of the increase in the maximum plasma lusutrombopag concentration (C_{max}) and the area under the plasma concentration-time curve in the first and second periods.

[b] Platelet count < 50,000/μL.

[c] Stopping criterion (platelet count ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline) applied on Days 5, 6, and 7.

[d] Stopping criterion (platelet count ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline) applied on Days 3, 4, 5, 6, and 7.

[e] The number of subjects totaled 101 as 1 subject was treated in both Group A/B-1 and Non-naive Group A/B.

[f] Stopping criterion (platelet count ⩾ 50,000/ μ L with an increase of ⩾ 20,000/ μ L from baseline) applied on Day 6 in Group A/B-1; not at all in Group A/B-2 (ie, subjects received lusutrombopag for a fixed 7-day period); and on Days 3, 5, 6, and 7 in Non-naive Group A/B.

[g] Subjects started with a dose of 0.5 mg once daily; the dose was titrated up to 2 mg (in 0.25-mg increments [up to 1 mg] and 0.5-mg increments [up to 2 mg]) based on platelet count.

2.4.2. Pharmacokinetics

A total of 21 studies, 4 of which were biopharmaceutic studies contributed PK and/or PD data. The clinical pharmacology program was devised to characterise the PK, potential for drug interactions and mass balance of lusutrombopag in healthy adult subjects and to assess the effect of hepatic impairment on the PK of lusutrombopag.

Both solution and tablet formulations of lusutrombopag for oral administration were used in the clinical development program. The applicant claims linear PK of lusutrombopag and therefore the possibility to extrapolate the results of the different formulations used in the different studies to the 3-mg tablet intended for marketing. PK linearity of the various tablet formulations used in the clinical trials wasshown by providing a comparison of the individual and mean dose adjusted AUC values at 3mg in a tabulated manner and as a graphical illustration. Sufficient comparability is therefore given which supports the claim for dose proportionality and PK linearity in the clinically relevant dosage strength.

Doses of 0.1 to 50 mg were administered as oral solutions in some initial Phase 1 studies using a constant volume for preparation. Tablet strengths in order of use in clinical studies were 2, 10, 0.1, 0.25, 1, 4, and 3 mg. The lusutrombopag formulation intended for marketing is the 3-mg tablet.

Analytical methods

The validations provided for the analytical methods to determine Lusutrombopag in human plasma and human urine are in accordance to the relevant guidelines. The analytical methods were validated across the calibration range with respect to selectivity, accuracy, precision, and stability under a variety of conditions. Plasma samples and urine samples for determination of lusutrombopag and metabolite concentrations were prepared by the protein precipitation method and analyzed by the liquid chromatography-tandem mass spectrometry (LC/MS/MS) method. Standard methods were applied.

Absorption

Bioavailability

In single dose studies conducted in healthy subjects, doses of 0.1 to 0.50 mg were administered. The median T_{max} values ranged from 3.5 to 6 hours post-dose.

In multiple dose studies conducted in healthy subjects, doses from 0.25 to 2mg were administered. The median T_{max} values ranged from 4 to 8 hours (day 7 or day 14) after ingestion.

In multiple dose studies conducted in subjects with CLD doses were between 0.25 to 2mg (study M0623) and 2.5 to 4mg (study M0625). The median T_{max} values ranged from 6 to 8 hours.

When looking at the Cmax and AUC values throughout the studies conducted, a dose proportional increase could be observed in both, healthy and thrombocytopenic subjects with CLD. In Study M0613 (Multiple dose in healthy subjects) and Study M0617 (DDI Study with Midazolam) steady state was achieved by day 5 and in study M0615 (multiple dose in healthy subjects) at day 7.

Study M0634 was conducted across multiple regions, with a mixed non-Japanese population to allow meaningful comparison by race/ethnicity and included subjects in North America, Europe, Asia, and the Rest of World. This allows for comparison of the PK results to the Japanese population. The median Tmax was 5.95 hours.

It is noted that when looking at the individual plasma concentration PK profiles, inter-individual variability could be observed. Furthermore the C_{max} and AUC_{0-t} were lower when compared to other studies conducted with lusutrombopag 3 mg. The applicant attributes both to the higher body weight in this study compared to other studies conducted in the Japanese Population (the applicant compared the mean body

weight of this study (intense PK group) [range]: 86.9 [57.1 to 123.4] kg) to studies M061B (56.3 [45.6 to 74.9] and M0633 63.8 [39.5 to 86.5] kg). The mentioned observations may be attributed to differences in body weight. Genetic polymorphism is most likely not to play a major role behind the above mentioned observed differences. From the data available no definite difference in metabolism between ethnicities is clearly evident. The observed differences in exposure seem to be mainly driven by differences in bodyweight in the Japanese and Caucasian population, as also observed in the pop PK model where bodyweight was identified as an influential covariate on PK.

As for Eltrombopag where differences between East Asian and non-East Asian were observed, it has to be noted that the metabolisation pathways differ in comparison to lusutrombopag. No evidence for pharmacogenomic implication on PK could be identified from the dataset provided.

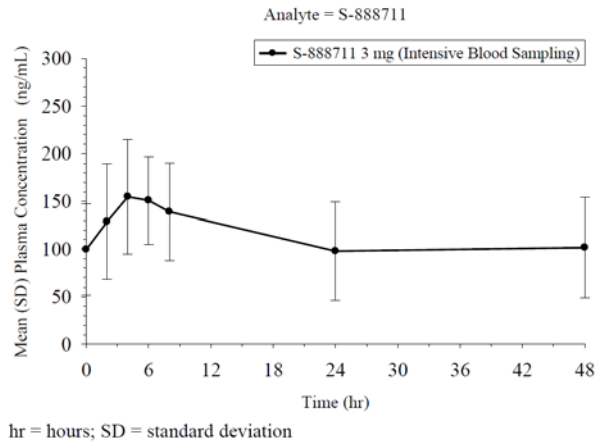
As already discussed, Lusutrombopag is metabolised mainly by CYP4 enzymes, including CYP4A11. It is worth noting that the CYP4A11 play an important role in regulation of blood pressure through the conversion of arachidonic acid into 20-HETE and its polymorphism may be an important risk factor for hypertension, coronary artery disease or cerebral infarction. Bearing in mind that the main metabolic route of lusutrombopag is related to CYP4A11, its polymorphism may change the exposure to lusutrombopag. CYP4A11 polymorphism is not considered to have a significant effect on metabolism of lusutrombopag. CYP4A11 can increase the AUC in poor metabolizers, but the fold increase in exposure is considered to be less than 2, at even maximum risk evaluation. Bearing in mind that there is a possibility that alternative metabolic pathways may be activated for poor metabolizers, the AUC in poor metabolizers might not change compared with that in extensive metabolisers.

The absolute oral bioavailability of lusutrombopag after administration to humans has not been established. The relative bioavailability of the 0.25-mg tablet used in Phase 2 Studies M0623 and M0625 to lusutrombopag solution was 88.1%, 81.7%, and 82.0% for C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$, respectively.

The relative bioavailability of the 2-mg tablet used in Phase 2 Study M0625 to lusutrombopag solution was 89.0%, 92.9%, and 93.1% for C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$, respectively.

The following figure shows the plasma concentration time course profile for study M0634, which was conducted across multiple regions, with a mixed non-Japanese population in patients with chronic liver disease undergoing elective invasive procedures.

Figure 3: plasma concentrations of lusutrombopag for intensive sampling group



hr = hours; SD = standard deviation

The following table summarizes the PK Parameters of lusutrombopag for the intensive Sampling group

Table 1: Pharmacokinetic parameters of lusutrombopag for intensive sampling group

C_{max} (ng/mL)	T_{max} (hr)	$AUC_{0-\tau}$ (ng·hr/mL)	CL/F (L/hr)
9	9	9	9
157 (34.7)	5.95 (2.03, 7.85)	2737 (36.1)	1.10 (36.1)

Geometric mean (%CV) other than for T_{max}, which is median (range)

The following table and figure show the relationship between C_{max} and $AUC_{0-\tau}$ and lusutrombopag dose in subjects with CLD after multiple-dose administration

Table 2: Exposure to lusutrombopag after multiple-dose administration in thrombocytopenic subjects with chronic liver disease

Daily Dose (mg)	Study M0623 (Day 7)		Study M0625 (Day 7)	
	C_{max} (µg/mL)	$AUC_{0-\tau}$ (µg·hr/mL)	C_{max} (µg/mL)	$AUC_{0-\tau}$ (µg·hr/mL)
0.25	0.0143 (32.6)	0.2666 (33.7)	NA	NA
0.5	0.0272 (20.6)	0.5480 (23.6)	NA	NA
1	0.0726 (39.5)	1.352 (36.6)	NA	NA
1.5	0.0996 (40.7)	1.843 (30.2)	NA	NA
2	0.115 (53.2)	2.146 (52.1)	NA	NA
2.5	NA	NA	0.182 (25.0)	3.540 (24.5)
3	NA	NA	0.250 (32.0)	4.799 (32.9)
4	NA	NA	0.342 (27.1)	6.264 (34.7)

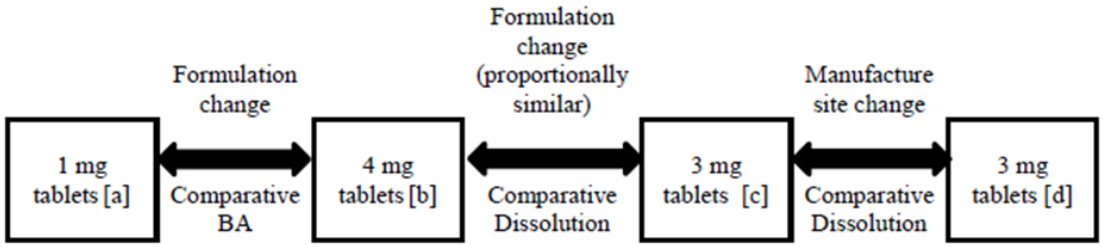
NA = not applicable

Geometric mean (% coefficient of variation).

Bioequivalence

Both, solutions and various tablet formulations of lusutrombopag for oral administration were used in the clinical development program. For the subsequent Phase 2b dose-finding Study M0626 in which doses of 2, 3, and 4 mg were evaluated, a tablet strength of 1 mg was required (with doses being achieved by intake of multiple 1-mg tablets). This 1-mg tablet was formulated to be similar to the tablets used in early-stage clinical studies. However, to improve stability of these first-generation tablets, a second-generation tablet formulation was developed and produced in 4-mg and 3-mg strengths. The 4-mg and 3-mg tablets contained active ingredient and excipients in the same proportions. The 4-mg and 3-mg tablets were demonstrated to have comparable dissolution profiles, and thus an *in vivo* bioequivalence study was not conducted.

Figure 4: overview of investigation of bioavailability of the lusutromboapg tablet formulation to be marked



BA = bioavailability
[a] Used in the Phase 2 dose finding study in CLD in Japan (Study M0626).
[b] Used in the Phase 1 relative BA of 4-mg tablet and food effect study in Japan (Study M061A).
[c] Used in the Phase 3 study in Japan (Study M0631).
[d] The drug product intended for marketing and used in the global Phase 3 study (Study M0634).
Source: CTD Section 2.7.1 Figure 1

The relative bioavailability of oral solution and tablet formulations was investigated at doses of 0.1 to 10 mg in 3 biopharmaceutic studies (Studies M0612, M0614, and M061A). All were open-label, single-dose, cross-over studies.

No notable difference with regards to relevant PK parameters between the oral solutions and tablet formulations used were identified. The C_{max} and AUC values seem to increased dose-proportionally indicating PK linearity over the various dosage strengths used. Dose proportionality and PK linearity in the clinically relevant dosage strength have been established.

For the Phase 2b final dose-finding Study M0626 in which doses of 2, 3, and 4 mg were evaluated, a tablet strength of 1 mg was required (with doses being achieved by intake of multiple 1-mg tablets). This 1-mg tablet was formulated to be similar to the tablets used in early-stage clinical studies.

When comparing the 1mg strength used in the Phase 2b dose finding study M0626 and the 4mg tablet used in study M061A, the C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ were lower after administration of the 4-mg tablet than those after administration of 4 × 1-mg tablets when given to subjects in the fasting state. However, the ratios of geometric least squares mean Cmax and AUC0-inf of 4-mg tablet to 1-mg tablet in the fasted state were both approximately 0.9 and the corresponding 90% CIs were within the predefined bioequivalence criteria of 80% to 125%. In conclusion, in Study M061A the Bioavailability of the 4 x 1mg tablets was comparable to that of 1 x 4 mg in Japanese subjects and the criterion set up to prove Bioequivalence were met indicating that the bioavailability of 4-mg tablet was comparable to that of 1-mg tablet.

To improve stability of these first-generation tablets, a second-generation tablet formulation was developed and produced in 4-mg and 3-mg strengths. The 4-mg and 3-mg tablets contained active ingredient and excipients in the same proportions.

The 4mg strength was used in study M061A, the 3mg strength in study M0631 (Phase 3 confirmatory study in Japan). For the Global Phase 3 study (M0634) the manufacturing site was changed. Based on the linear PK of lusutrombopag, the comparability between the 4mg and the 3mg strength, and the 3mg strengths from different manufacturing sites was based on *in vitro* dissolution profiles waiving additional *in vivo* bioequivalence testing.

The 3-mg drug product for commercialisation (and 4-mg tablet used in Study M061A) was designed so that the tablets had a proportionally similar composition as the 2-mg formulation batch. The various 2mg tablet strengths underwent dissolution profile testing indicating comparable dissolution behaviour. This selection is not comprehensible as there is no obvious effect on solubility due to the surfactants used.

Influence of Food

For all relevant studies investigating food effect, the ratio for the geometric last squares mean can be deemed comparable with regards to C_{max}, $AUC_{0\text{-}last}$ and $AUC_{0\text{-}inf}$. Therefore, comparable plasma exposure of lusutrombopag can be concluded.

For study M0612 the C_{max} and AUC in the fed state were lower than those in the fasted state (GLS mean ratios (90% CI) (fed versus fasted) for C_{max}, $AUC_{0\text{-}last}$, and $AUC_{0\text{-}inf}$ were 0.904 (0.864 to 0.945), 0.921 (0.887 to 0.956), and 0.920 (0.886 to 0.956)). However the differences were rather negligible and the corresponding 90% CIs were within the predefined bioequivalence criteria of 80% to 125%. Food only had a small effect on the PK of lusutrombopag at a dose of 2 mg.

The analysis of PK parameters of lusutrombopag after administration of a single 2-mg dose of lusutrombopag in the fed state in healthy adult Japanese male subjects (Study M0612) and in healthy white adult male subjects living in Japan (Study M0614) showed that the plasma concentration-time profiles after administration of single doses of lusutrombopag 2 mg were similar. In the ANOVA, t1/2,z tended to be longer in white subjects than Japanese subjects, but other PK parameters showed no statistically significant difference. PK results were comparable between the non-Japanese subjects living in Japan and elsewhere, taking into account the different doses used in the various studies conducted. For study M061A, the ratios of geometric least squares mean C_{max} and $AUC_{0\text{-}inf}$ of 4-mg tablet in the fed state to those in the fasted state were both approximately 0.9 and the corresponding 90% CIs were within the predefined bioequivalence criteria of 80% to 125%, indicating that food intake had no effect on the PK of 4-mg tablet. It can therefore be concluded that no influence of food was observed on the relative bioavailability of the 4-mg tablet, the composition of which is quantitatively proportional to the 3-mg tablet intended for marketing. In the study protocol M061A no statistical testing for Tmax was established. However, Tmax for the fed condition was comparable to that for the fasted condition.

The relevant PK parameters in study M0618 were comparable between subjects with or without calcium intake and the ratios for B/A were approximately near 1 and the corresponding 90% CIs were within the predefined bioequivalence criteria of 80% to 125%. Therefore it can be concluded that the co-administration with 4000mg of calcium did not significantly affect the PK of 0.75mg single dose of lusutrombopag administered in healthy subjects. The findings also suggest no influence of multivalent cations contained in antacids, mineral supplements, dairy products, etc. on the PK of lusutrombopag. The same applies for high-fat and high-calorie meal.

Overall it can be concluded that the influence of high-fat, high-calorie meal and calcium on the PK and BA of lusutrombopag is only minimal and very likely clinically not meaningful.

Distribution

The PK parameters of radioactivity and S-888711 were well characterised in the mass balance study M0619. In blood, [14C]-lusutrombopag was distributed mainly in the plasma.

The total radioactivity concentrations of lusutrombopag in whole blood were 52.9% to 56.9% of plasma radioactivity concentrations. The volume percentage of plasma in whole blood was approximately 55%. In this context in study M061E, it could be observed, that the geometric mean (% CV) apparent volume of distribution during the terminal phase of lusutrombopag in healthy adult subjects was 39.5 L (23.5%) after the administration of a 3mg tablet in 16 subjects.

The distribution of radioactivity into blood cells was observed to be minimal, with essentially no binding to the red blood cells as indicated in the individual and descriptive statistics for distribution (%) of radioactivity in red blood cells. The whole blood/plasma radioactivity exposure ratios were close to the ratio of plasma/whole blood volume. Taken together, it could be concluded that the amount of radioactivity in blood was approximately equal to the amount in plasma and [14C]-S-888711 is therefore primarily distributed in plasma.

Lusutrombopag was shown to be highly bound to human plasma proteins, with a high binding ratio of 99.996% or more at concentrations ranging from 5 to 50 µg/mL (Study R-888711-PF-057-N). A change in protein binding may cause a clinically important change in the relationship between total and unconjugated concentrations of the drug (Fu). This is particularly important bearing in mind that a very limited number of Child-Pugh class C patients took part in pivotal studies and that there were few patients with severe hypoalbuminaemia (<28g/l) in the patient population undergoing the studies. PK parameters appeared to be comparable between patients with and without severe hypoalbuminemia.

Elimination

The primary route of excretion of Lusutrombopag is via the feces. The terminal elimination half-life t1/2,z was:

- 19.3 to 29.5 hours (geometric mean) in single dose studies in healthy subjects
- 27.0 to 32.0 hours in multiple-dose studies in healthy subjects
- 31.9 to 43.9 hours in multiple-dose studies in subjects with CLD

Approximately 83% was excreted into feces, approximately 1% into urine.

Metabolism

In the mass balance study (M0619), which used [14C]-lusutrombopag, the metabolism of lusutrombopag was well characterised. Approximately 97% of plasma radioactivity was detected as unchanged lusutrombopag. The metabolites (deshexyl, β oxidated carboxylic acid, taurine conjugate of β-oxidated carboxylic acid, and acyl-glucuronide) were only detected at a trace level (each constituting ≤ 2.6% of plasma radioactivity). Metabolite profiling in the mass balance study suggested that lusutrombopag may be primarily metabolised by oxidation of the hexyl group followed by β-oxidation of O-hexyl side chain in the liver. According to the guideline, preferably total recovery of radioactivity in urine and faeces should exceed 90% of the dose with over 80% of the recovered radioactivity being identified. In the mass balance study (Study M0619), a small proportion of total radioactivity was excreted into the faeces on the last sampling day (Day 15), suggesting further recovery of radioactivity from the faeces after Day 15.

The main elimination pathway is via the feces were unchanged lusutrombopag was detected as 16.22% of administered radioactivity, and a mixture of deshexyl and O-propanol (or O-acetic acid) metabolites was detected as 17.93% of administered radioactivity.

In vitro studies revealed that CYP4 enzymes including CYP4A11 and partially CYP3A4 enzyme were contributed to ω-oxidation to form 6-hydroxylated lusutrombopag. Furthermore, lusutrombopag was shown to be a substrate of P-gp and BCRP, but not a substrate of OATP1B1, OATP1B3 or OCT1 based on in vitro results. Results from the clinical DDI study M061E indeed indicate that P-gp and BCRP inhibition modestly increases lusutrombopag plasma. The cut off values for criteria (as by the mentioned guideline) were net exceeded for OATB1B1. Thus, *in vivo* inhibition is not expected. PK of metabolites was not specifically investigated in a human study, but in the mass balance study M0619, the ratio for Cmax of deshexyl relative to radioactivity in plasma was below 1%. The concentration of 5-keto derivative was

BLQ. These findings suggested the presence of a large number of undetectable, trace amounts of metabolites in plasma.

Dose proportionality and time dependencies

In study M0634 (Phase 3 Study in Thrombocytopenic Subjects with Chronic Liver Disease) the C_{max} and AUC_{0-T} exhibited moderate interindividual variability which seem to be related to the variability in body weight.

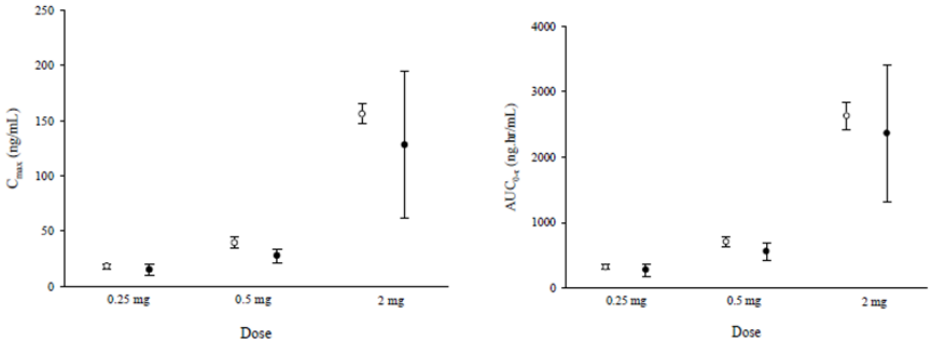
When comparing relevant PK parameters between healthy Japanese subjects and subjects with CLD (study M0613 and Study M0623) it could be observed, that variability of C_{max} and AUC_{0-t} seems to be higher in subjects with CLD.

Special populations

Pharmacokinetic in target population

The applicant provided a comparison of relevant PK parameters between healthy Japanese subjects and subjects with CLD. Overall, the PK parameters seem to be comparable to some extend with no major differences. However, as can be seen in Figure 31 and Table 3 below, the variability of C_{max} and AUC_{0-t} seems to be higher in subjects with CLD.

Figure 5: comparison of pharmacokinetic parameters of mean plasma concentration of lusutrombopag in healthy adult subjects and subjects with chronic liver disease



SD = standard deviation

Mean ± SD. Open circle: healthy Japanese subjects (5 to 6 subjects/group). Closed circle: Japanese subjects with CLD (5 to 9 subjects/group).

Table 3: pharmacokinetic parameters of lusutrombopag in healthy adult subjects and subjects with chronic liver disease:

Parameter	0.25 mg		0.5 mg		2 mg	
	Healthy Subjects (N = 6)	Subjects With CLD (N = 5)	Healthy Subjects (N = 5)	Subjects With CLD (N = 6)	Healthy Subjects (N = 5)	Subjects With CLD (N = 9)
C_{max} (ng/mL)	18.0 (11.7)	14.3 (32.6)	38.9 (13.7)	27.2 (20.6)	156 (5.7)	115 (53.2)
T_{max} (hr)	6.5 (4.0, 10.0)	8.0 (6.0, 8.0)	6.0 (4.0, 6.0)	8.0 (4.0, 8.0)	4.0 (4.0, 4.0)	6.0 (6.0, 8.0)
$AUC_{0-\tau}$ (ng·hr/mL)	317 (13.0)	266.6 (33.7)	703 (10.4)	548.0 (23.6)	2630 (8.1)	2146 (52.1)
$t_{½,z}$ (hr)	30.1 (22.6)	43.9 (22.1)	23.8 (21.2)	31.9 (11.8)	29.3 (26.8)	39.5 (23.5)
CL/F (L/hr)	-	0.938 (33.7)	-	0.912 (23.6)	-	0.932 (52.1)

CLD = chronic liver disease

Geometric mean (% coefficient of variation) except for Tmax. Median (minimum, maximum) for Tmax.

Study M0631 was a multicentre placebo-controlled study which also evaluated the PK of lusutrombopag in Japanese thrombocytopenic subjects (those with a platelet count of < 50,000/μL) with CLD after multiple oral doses. Only the evaluation of plasma concentration was a secondary objective in this study. Individual plasma S-888711 concentrations were listed and summarised for patients with completion of 5- to 7-day administration by dose group and nominal time (prior to administration on Day 5, 6 to 8 hours after the administration on Day 7, and 24, 48, and 72 hours after the last administration). The collection of blood samples for determination of plasma concentration differed depending on the duration of drug administration. Overall, when looking at the Plasma concentration of lusutrombopag comparability to the results of study M0626 could be observed.

Study M0633 was an open-label Phase 3 study evaluated the PK of a 3-mg dose of lusutrombopag administered once daily for up to 7 days in Japanese subjects with CLD and who were Child-Pugh class A or B and also evaluated differences in PK between subjects who had previously received lusutrombopag and subjects who were treatment-naïve was evaluated in this multiple-dose study.

When looking at the plasma concentration profiles of S-888711comparabilty between the naive and non-naive patients could be observed. The geometric least squares mean ratios of C_{max} and $AUC_{0-\tau}$ were 1.06 (90% CI: 0.86 to 1.32) and 1.11 (90% CI: 0.89 to 1.38), respectively which indicates comparable exposure. Comparability could also be observed with regards to CL/F. With regards to the terminal elimination rate constant λz and the terminal elimination half-life (t½,z) statistically significant differences could be observed. the geometric mean values of t1/2,z for the naive and non-naive patients were 37.7 and 43.9 hours. A clinical impact is therefore rather unlikely.

The plasma concentrations of lusutrombopag were similar between Child-Pugh class A and B subjects (as can be seen in Figure 16). The GLS mean ratios of C_{max} and $AUC_{0-\tau}$ were 0.90 (90% CI: 0.71 to 1.15) and 1.00 (90% CI: 0.76 to 1.33), respectively which indicates comparable exposure with only slight numerically differences. Comparability could also be observed for the other relevant PK parameters.

Study M0634 was a phase 3 study which was conducted across multiple regions, with a mixed non-Japanese population to allow meaningful comparison by race/ethnicity and included subjects in North America, Europe, Asia, and the Rest of World. This allows for comparison of the PK results to the Japanese population

A total of 63 concentrations were obtained from 9 subjects in the intensive sampling group. Of 63 concentrations, 11 samples were out of allowance windows of blood samplings for the intensive sampling group, but they were included in the PK analysis since the PK parameters were estimated appropriately by using the actual sampling time.

With regards to the intense PK sampling group (PK Parameter Population) geometric mean values (CV% Geometric Mean) for C_{max}, AUC_{0-t}, and CL/F were 157 ng/mL (34.7%), 2737 ng·hr/mL (36.1%), and 1.10 L/hr (36.1%), respectively. The median Tmax was 5.95 hours.

Inter-individual variability could be observed when looking at the individual plasma concentration PK profiles. Furthermore the C_{max} and AUC_{0-t} were lower when compared to other studies conducted with lusutrombopag 3 mg. The applicant attributes both to the higher body weight in this study compared to other studies conducted in the Japanese Population. Genetic polymorphism is most likely not to play a major role behind the above mentioned observed differences. From the data available no definite difference in metabolism between ethnicities is clearly evident. The observed differences in exposure seem to be mainly driven by differences in bodyweight in the Japanese and Caucasian population, as also observed in the pop PK model where bodyweight was identified as an influential covariate on PK. No evidence for pharmacogenomic implication on PK could be identified from the dataset provided.

Study S-888711-CB-315-N: “Population pharmacokinetic (PK) and pharmacokinetic / pharmacodynamic (PK/PD) was performed to describe the plasma concentration of lusutrombopag and evaluate the effects of influencing factors on the PK of lusutrombopag based on the pooled data from healthy subjects and thrombocytopenic subjects with CLD in 3 Phase 1 studies and 7 Phase 2 and Phase 3 studies (Studies M0611, M0613, M0615, M0623, M0625, M0626, M0627, M0631, M0633, and M0634).

A total of 4196 plasma lusutrombopag concentrations from 427 subjects (78 healthy subjects and 349 thrombocytopenic subjects with CLD) were included in the population PK analysis. Non-linear mixed effects modeling was performed using NONMEM. A 3-compartment model was used as a structural PK model. An exponential error model was used for inter-individual variability, and a proportional error model was used for intra-individual variability.

For covariate modeling, age, body weight, creatinine clearance (CLcr), Child-Pugh class (normal, Child-Pugh class A, B, or C), sex (male or female), ethnicity/race (Japanese or non-Japanese), and subject population (healthy subjects or thrombocytopenic subjects with CLD) were tested as covariates on CL/F. Age, body weight, sex, ethnicity/race, and subject population were tested as covariates on V2/F. Body weight was tested as a covariate on volume of distribution in the peripheral compartment (V3/F).

The following table shows steady-state Cmax and AUC0-τ estimated from individual post-hoc parameters with empirical Bayesian estimation of the final model by subpopulation:

Table 4: Summary of individual steady-state Cmax and AUC 0-T by subpopulation estimated using post-hoc PK parameters following 3 mg doses once daily for 7 days:

Subject	Subpopulation	N	C_{max} (ng/mL)	$AUC_{0-\tau}$ (ng·hr/mL)
Healthy Subjects	All	78	181 (87.6-295)	3381 (1684-5258)
	Japanese	54	207 (146-295)	3843 (2580-5258)
	Non-Japanese	24	122 (87.6-176)	2341 (1684-3430)
	White	21	121 (87.6-176)	2300 (1684-3430)
	Non-white	57	203 (108-295)	3779 (2176-5258)
Thrombo-cytopenic Subjects with CLD	All	349	191 (58.0-382)	4187 (1110-10150)
	Age < 65 years old	159	170 (58.0-339)	3662 (1110-8518)
	Age ≥ 65 years old	190	209 (85.0-382)	4626 (1710-10150)
	WT < 45 kg	18	258 (186-376)	5529 (3271-9093)
	WT 45 to < 60 kg	115	224 (111-382)	4949 (2315-10150)
	WT 60 to < 80 kg	163	178 (93.0-313)	3894 (1383-7812)
	WT 80 to < 100 kg	44	142 (63.9-251)	3147 (1276-6227)
	WT ≥ 100 kg	9	101 (58.0-154)	2140 (1110-3780)
	Child-Pugh class A	207	193 (63.9-376)	4201 (1276-9093)
	Child-Pugh class B	135	190 (67.2-382)	4209 (1319-10150)
	Child-Pugh class C	7	142 (58.0-220)	3328 (1110-5725)
	CLcr ≥ 90 mL/min	142	169 (58.0-339)	3690 (1110-8279)
	CLcr 60 to < 90 mL/min	139	203 (90.7-382)	4470 (1465-10150)
	CLcr 30 to < 60 mL/min	67	213 (102-362)	4664 (2198-8197)
	CLcr < 30 mL/min	1	170 (170-170)	3226 (3226-3226)
	Male	192	170 (63.9-296)	3678 (1276-7172)
	Female	157	217 (58.0-382)	4808 (1110-10150)
	Japanese	248	205 (63.9-382)	4501 (1364-10150)
	Non-Japanese	101	158 (58.0-332)	3415 (1110-8518)
	White	78	157 (58.0-299)	3378 (1110-7646)
	Non-White	271	201 (63.9-382)	4419 (1364-10150)

CLcr = creatinine clearance; WT = body weight

Mean (range) of parameters estimated using the final model.

Impaired renal function:

Due to the fact that Lusutrombopag is primarily eliminated via the faces, no influence on the PK is to be expected from altered renal functionality. This is further emphasised by Results from the mass balance study conducted (Study M0619) and population PK analysis indicate only minimal influence of renal function on the PK of lusutrombopag. Therefore no dose adjustment is deemed necessary for patients with impaired renal function.

Impaired hepatic function:

The applicant conducted a hepatic impairment study (study M0616) which compared 8 healthy subjects with 16 subjects with hepatic impairment (8 Child Pugh A and 8 subjects with child Pugh B). Trends to increase of exposure with increased degree of hepatic impairment compared with healthy subjects could be observed. The exposure increased by 5% and 20% in mild and moderate hepatic impairment compared with the healthy subjects. The limits of the 90% confidence intervals (CIs) for % mean ratios of C_{max} and AUCs were outside of the 80% to 125% equivalence interval in the hepatic impairment (mild or moderate) groups. In subjects with moderate hepatic impairment (Child-Pugh class B), the C_{max} of lusutrombopag was comparable (increase of 5%) but the AUC_{0-inf} was 20% higher than in healthy adults.

Study M0627 evaluated the PK after administration of lusutrombopag 3 mg once daily for 7 days in thrombocytopenic Patients with Child-Pugh Class C Liver Disease. A total of 5 subjects (1 male and 4 females, 50 to 74 years of age, mean 62.0 years) were enrolled. The applicant compared the PK results with study M0633. The mean exposure was found to be generally lower in subjects with Child-Pugh class C liver disease compared to Child-Pugh class A or B. The ranges of C_{max} and $AUC_{0-\tau}$ observed overlapped in subjects with Child-Pugh class A, B, and C liver disease and the C_{max} and $AUC_{0-\tau}$ of all subjects with Child-Pugh class C liver disease did not exceed the maximum values from Child-Pugh class A and class B.

In the population PK model, the mean post-hoc C_{max} and $AUC_{0-\tau}$ in 7 subjects with Child-Pugh class C liver disease (excluding the 1 subject with the Child-Pugh score of 9 in Study M0627) were lower than in subjects with Child-Pugh class A and B liver disease, as also indicated in noncompartmental analyses in Study M0627.

The PK/PD modelling included a very limited number of patients with Child-Pugh class C (n=7). In the only study with class C patients (study 1525M0627), there were only 4 patients with Child-Pugh score above 9. Moreover, the division into groups with Child-Pugh score ≥ 9 and <9 made in the modelling, does not correspond to the Child-Pugh classification (Class A – score 5-6; class B – score 7-9; class C – score 10–15). In the PK covariate modeling, it was confirmed that the inclusion of Child-Pugh classes (Child-Pugh class A vs B/C) into CL/F slightly improved the model based on the change of objective function value (ΔOBJ of -3.895, $p > 0.01$). In the PK/PD covariate modelling, the inclusion of Child-Pugh classes into the PD parameter (SLOP) was statistically significant (change in NONMEM objective function [ΔOBJ] of -11.878). However, it was found that SLOP increased for the higher Child-Pugh score group with a cut-off of 9, and the inclusion of Child-Pugh score (< 9 or ≥ 9) provided more statistically significant model improvement (ΔOBJ of -13.972) than the inclusion of Child-Pugh classes. Based on the comparison of ΔOBJ, the Child-Pugh score was selected as a covariate.

Overall, when considering the main elimination pathway, impact on the PK of lusutrombopag seems to be likely since lusutrombopag is excreted mainly via the feces.

Gender:

Population PK analysis revealed that CL/F was 13% lower in women. However the applicant's data and further analysis (plot for inferential assessment of covariate effect) support that differences in gender are rather negligible and do not require dose adjustments.

Race:

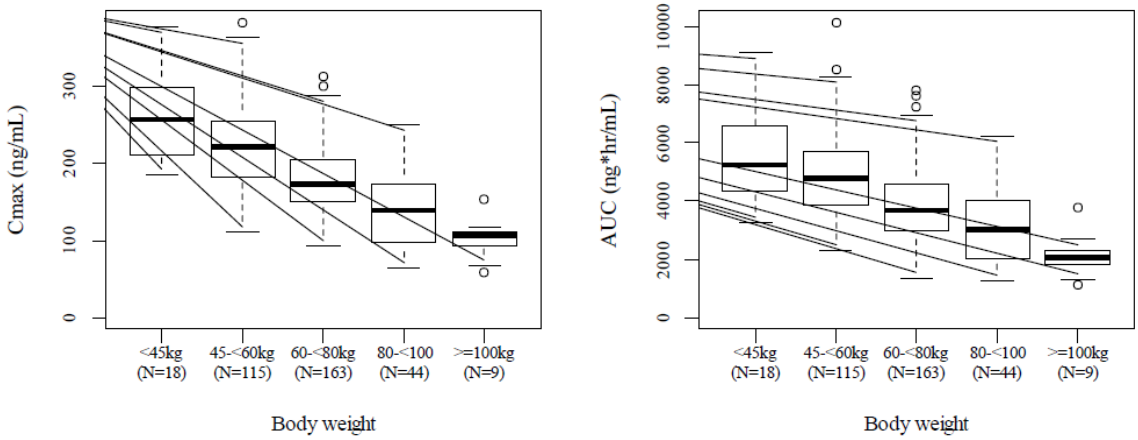
No relevant differences in the PK of lusutrombopag between black and non-black subjects have become apparent considering study M0615, M0616 and the pop PK Analysis.

In the ANOVA in study M0614, t1/2,z tended to be longer in white subjects than Japanese subjects without being statistically significant.

The effect of weight on the pharmacokinetics of Lusutrombopag was included in the population PK analysis as a significant covariate on CL/F, V2/F, and V3/F. It could be observed that the Cmax and AUC0-τ decreased with increasing body weight, indicating body weight was an influential covariate on PK. The C_{max} and $AUC_{0-\tau}$ decreased with increasing body weight, indicating body weight was an influential covariate on PK.

Subject	Subpopulation	N	C_{max} (ng/mL)	AUC0-τ (ng·hr/mL)
Thrombocytopenic Subjects with CLD	WT < 45 kg	18	258 (186-376)	5529 (3271-9093)
	WT 45 to < 60 kg	115	224 (111-382)	4949 (2315-10150)
	WT 60 to < 80 kg	163	178 (93.0-313)	3894 (1383-7812)
	WT 80 to < 100 kg	44	142 (63.9-251)	3147 (1276-6227)
	WT ≥ 100 kg	9	101 (58.0-154)	2140 (1110-3780)

Figure 6: boxplots of Cax and AUC 0-T in patients by body weight froups estimated using post-hoc PK parameters following 3 mg doses once daily for 7 days



Box plot: thick center line represents median, top and base of the box represent first and third quartiles [interquartile range (IQR)], whiskers represent the most extreme data within 1.5 × IQR, and circles represent outliers beyond 1.5 × IQR.

AUC = $AUC_{0-\tau}$

Elderly:

Patients over a wide range of age were included in the clinical development program. The effect of age was not specifically investigated, but population PK analysis indicated only minimal influence of age on the PK of lusutrombopag. No dose adjustment is regarded necessary.

Subject	Subpopulation	N	C_{max} (ng/mL)	AUC0-τ (ng·hr/mL)
Thrombo-cytopenic Subjects with CLD	All	349	191 (58.0-382)	4187 (1110-10150)
	Age < 65 years old	159	170 (58.0-339)	3662 (1110-8518)
	Age ≥ 65 years old	190	209 (85.0-382)	4626 (1710-10150)

Children: No pharmacokinetic data have been obtained in children.

Pharmacokinetic interaction studies

Lusutrombopag was suggested to primarily bind to the warfarin and diazepam sites on HSA. In investigation with [14C]-lusutrombopag (1 and 5 µg/mL) and 4% HSA (in vitro), the protein binding ratio

was not changed with the inhibitors (warfarin and diazepam, 1 and 10 µmol/L). Therefore, a drug interaction with lusutrombopag due to a change of the protein binding ratio is considered unlikely.

The applicant conducted a study into potential interactions of lumbotromopag with drugs highly binding to the protein (warfarin and diazepam) assuming proper albumin concentration (4%), which causes that the abovementioned disturbances resulting from altered FU / total ratio and liver dysfunction, were not included in the way imprecisely modeling of clinical situations of patients with hepatic insufficiency. This is particularly important bearing in mind that a very limited number of Child-Pugh class C patients took part in pivotal studies and that there were few patients with severe hypolabuminemia (<28g/l) in the patient population undergoing the studies.

The inducing and inhibitory effect of lusutrombopag on various cytochrome P450 enzymes and transporter proteins most commonly involved in drug metabolism have been investigated *in vitro*, as required by the EMA Guideline on the investigation of drug interactions. Bearing in mind that the in vitro induction study did not show increases in marker activities for the investigated enzymes (CYP1A2, 2C9, 3A4, UGT1A2, 1A6, and 2B7), this could indicate that CAR and PXR is not activated by lusutrombopag. In addition, the pharmacokinetics of midazolam, which is a CYP3A4 inhibitor, were not clinically significantly affected by co-administration of lusutrombopag in vivo. Concluding, the omission of investigating CYP2B6 for the inducing potential of lusutrombopag can be accepted based on the applicant's justification.

Based on the *in vitro* results, lusutrombopag was demonstrated to have an inhibitory effect on BCRP (breast cancer resistance protein), P-gp (P-glycoprotein), OATP1B1 and OATP1B3 (organic anion-transporting polypeptide) as well as OCT1 (organic cation transport). Further investigations demonstrated that lusutrombopag is a P-gp and BCRP-substrate, but is not a substrate of OATP1B1, OATP1B3 or OCT1. For potential inhibitory effects on OATP1B1, the Applicant provided detailed calculations in accordance with the EMA guideline on drug interactions, which show that the cut off values for criteria (as by the mentioned guideline) were net exceeded for OATB1B1. Thus, *in vivo* inhibition is not expected. The DDI potential of lusutrombopag for transporters other than BCRP would be low because the calculated values for criteria did not exceed the cut-off value for each transporter (in accordance with the EMA guideline on drug interactions). According to the applicant, the DDI potential of lusutrombopag for BCRP would be low because of the high plasma protein binding and low solubility (see further discussion below).

Effect of other drugs on Pharmacokinetics of lusutrombopag

Based on the *in vitro* results, lusutrombopag was shown to be a substrate of P-gp and BCRP. To address these *in vitro* findings, the clinical DDI study 1514M061E was conducted, which was a randomized, open-label, 3-period crossover study in healthy Japanese adult male subjects.

Co-administration with cyclosporine, which is a BCRP and P-gp dual inhibitor, increased lusutrombopag Cmax by 18% and AUCs by 19% compared with lusutrombopag alone. The upper limit of 90% CI (geometric means) for Cmax was only slightly lower than 125%, and for AUClast and AUCinf slightly exceeded 125%, indicating that that P-gp and BCRP inhibition slightly increases lusutrombopag plasma exposure.

The results from study M061E show that mean Cmax and AUC is increased by roughly 20% upon co-administration of cyclosporine and with the upper limit of the 90%CI being >125 % do not support the statement that the effect of co-administration with a BCRP/P-gp inhibitor is only "slight". Therefore, a potential for drug interactions cannot be excluded and a respective statement was requested to be included in the SmPC. However, it was agreed with the applicant that platelet monitoring seems not necessary as an additional precaution, also considering that exceeding 200,000/µL platelets is not a validated surrogate for the risk of thrombotic events.

Lusutrombopag is mainly metabolized by CYP4 enzymes, including CYP4A11. CYP3A4 was also suggested to be contributing to the ω-oxidation of lusutrombopag (production of 6-hydroxylated lusutrombopag). Drugs known to inhibit or induce CYP4A11 and CYP3A4 could therefore potentially affect the PK of lusutrombopag. With regard to CYP4 enzyme inhibition, no drugs have been reported to cause a drug interaction in clinical use. While peroxisome proliferator-activated receptor-α (PPARα) is known to regulate expression of CYP4A enzymes, the induction potential of CYP4A by fibrates (PPARα agonists) is very low in humans and drug interactions via induction of any CYP4A enzymes have not been reported in clinical use. Therefore, inducers and inhibitors of CYP4A enzymes, including CYP4A11, are unlikely to affect the pharmacokinetics of lusutrombopag. It is worth noting that the CYP4A11 play an important role in regulation of blood pressure through the conversion of arachidonic acid into 20-HETE and its polymorphism may be an important risk factor for hypertension, coronary artery disease or cerebral infarction. Bearing in mind that the main metabolic route of lusutrombopag is related to CYP4A11, its polymorphism may change the exposure to lusutrombopag. Therefore, the applicant should discuss the importance of CYP4A11 polymorphism in metabolism of lusutrombopag. The applicant further assumed that the PK of lusutrombopag would be minimally changed even if CYP3A4 activity were inhibited, since the contribution of CYP3A4 to ω–oxidation is considered to be limited compared to that of CYP4 enzymes. Given that CYP3A4 is contributing to the metabolic pathway of lusutrombopag (contribution to ω–oxidation) and in order to support that co-administration of CYP3A4 inhibitors or inducers do not affect the PK/PD of lusutrombopag to a clinically significant extent (e.g., consistently resulting in higher exposures or higher platelet counts), the applicant compared PK/PD parameters (C_{max}, AUC, and peak platelet count) between CLD patients with and without co-administration of moderate and strong CYP3A4 inhibitors or inducers (using the population PK and PK/PD dataset used for Study S-888711-CB-315-N). The PK/PD parameters were in the same range for all patients and did not show a trend for increasing or decreasing PK or PD parameters of lusutrombopag, when co-administered with moderate and strong CYP3A4 inhibitors or inducers. Although the number of patients receiving either CYP3A4 inhibitors or inducers is generally low, there is no indication that co-administration of a CYP3A4 inhibitor or inducer affects the PK and PD (i.e., peak platelet counts) of lusutrombopag to a clinically significant extent.

Study 0924M0618 investigated the effect of calcium (4 g as calcium carbonate) on the PK of lusutrombopag after administration of 0.75 mg. Based on the results, it can be concluded that Calcium does not have a substantial effect on the PK of lusutrombopag. The findings also suggest no influence of multivalent cations contained e.g. in antacids, mineral supplements or dairy products on the PK of lusutrombopag. Given the linear PK of lusutrombopag, a similar lack of effect as for the 0.75 mg dose is anticipated with the 3-mg dose.

The pharmacokinetics of midazolam, which is a CYP3A4 inhibitor, are not clinically significantly affected by co-administration of lusutrombopag. This conclusion is based on the results from the clinical DDI study 0912M6017 as well as the PBPK (physiologically based pharmacokinetic) modelling and simulation (Study S-888711-CB-288-N).

Study 0912M6017 was a fixed-sequence drug interaction study in healthy adult subjects. A single 5-mg dose of midazolam (as syrup) was administered alone on Day 1 under fasting conditions with 240 mL water, followed by administration of a 1.5 mg dose (6 × 0.25 mg) lusutrombopag on Day 2 after which 0.75-mg doses (3 × 0.25 mg) lusutrombopag were administered once daily for 6 days (Days 3 to 8). On Day 8, a single 5-mg dose of midazolam was co-administered with the last dose of lusutrombopag.The 90% CIs for the geometric least squares mean ratios of Cmax, AUC0-last, and AUC0-inf of midazolam (co-administration with lusutrombopag to single administration of midazolam) were within the pre-specified standard bioequivalence margin of 0.80 to 1.25. This is in accordance with the EMA Guideline on the Investigation of Drug Interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**, 2012), stating that a drug inducing a <1.25 fold increase in the plasma AUC of the probe drug is not classified as a CYP3A

inhibitor. It can therefore be concluded that multiple-dose administration of 0.75 mg lusutrombopag does not affect the PK of midazolam.

The PBPK modelling and simulation was performed for 100 subjects (10 trials and 10 subjects per trial) under the scenario that lusutrombopag 3 mg or 6 mg was administered once daily on Day 1 to 14 and midazolam 5 mg was co-administered with lusutrombopag as a CYP3A4 inhibitor on Day 15. A statistically significant difference was demonstrated for Cmax and AUC following co-administration of 5 mg midazolam with lusutrombopag (3 mg and 6 mg) compared to administration of midazolam alone, as the 90%PI for the ratios did not contain 1, indicating a higher exposure of lusutrombopag when co-administered with a CYP3A4 inhibitor. As the 90% PIs were entirely contained within the pre-specified margins of 0.8-1.25, it can be agreed that there is no clinically significant effect of lusutrombopag 3 mg on the PK of midazolam, a CYP3A4 inhibitor.

In conclusion, lusutrombopag seems to have a low potential for CYP induction or inhibition in humans and is not considered a CYP3A4 enzyme inhibitor or inducer. However, according to the study report, the 0.75mg dose of lusutrombopag was chosen as a likely clinical dose, but the extent of exposure to lusutrombopag during study 0912M6017 was 6 mg (1.5 mg + 6 x0.75mg), which does not correspond to exposure achieved through administration of lusutrombopag according to recommended posology (3 mg x 7 days). Although the simulations using the PBPK model indicated no clinically significant DDI potential of lusutrombopag 3 mg once daily on CYP3A4 activity, the Applicant was asked to discuss the interaction study conducted at a dose of 0.75 mg (total exposure of 6mg) of lusutrombopag, reflect the clinical conditions where patients should receive lusutrombopag at a dose of 3mg for 7 days. In response to the questions raised in the day 120 LoQ, the applicant further indicated, that a clinical DDI study for evaluating the DDI potential of multiple doses of lusutrombopag 3 mg in healthy subjects could not be conducted on ethical grounds due to a risk of overshooting platelet counts. Therefore, the PBPK modelling approach reported in Study S-888711-CB-288-N was performed to extrapolate the DDI potential of lusutrombopag 3 mg once daily from the result in the clinical DDI study with the lower dose (Study M0617). Based on the Guideline on the investigation of Drug Interactions a mechanistic static model with the result of reversible inhibition study was used, which indicated that lusutrombopag is unlikely to inhibit the CYP3A4 enzymes at the clinical dose of 3 mg once daily according to the decision criterion.

Clinically significant drug interactions involving glucuronidation are not anticipated as the major elimination pathway for lusutrombopag is primarily primarily ω-oxidation followed by β-oxidation of O-hexyl group.

Number of subjects within age subgroup/ total number of subjects

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
PK Trials	120/427 (28.1%)	70/427 (16.4%)	0/427

2.4.3. Pharmacodynamics

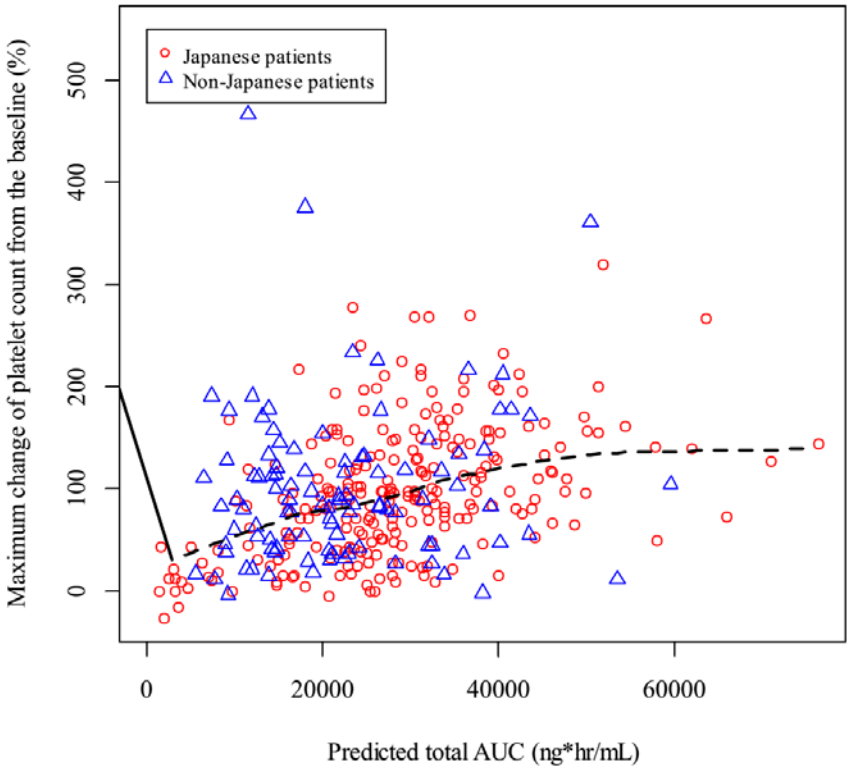
Mechanism of action

Lusutrombopag is an orally active, small-molecule thrombopoietin (TPO) receptor agonist. It acts on the transmembrane domain of human TPO receptors to stimulate megakaryocytes to proliferate and differentiate via the signal transduction pathway, thus upregulating platelet production. The mechanism of action confirms the legitimacy of using lusutrombopag in the treatment of thrombocytopenia.

Primary and Secondary pharmacology

For the studies of multiple-dose administration in thrombocytopenic subjects with CLD (M0625, M0626, M0627, M0631, M0633, and M0634), a relationship between the observed maximum percent change in platelet count from baseline and the total exposure of lusutrombopag calculated from the PK parameters in individual subjects is shown below.

Figure 7: Relationship Between Observed Maximum % of Change in Platelet Count from Baseline and Predicted Total AUC of Lusutrombopag in Subjects with Chronic Liver Disease



With multiple-dose administration of lusutrombopag to thrombocytopenic subjects with CLD (Studies M0623, M0625, M0626, M0627, M0631, M0633, and M0634), the percent of platelet count increase correlated to the total exposure of lusutrombopag in plasma; the maximum percent change in platelet count from baseline increased in an exposure-dependent manner. The relationship was similar between Japanese and no-Japanese thrombocytopenic subjects with CLD.

Based on Phase 1 studies, no PD differences were observed between non-Japanese subjects and Japanese subjects that would suggest the dose modification is not required in these two populations. Additionally, bioavailability study has demonstrated the full comparability of the primary PK parameters between EU subjects and Japanese subjects.

A simplified platelet aggregation test was performed in 71 healthy subjects with a single agonist concentration (adenosine diphosphate of 2 µM or collagen of 1 µg/mL) in Study M0611 (36 receiving lusutrombopag [6 per dose level] and 11 receiving placebo) and in the multiple-dose study (Study M0613, 18 receiving lusutrombopag [6 per dose level] and 6 receiving placebo). Mean values of the maximum platelet aggregation rate, the number of subjects with abnormal platelet aggregation, and the incidence of abnormal platelet aggregation in each lusutrombopag group (1 to 50 mg) showed similar profiles to those in the placebo group at all the time points in Study M0611. After multiple dosing for 14 days in Study M0613 (2-mg tablet, 0.25- or 0.5-mg lusutrombopag solution, or placebo), platelet

aggregation was within the normal range. In the study of multiple-dose administration of lusutrombopag in subjects with CLD (Study M061B), lusutrombopag did not alter the platelet aggregation ability and platelet release ability.

No clinically significant changes from baseline were observed in the aggregation and activation of platelets in subjects with CLD or healthy subjects, thus suggesting that lusutrombopag is unlikely to affect platelet function (M0613and M061B).

Change in QTcF from baseline after the single administration of lusutrombopag 6 mg and 24 mg in healthy adults was comparable to that in the placebo group. Additionally, no correlation was found between plasma lusutrombopag concentration and the time-matched difference of the change from baseline in QTcF between active and placebo groups.

Anemia, neutropenia, and thrombocytopenia are the major types of blood cell cytopenias of myelodysplastic syndrome (MDS) patients. Lusutrombopag did not induce formation of erythroid colonies at the concentration at which formation of megakaryocyte colonies was induced, and the number of erythroid colonies was not significantly different in concomitant treatment with EPO and lusutrombopag, as compared to treatment with EPO alone. Similarly, lusutrombopag did not induce formation of granulocytic/macrophage colonies, and the number of colonies neither increased nor decreased in concomitant treatment with G-CSF and lusutrombopag as compared to in treatment with G-CSF alone. The results indicate that lusutrombopag had no effect on EPO or G-CSF-induced hematopoietic colony formation. Administration of lusutrombopag is unlikely to affect the pharmacological effect of EPO and G-CSF in MDS patients on monotherapy with EPO or concomitant therapy with EPO and G-CSF.

Platelet response was observed in thrombocytopenic subjects with CLD with once-daily doses ranging from 2 to 4 mg. In the Phase 2b Study M0626, the proportion of subjects who received no preprocedural platelet transfusion (the primary endpoint) was significantly greater with lusutrombopag doses of 2, 3, and 4 mg/day than with placebo. This proportion was 80% or more in each lusutrombopag dose group and tended to increase modestly with increasing dose of lusutrombopag.

The proportion of responders exceeded 50% on 2 days (Days 12 and 14) in the 2-mg group, 12 days (Days 10 to 21) in the 3-mg group, and 14 days (Days 8 to 21) in the 4-mg group, showing that the treatment effect was observed earlier and maintained for a longer duration with the 3- and 4-mg doses of lusutrombopag than with the 2-mg dose. Thus, doses greater than 2 mg would afford the clinician increased flexibility if a patient's schedule or condition required a delay of the elective procedure for preprocedural platelet transfusion or other reasons. As the lusutrombopag adverse event profile was not dose dependent at doses up to 4 mg/day in this patient population, the longer window of platelet response achievable with doses higher than 2 mg offered increased clinical benefit without increased risk to the patient. Thus, the once-daily dose of 2 mg was eliminated from further consideration as the to-be-marketed dose.

High variability in platelet count may occur in individuals over a short period of time. Considering the risk of high variability in platelet count, that platelet counts of ≥200,000/μL were associated with an increased risk of thrombosis in a clinical study of another TPO receptor agonist in thrombocytopenic subjects with CLD, and that the goal of treatment is to achieve a platelet count of ≥50,000/μL to avoid preprocedural platelet transfusion, the 4-mg dose was eliminated from further consideration as the to-be-marketed dose. However, there was no evidence of an increase in incidence of adverse events with increasing dose of lusutrombopag in thrombocytopenic subjects with CLD undergoing elective invasive procedures. Therefore, analyses to assess the relationship between exposure of lusutrombopag and adverse events were not performed.

For the lusutrombopag 3-mg dose, the probabilities of attaining a platelet count of 50,000/μL were > 80% and the probabilities of platelet count exceeding 200,000/μL were ≤ 0.5% for any population. The

simulation supports the dose regimen of 3 mg once daily for 7 days in non-Japanese as well as Japanese thrombocytopenic subjects with CLD.

Summary of Simulated Platelet Indices for Dose Response

Population	Dosage Regimen	Peak PLT Count Percentile ($*10^4$/μL)			Pr(PLT ≥ 5) on Days 9 to 14 (%)	Pr(PLT > 20) (%)
		5th	50th	95th		
All thrombocytopenic subjects	2 mg QD	4.00	6.34	10.6	75.9	0.07
	3 mg QD	4.35	7.21	12.9	85.2	0.39
	4 mg QD	4.68	8.05	15.0	90.4	1.05
Japanese thrombocytopenic subjects	2 mg QD	4.07	6.49	11.0	78.0	0.09
	3 mg QD	4.47	7.44	13.4	87.1	0.50
	4 mg QD	4.84	8.35	15.6	92.0	1.34
Non-Japanese thrombocytopenic subjects	2 mg QD	3.84	6.01	9.58	70.7	0.02
	3 mg QD	4.15	6.73	11.4	80.8	0.13
	4 mg QD	4.43	7.43	13.1	86.6	0.33

Simulations were performed with 200 replicates using the original dataset. QD = once daily; PLT = platelet

To evaluate the pharmacological activity of lusutrombopag on various enzymes and receptors, *in vitro* ion channels and inhibitory assay for 11 enzymes or binding assay for 30 receptors were performed and the IC50 values were determined. Based on the comprehensive assay, lusutrombopag was shown to have inhibitory activities (≥50%) for 2 receptors and 3 enzymes at 10 μmol/L. The IC50 of adrenergic α2C, leukotriene B4, COX-1, COX-2, and phosphodiesterase 1 were calculated as 2.75 μmol/L (1.63 μg/mL), 2.78 μmol/L (1.64 μg/mL), 16.2 μmol/L (9.58 μg/mL), 4.08 μmol/L (2.41 μg/mL), and 1.36 μmol/L (0.80 μg/mL), respectively. In the clinical trial in thrombocytopenic patients with CLD treated with lusutrombopag 3 mg once daily for up to 7 days, the Cmax was determined to be 157 ng/mL on Day 5 [refer to Study 1423M0634]. In addition, the protein binding ratio of lusutrombopag in human plasma was extremely high (≥99.9%); the Cmax of non-binding unchanged lusutrombopag should be equal to or less than 0.157 ng/mL (157 ng/mL × <0.001). By considering these evidences, IC50 values of 2 receptors and 3 enzymes were estimated to be approximately 5100-fold higher than the plasma concentration of unbound unchanged lusutrombopag. In conclusion, it is considered that lusutrombopag at 3 mg may have no or little effect on enzymes, ion channels, or other receptors except for the TPO receptor.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

In total, 21 clinical studies contributed to PK and or PD data. Furthermore, a Pop PK Analysis was conducted. From the data set provided, following information could be derived:

Absorption: After oral administration, lusutrombopag is absorbed with a peak concentration occurring 6.0 to 8.0 hours in multiple dose studies conducted in thrombocytopenic subjects with CLD. In multiple dose studies in healthy subjects, median Tmax values ranged from 4 to 8 hours (day 7 or day 14) after ingestion.

After multiple dosing, steady state appears to be achieved by day 5 [Study M0613 (Multiple dose in healthy subjects) and Study M0617 (DDI Study with Midazolam)] to day 7 [M0615 (multiple dose in healthy subjects)].

Distribution: Lusutrombopag is highly bound to human plasma proteins, with a high binding ratio of 99.996%. In study M061E, it could be observed, that the geometric mean (% CV) apparent volume of distribution during the terminal phase of lusutrombopag in healthy adult subjects was 39.5 L (23.5%) after the administration of a 3mg tablet in 16 subjects. The distribution of radioactivity into blood cells was observed to be minimal, with essentially no binding to the red blood cells. In blood, [14C]-lusutrombopag was distributed mainly in the plasma.

Metabolism: Lusutrombopag was suggested to be metabolized primarily by ω-oxidation followed by β-oxidation of O-hexyl group. In *in vitro* studies revealed that CYP4 enzymes including CYP4A11 and partially CYP3A4 enzyme were contributed to ω-oxidation to form 6-hydroxylated lusutrombopag. Metabolite profiling in the mass balance study suggested that lusutrombopag may be primarily metabolized by oxidation of the hexyl group followed by β-oxidation of O-hexyl side chain in the liver.

Results of *in vitro* studies indicate, that lusutrombopag is a substrate of P-gp and BCRP, but is not a substrate of OATP1B1, OATP1B3 or OCT1.

Approximately 97% of plasma radioactivity was detected as unchanged lusutrombopag. The metabolites (deshexyl, β oxidated carboxylic acid, taurine conjugate of β-oxidated carboxylic acid, and acyl-glucuronide) were only detected at a trace level (each constituting ≤ 2.6% of plasma radioactivity).

Elimination: The primary route of excretion of Lusutrombopag is via the faeces. The terminal elimination half-life t1/2,z was: 19.3 to 29.5 hours (geometric mean) in single dose studies in healthy subjects

27.0 to 32.0 hours in multiple-dose studies in healthy subjects

31.9 to 43.9 hours in multiple-dose studies in subjects with CLD

Terminal elimination half-life and apparent total clearance (CL/F) did not show a dose dependent change.

In the feces unchanged lusutrombopag was detected as 16.22% of administered radioactivity and a mixture of deshexyl and O-propanol (or O-acetic acid) metabolites were detected as 17.93% of administered radioactivity.

Exposure: When looking at the Cmax and AUC values throughout the studies conducted, a dose proportional increase could be observed in both, healthy and thrombocytopenic subjects with CLD suggesting PK linearity across the dose range studied (1 to 50 mg for a single dose in healthy subjects; 0.25 to 2 mg for multiple doses in healthy subjects; and 0.25 to 4 mg for multiple doses in thrombocytopenic subjects with CLD). Cmax and AUC0-τ can be deemed comparable between healthy Japanese subjects and Japanese thrombocytopenic subjects with CLD after multiple-dose administration with only slight differences. Differences between Caucasian (Study M0634) and Asian ethnicity seem to be related to the different bodyweight these populations (M0634 mixed non-Japanese population: (intense PK group) [range]: 86.9 [57.1 to 123.4] kg) in comparison to studies M061B (56.3 [45.6 to 74.9] and M0633 63.8 [39.5 to 86.5] kg) (Japanese population). Furthermore, the pop PK model identified bodyweight as an influential covariate on PK.

Lusutrombopag is metabolised mainly by CYP4 enzymes, including CYP4A11. It is worth noting that the CYP4A11 play an important role in regulation of blood pressure through the conversion of arachidonic acid into 20-HETE and its polymorphism may be an important risk factor for hypertension, coronary artery disease or cerebral infarction. Bearing in mind that the main metabolic route of lusutrombopag is related to CYP4A11, its polymorphism could potentially change the exposure to lusutrombopag. However, as outlined by the applicant CYP4A11 can increase the AUC in poor metabolizers, but the fold increase in

exposure is considered to be less than 2, at even maximum risk evaluation. Bearing in mind that there is a possibility that alternative metabolic pathways may be activated for poor metabolizers, the AUC in poor metabolizers might not change compared with that in extensive metabolizers.

From the data provided it can be concluded that the influence of high-fat, high-calorie meal and calcium on the PK and BA of lusutrombopag is only minimal and very likely clinically not meaningful. No specific restriction with regards to food intake is deemed necessary.

All PK studies showed consistent results with no major discrepancies with regards to the PK of Lusutrombopag and the PK analysis were performed by non-compartmental methods.

The population PK analysis performed describes the plasma concentration of lusutrombopag and evaluates the effects of influencing factors on the PK of lusutrombopag based on the pooled data from healthy subjects and thrombocytopenic subjects with CLD in 3 Phase 1 studies and 7 Phase 2 and Phase 3 studies (Studies M0611, M0613, M0615, M0623, M0625, M0626, M0627, M0631, M0633, and M0634).

A total of 4196 plasma lusutrombopag concentrations from 427 subjects (78 healthy subjects and 349 thrombocytopenic subjects with CLD) were included in the population PK analysis. Non-linear mixed effects modeling was performed using NONMEM. A 3-compartment model was used as a structural PK model. An exponential error model was used for inter-individual variability, and a proportional error model was used for intra-individual variability.

After covariate modeling, the effects of body weight, sex, ethnicity, and subject population on CL/F, body weight and subject population on V2/F, and body weight on V3/F were retained in the final model.

The final model indicated that CL/F in females was 13% lower than that in males. CL/F in the thrombocytopenic subjects was 13% lower than that in the healthy subjects. CL/F in the Japanese subjects was 13% lower than that in the non-Japanese subjects. Inferential assessment of each covariate effect with the median and the confidence interval from the bootstrap effect of sex, subject population and ethnicity on CL/F, all were within or close to the limits of the confidence interval defined suggesting rather negligible clinical relevance.

The final model indicated that Body weight was an influential covariate on lusutrombopag PK for healthy subjects and subjects with CLD. When looking at body weight, the Cmax and AUC0-τ decreased with increasing body weight in thrombocytopenic subjects with CLD. Although body weight affects the PK of lusutrombopag, the platelet count profiles seem to be only modestly influenced according to the PK/PD simulation, suggesting that no dose adjustment based on body weight is considered necessary. From a pharmacodynamics perspective, the provided data show a trend of higher peak platelet counts in patients with lower body weight. Recommendations in section 4.4 of the SmPC were requested to be added with regard to additional platelet monitoring for this subpopulation.

As regards the effect of ascites and albumin concentration on the PK/PD analysis, the applicant provided further discussion in this context. No clinically relevant effect seems to be apparent, since most of the relevant PK parameters and platelet counts were comparable.

Despite the fact that population PK analysis was based on data from healthy adult subjects and thrombocytopenic subjects with CLD, age was not identified as a statistically significant covariate for the PK of lusutrombopag. Using a noncompartmental method in the multiple-dose study (Study M0615) it could be observed that the CL/F (apparent total clearance) tended to increase with increasing body weight (regression equation CL/F = 0.357 × body weight 1.03).

With regards to hepatic impairment some uncertainties remain. Impact on the PK of lusutrombopag is likely since lusutrombopag is excreted mainly via the faeces. Unfortunately only very few subjects with child Pugh class C were available for evaluation (n=7 – study 1525M0627 and 1423M0634), therefore no firm conclusions can be drawn for severe cases of hepatic impairment. It is furthermore important to note

that in the studies used for PK/PD modelling, Child-Pugh class C was exclusion criterion (even in the study 1423M0634, 3 patients in class C were included incorrectly because they did not meet inclusion criteria - Child-Pugh class A or B). In the only study with class C patients (study 1525M0627), there were only 4 patients with Child-Pugh score above 9.

The division into groups with Child-Pugh score ≥9 and <9 does not correspond to the Child-Pugh classification (Class A – score 5-6; class B – score 7-9; class C – score 10 – 15). In order to address this issue, the applicant has provided a discussion on this matter in response to the questions raised in the day 120 LoQ. In the PK covariate modelling, it was confirmed that the inclusion of Child-Pugh classes (Child-Pugh class A vs B/C) into CL/F slightly improved the model based on the change of objective function value (ΔOBJ of −3.895, $p > 0.01$). In the PK/PD covariate modelling, the inclusion of Child-Pugh classes into the PD parameter (SLOP) was statistically significant (change in NONMEM objective function [ΔOBJ] of -11.878). However, it was found that SLOP increased for the higher Child-Pugh score group with a cut-off of 9, and the inclusion of Child-Pugh score (< 9 or ≥ 9) provided more statistically significant model improvement (ΔOBJ of -13.972) than the inclusion of Child-Pugh classes. Based on the comparison of ΔOBJ, the Child-Pugh score was selected as a covariate.

While for Child Pugh class A and B only modest differences in PK were observed the data presented so far is not thoroughly convincing with regards to the applicants conclusion, that no dose adjustments or precaution measures are necessary. This is especially true considering the already described main elimination pathway of lusutrombopag, the results of the hepatic impairment study M0616 and the overall limited sample size of subjects with Child-Pugh class C. The applicant proposes warning statements within section 4.4. of the SmPC concerning close monitoring for early signs of worsening and platelet counts monitoring in Child Pugh Class C subjects in order to ensure safety in this subgroup of patients with an unmet medical need. Considering that the PK/PD modelling seem to indicate that no clinically significant differences are to be expected on platelet increase of lusutrombopag in patients with different severity of hepatic impairment, the proposed warning statements in section 4.4. of the SmPC are deemed adequate from a PK perspective.

Regarding the effect of lusutrombopag on transporter proteins, lusutrombopag was shown *in vitro* to be a substrate of P-gp and BCRP, but not a substrate of OATP1B1, OATP1B3, and OCT1. In the clinical DDI study M061E, lusutrombopag exposure was indeed increased, i.e. Cmax by 18% and AUCs by 19%, with co-administration of cyclosporine (a P-gp and BCRP dual inhibitor) compared with lusutrombopag alone. The upper limit of 90% CI (geometric means) for Cmax was only slightly lower than 125%, and for AUClast and AUCinf slightly exceeded 125%, indicating that that P-gp and BCRP inhibition modestly increases lusutrombopag plasma exposure. The potential for drug interactions with BCRP/P-gp inhibitors cannot be excluded and a respective statement referring to concomitant administration with either BCRP or P-gp inhibitors was included into section 4.4. of the SmPC.

Regarding the effect of lusutrombopag on cytochrome P450 enzymes, lusutrombopag seems to have a low potential for CYP induction or inhibition in humans based on the results of the conducted DDI study (-M0617). In this DDI study -M0617, the 0.75mg dose of lusutrombopag was chosen as a likely clinical dose, but the extent of exposure to lusutrombopag during study 0912M6017 was 6 mg (1.5 mg + 6 x0.75mg), which does not correspond to exposure achieved through administration of lusutrombopag according to recommended posology (3 mg x 7 days). However, the applicant has further addressed this matter and indicated that a clinical DDI study for evaluating the DDI potential of multiple doses of lusutrombopag 3 mg in healthy subjects could not be conducted on ethical grounds due to a risk of overshooting platelet counts. Therefore, the PBPK modelling approach reported in Study S-888711-CB-288-N was performed to extrapolate the DDI potential of lusutrombopag 3 mg once daily from the result in the clinical DDI study with the lower dose (Study M0617). Based on the Guideline on the investigation of Drug Interactions a mechanistic static model with the result of reversible inhibition study

was used, which indicated that lusutrombopag is unlikely to inhibit the CYP3A4 enzymes at the clinical dose of 3 mg once daily according to the decision criterion.

No substantial effect of calcium on the PK of lusutrombopag has become apparent. The findings also suggest no influence of multivalent cations contained in antacids, mineral supplements, dairy products, etc. on the PK of lusutrombopag. Lusutrombopag is metabolized mainly by CYP4 enzymes, including CYP4A11. CYP4A11 polymorphism is not considered to have a significant effect on metabolism of lusutrombopag. Further, taking into account that CYP3A4 is contributing to the ω–oxidation, further elaboration was asked to be provided on the potential effect of co-administration with CYP3A4 inhibitors or inducers on the PK of lusutrombopag. From the clinical studies, there was however no indication that the PK and PD (i.e., peak platelet counts) of lusutrombopag would be affected to a clinically significant extent when co-administrated with CYP3A4 inhibitors or inducers.

In investigation with [14C]-lusutrombopag (1 and 5 µg/mL) and 4% HSA, the protein binding ratio was not changed with the inhibitors (warfarin and diazepam, 1 and 10 µmol/L). Therefore, a drug interaction with lusutrombopag due to a change of the protein binding ratio is unlikely. In response to the questions raised in the day 120 LoQ, the applicant has provided further analysis, indicating no clear relationship between PK/PD parameters and albumin concentration. Furthermore, PK parameters appeared to be comparable between patients with and without severe hypoalbuminemia.

Pharmacodynamics

The primary pharmacodynamic effect of lusutrombopag, i.e. the increase in platelet count, has been assessed in 8 clinical phase 2 and phase 3 studies in thrombocytopenic subjects with CLD.

Relevant pharmacodynamics endpoints that were assessed were time course of platelet count, mean maximum platelet counts, mean time to reach maximum platelet counts as well as change from baseline in platelet counts.

Overall, platelet count increased with increasing doses of lusutrombopag up to 4 mg, supporting the plausibility of the postulated mechanism of action.

The initially investigated lower doses of 0.25, 0.5, 1 mg and 1.5 mg did not show evidence of efficacy, but platelet count increased over time in the 1.5- and 2-mg groups. Eventually, a dose of 3 mg once daily was chosen by the Applicant based on the best benefit risk profile of lusutrombopag: longer duration of platelet response achievable with lusutrombopag doses higher than 2 mg, and reduction of the risk of excessive platelet counts with the 4 mg dose.

For the 3 mg dose, the mean maximum platelet count was 80,000 to 95,000/µL and the range of maximum platelet counts was 25,000 to 195,000/µL (excl. one patient) throughout the clinical studies in thrombocytopenic patients with CLD. Maximum platelet counts did not exceed 200,000/µL, except in one patient related to unallowed previous medication with another TPO receptor agonist. The mean time to reach maximum platelet counts was 12 to 14 days (range 5-35 days) and the mean number of days during which platelet count was ≥50,000/µL was 19 to 24 days in all studies with patients.

A sequential PK and PD modelling approach was applied, including the 4196 plasma concentration data from the 427 subjects (78 healthy subjects and 349 patients) and 3526 platelet count data from 347 patients were used for the population PK and PK/PD analyses. Overall, conclusions deduced from the model do not stand in contradiction to the data generated in the clinical studies and the model is considered of supportive character only.

All efficacy and safety studies were conducted applying a study treatment stopping criterion, except one phase 3 B study (-M0633) in Japanese thrombocytopenic patients with CLD.

This latter study is used to support the 7 days fixed dosing regimen with no need of additional platelet monitoring in the intended study population. Indeed, no clear difference in platelet response for patients without platelet transfusion was found between the group receiving a fixed dosing regimen of 7 days and the group where a stopping criterion was applied. No platelet counts >200,000/µL were observed in any studies in patients, including those having received at least one more dose of study drug than would have been administered had the stopping criterion been applied (n=20; maximum platelet count was 173,000/µL). The PK/PD model suggests a low probability (i.e. 0.43%) of reaching excessive platelet counts, which could be reduced only to 0.2-0.3% if one day of platelet monitoring was performed. Overall, however, clinical data in patients without applying a stopping criterion is very sparse. Additional platelet monitoring at least once approximately 5 days after the first lusutrombopag dose is advised for the different subsets of patients at higher risk, i.e, patients with Child Pugh C liver disease and patients with body weight <45 kg. Appropriate measures such as discontinuation of lusutrombopag should be taken, if the platelet count reaches ≥50,000/µL as a result of a 20,000/µL increase from baseline.

Certain subpopulations were identified with differences in exposure of lusutrombopag, e.g. patients with Child-Pugh class B/C or score ≥9/<9, Japanese versus Non-Japanese patients or patients with lower body weight. The PK/PD model suggested a higher platelet count increase in patients with low body weight (< 45 kg) and a higher probability (2.05%) with a 7 day fixed dosing regimen compared to the general intended population (0.43%) was estimated based on this model. Further analyses of the platelet count profiles classified by body weight groups, Child Pugh A/B and C class as well as by ethnicity were asked to be provided. These analyses confirmed a trend for higher peak platelet count in patients with lower body weight. Section 4.4. of the SmPC was amended in this regard. Observed differences in exposure between Japanese and Non-Japanese patients are likely influenced by differences in body weight based on the analyses provided. No robust conclusions can therefore be drawn in this regard. It is however considered unlikely that Non-Japanese patients will show a differential response compared to Japanese patients. Based on the provided data, there seems to be a trend in patients with Child Pugh C liver disease for lower mean platelet count profiles compared to patients with Child Pugh liver disease A and B, although more obvious in Non-Japanese patients. This may however also be influenced by body weight. Overall, an insufficient number of patients with Child-Pugh class C liver disease was included in the studies, therefore no robust conclusions on the pharmacological response in this subpopulation can be drawn. Hence, the warning in section 4.4. of the SmPC.

Platelet function was assessed in a dedicated study in thrombocytopenic patients with CLD (study -1301061B). Overall, no abnormal results on platelet aggregation or platelet release were found and no tendency of increase in morphologically abnormal platelet was shown after administration of lusutrombopag.

No secondary pharmacological effects of lusutrombopag were observed, e.g. white or red blood cell increase, which seem plausible based on similarity of EPO- or GM-CSF- and TPO-receptors. The effect of lusutrombopag on the QTc interval was investigated in a dedicated thorough QT/QTc study. Based on the provided data from a dedicated thorough QT/QTc study, an effect of lusutrombopag on the QT interval is considered unlikely. In a DDI study investigating co-administration with cyclosporine, a slight prolongation of heart rate and QT intervals was observed. However, this was likely associated with the cyclosporine administration and not attributed to lusutrombopag.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics

In conclusion, the PK of lusutrombopag was well characterised by various clinical studies and Pop PK modelling included in the dossier, with no major discrepancies between the study results.

Pharmacodynamics

The pharmacodynamic effect of lusutrombopag, i.e. the increase of platelet counts, has been well demonstrated in healthy subjects as well as in thrombocytopenic patients with chronic liver disease. The recommended 3 mg dose of lusutrombopag was chosen based on the exposure response relationship.

2.5. Clinical efficacy

2.5.1. Dose response studies

The efficacy of lusutrombopag as treatment for subjects who have CLD and are at increased risk for bleeding associated with elective invasive procedures was evaluated in 6 studies. Lusutrombopag was administered for up to 7 days in all studies (with duration of treatment determined by platelet response in all but 1 of the studies). In particular, in 5 of the 6 studies, platelet count was determined on at least Days 5, 6, and 7 to monitor subjects for an excessive increase in platelets and to allow treatment to be stopped.

Although elevated platelet numbers are intended and protective against bleeding events in thrombocytopenia before invasive procedures, at the same time there is concern that a too high increase could lead to complications with regard to thromboembolic events. This concerns stems in part from a phase III trial with eltrombopag (Afdahl *et al* 2012), a small molecule TPO agonist in 292 patients with chronic liver disease and severe thrombocytopenia who received eltrombopag or placebo for 14 days and subsequently underwent an elective invasive procedure. The trial was terminated early due to thrombotic events of the portal venous system which were observed in 6 patients who received eltrombopag, as compared with 1 who received placebo. An association between platelet counts of 200,000 per cubic millimetre or higher and an increased risk of thrombotic events was identified in a post hoc analysis. The investigators concluded that changes in dosing (a decreased dose, less-frequent dosing, or a shorter duration of dosing) could be used to minimise the proportion of patients who have a platelet count of 200,000 per cubic millimetre or higher, while maintaining a platelet count that is sufficiently high for the patient to undergo an elective invasive procedure without having substantial bleeding or requiring a platelet transfusion.

Phase II:

All three phase II trials enrolled patients with chronic liver disease, Child-Pugh Class A or B and severe thrombocytopenia planned to undergo percutaneous liver ablation. In the initial Phase II study M0623, low doses of lusutrombopag (0.25, 0.5, and 1 mg/day) were evaluated, followed by evaluation of doses of 1.5 and 2 mg/day. It was observed that doses below 2 mg did not show an appreciable impact on platelet counts. In the subsequent Phase II study M0625, lusutrombopag doses of 2.5 mg (n=6), 3 mg (n=7) and 4 mg (n=8) per day up to 7 days were evaluated. The investigated doses lead to indistinguishable efficacy responses in these limited patient numbers.

The double-blind, parallel-group, placebo (n=15) controlled trial M0626 investigated doses of 2 mg (n=15), 3 mg (n=16) and 4 mg (n=15) of lusutrombopag administered for up to 7 days. The primary endpoint was defined as avoidance of preprocedural platelet transfusion. In this small trial, efficacy was not unequivocally separated by lusutrombopag dose level, although a trend to a higher platelet response and a longer duration of this response could be observed for the 3 and 4 mg dose. Comparable robust efficacy over placebo was noted for both the 3 and 4 mg dose. However, due to safety considerations and the desire to avoid excessive platelet count increases with potential thrombotic complications, the 3 mg dose was finally carried forward into the phase III trials.

A lusutrombopag 3-mg/day dose was evaluated versus (vs) placebo in 2 Phase III studies M0631 and M0634. The phase IIIb trial M0633 investigated retreatment with lusutrombopag and if omitting the stopping criterion and administering a fixed 7-day course of treatment were safe and feasible.

2.5.2. Main studies

M0631

Methods

Study participants

Inclusion Criteria

Patients who fulfilled the following criteria were included in the study:

1. Patients who were able to understand the study and comply with all study procedures, and were willing to provide written informed consent prior to screening

2. Male or female patients aged 20 years or older at the time of signing the informed consent form

3. Thrombocytopenic patients due to chronic liver disease

4. Patients with a platelet count of < 50,000/μL at screening

5. Patients who were undergoing invasive procedures fulfilling the following criteria:

– procedures were to be completed between 9 and 14 days after the initiation of the study treatment

– procedures which were not involving any of the following situations: laparotomy, thoracotomy, craniotomy, open-heart surgery, organ resection, or partial organ resection (except for procedures comparable to tissue resection)

6. Patients with the Eastern Cooperative Oncology Group (ECOG) performance status grade 0 or 1

7. Patients who were able to stay in the hospital between the day before the invasive procedure and the 14th day after the initiation of the study treatment

8. Only for male patients, patients who were sterile or who agreed to use an appropriate method of contraception (including use of a condom with spermicide) from enrollment to completion of the post-treatment assessment

9. Only for female patients, patients who agreed to use barrier contraception (including condom, diaphragm, and cervical cap) with spermicide or to use highly-effective contraception (including contraceptive implant, injectable contraceptive, combination oral contraceptive, intrauterine contraceptive device, and vasectomized partner) from enrolment to completion of the post-treatment assessment, except for female patients who were postmenopausal or who were surgically sterile

Exclusion Criteria

Patients who met any of the following criteria were excluded from the study:

1. Patients with any of the following diseases: hematopoietic tumour, aplastic anaemia, myelodysplastic syndrome, myelofibrosis, congenital thrombocytopenia, drug-induced thrombocytopenia, generalized infection requiring treatment except for viral liver disease, immune thrombocytopenia

2. Patients with any of the following concomitant malignant tumours other than the treatment target of the primary invasive procedure in the study: malignant tumours which were not included in the categories of skin cancer (except for melanoma), intramucosal cancer, or carcinoma *in situ*, malignant tumours involving nodal metastasis, distant metastasis, or invasion to the surrounding organ, malignant tumours requiring any treatment during the study

3. Patients who had undergone splenectomy

4. Patients who had undergone liver transplantation

5. Patients with any of the following at the screening examination: Child-Pugh class C liver disorder, uncontrollable hepatic encephalopathy with drugs, uncontrollable ascites with drugs

6. Patients with portal vein tumor embolism

7. Patients with past or present thrombosis (eg, cerebral infarction, myocardial infarction, angina pectoris, pulmonary thromboembolism, deep vein thrombosis, disseminated intravascular coagulation syndrome)

8. Patients with a complication or with a history of any of the following diseases: congenital thrombotic disease (eg, antithrombin deficiency, protein C deficiency, protein S deficiency, coagulation factor [Factor V Leiden] mutation), acquired thrombotic disease (eg, antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, hyperhomocysteinemia, increased factor VIII), Budd-Chiari syndrome

9. Patients with portal vein thrombosis based on imaging evaluation within 28 days prior to enrolment or with a history of portal vein thrombosis

10. Patients for whom no hepatopetal portal blood flow was demonstrated by Doppler ultrasonography within 28 days prior to enrolment

11. Patients who required antithrombotic drugs within 14 days prior to enrolment and thereafter

12. Patients with untreated gastroesophageal varices which were bleeding or found to require treatment based on upper gastrointestinal endoscopy within 180 days prior to enrolment (except for patients in whom the primary invasive procedure were for the treatment of gastroesophageal varices)

13. Patients with a complication or with a history of disease associated with a risk of bleeding (eg, coagulation factor deficiency, von Willebrand factor deficiency)

14. Patients with Grade 2 or more severe bleeding at screening according to the World Health Organization (WHO) Bleeding scale

15. Patients who had received any of the following drugs or therapies within 90 days prior to enrolment: anticancer drugs except for transcatheter arterial chemoembolization (TACE) and lipiodolization, interferon preparations, radiation therapy, exsanguination

16. Patients who had received any of the following invasive procedures within 90 days prior to enrolment:

– procedures involving laparotomy, thoracotomy, craniotomy, or open-heart surgery

– procedures involving any organ resection or any partial organ resection

– partial splenic embolization

17. Patients who had received any invasive procedures (except for the treatment of gastroesophageal varices) within 14 days prior to enrolment

18. Patients who had received blood transfusions (except for red blood cell preparations and albumin preparations) within 14 days prior to enrolment

19. Patients who previously received TPO receptor agonists

20. Female patients who were pregnant, possibly pregnant, or lactating

21. Patients who received other investigational products within 90 days prior to enrolment

22. Patients who were considered ineligible for the study by the investigator or sub-investigator for any other reasons

Treatments

A 3-mg tablet of S-888711 or a matching placebo tablet was administered orally once daily. The duration of the study treatment was 7 days.

Administration of the study drug on Day 2 was performed at 12 hours or longer after administration on Day 1. The study drugs were administered at the same time of the days between Days 2 and 7 to the extent possible.

Platelet count on Day 5 to 7 had to be measured before the administration on respective days and the study drug was to be administered after confirming that the platelet count measured on that day did not meet the following withdrawal criterion: platelet count ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline

Invasive Procedures

Planned invasive procedure was performed between Days 9 and 14. In case patients met any of the following conditions, the need for the invasive procedure was determined to ensure the safety of the patient:

1. Platelet count reached ≥ 200,000/μL.

2. Antithrombotic drug was administered.

3. AEs, which led the investigator or sub-investigator to consider that the procedure should not be performed, occurred.

4. Other problems, which led the investigator or sub-investigator to consider that the procedure should be cancelled, occurred.

5. A patient requested to cancel the procedure after the start of the study.

In case that the invasive procedure was not performed between Days 9 and 14 because of meeting items 1 to 4 above, the procedure was allowed to perform after Day 15. In case that the effectiveness of the invasive procedure performed between Days 9 and 14 was considered to be insufficient, same procedures were allowed to additionally perform after Day 15.

Determination of the Need for Preoperative Platelet Transfusion

The need for preoperative platelet transfusion, prior to the initial invasive procedure (ie, the primary invasive procedure in the study for the patient), was determined based on platelet count measured after Day 8 and immediately before performing the invasive procedure (ie, within 2 days before the day of the invasive procedure). Preoperative platelet transfusion was performed only when the platelet count was < 50,000/μL.

The date of platelet measurement used for determining the need for platelet transfusion, measured value, date of transfusion, dose (units) transfused, and reason for platelet transfusion performed during the study were recorded on the CRF.

Objectives

Primary Objective

- To evaluate the superiority of S-888711 over placebo in efficacy in thrombocytopenic patients with chronic liver disease receiving 3 mg of S-888711 as a pre-treatment of invasive procedures based on the proportion of patients who required no platelet transfusion prior to invasive procedures.

Secondary Objectives

- To compare the efficacy, safety, and pharmacokinetics of S-888711 with those of placebo in thrombocytopenic patients with chronic liver disease receiving 3 mg of S-888711 as a pretreatment of invasive procedures based on the following variables:
- Proportion of patients who required no platelet transfusion during the study
- Proportion of patients who had a platelet count of ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline
- Duration of increase in platelet count (the number of days during which increased platelet count was maintained as ≥ 50,000/μL, ≥ 70,000/μL, or ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline)
- Time course of platelet count
- AEs and ADRs
- Bleeding-related AEs
- Thrombosis-related AEs
- Assessment of portal vein thrombosis and portal blood flow
- Laboratory test, vital sign, and electrocardiogram
- Plasma S-888711 concentration

Outcomes / endpoints

Primary Efficacy Variable

- Proportion of patients who required no platelet transfusion prior to the initial invasive procedure

Secondary efficacy variables

- Proportion of Patients Who Required No Platelet Transfusion during the Study
- Proportion of Responders (A responder was defined as patient who achieved platelet count of ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline.)
- Duration of Maintenance of Increase in Platelet Count
- Time Course of Platelet Count

Sample size

The target sample size of this study was 45 per the treatment group (90 in total) considering 2 key points shown below.

- To assure at least 90% power in the efficacy evaluation of S-888711: Since the proportion of patients who required no platelet transfusion prior to invasive procedure was 20.0% in placebo and 81.3% in 3-mg groups in Study 1208M0626, it was assumed that similar results would be obtained in this study but the minimumrequired proportion would be 70% in clinical practice. Based on the assumption, 24 patients per group was required to detect the difference in the proportion between placebo and S-888711 groups, with 90% or higher power at significance level 0.05 (2-sided). Incidentally, the power is higher than 99% with sample size of 45 per group.
- To minimize the risk of overlooking thrombosis-related AEs: The incidence of thrombosis-related AEs was 6.5% (3/46 patients) in Study 1208M0626. Based on the result, at least 45 per group is required to reduce the probability that this study cannot detect AEs with incidence of 6.5% to less than 5%.

Randomisation

Patients were randomized to either of the treatment groups (3 mg of S-888711 or placebo) in a ratio of 1:1. The patients were randomized by using a stochastic minimization method for balancing the following 2 factors by the registration center:

- Primary invasive procedure (liver ablation/coagulation or other invasive procedures)
- platelet counts at screening (< 35,000/μL, ≥ 35,000/μL to < 45,000/μL, or ≥ 45,000/μL)

Blinding (masking)

The study was conducted in a double-blind fashion by using a placebo matching the active drug canisters in appearance, labelling, and packaging. Study drug assignment was performed by block randomization for 4 patients in each block. Prior to study drug assignment, the person responsible for study drug assignment generated random numbers using random number generation function RANUNI of SAS®, transferred them from SAS to Microsoft Excel, and prepared the allocation table using Visual Basic program in Microsoft Excel. A total of 640 subjects (320 subjects each for the 3-mg group and the placebo group) were assigned to 160 cohorts by the person responsible for allocation.

Of the allocated study drugs, one set was used for assessment of indistinguishability, and another set was provided to the regulatory authority at the end of the study (before blind was broken). A total of 104 sets of study drugs were supplied to each medical institution (81 centers), and 54 sets were not used.

The person responsible for study drug assignment verified indistinguishability from the point of view such as the appearance, shape, and smell prior to study drug allocation and after completion of administration to all patients (before scheduled unblinding) according to a separate document. In the verification after completion of administration to all patients, it was performed from the point of view such as the packaging and labelling. No problem was identified in the indistinguishability of study drugs at specified time points. The person responsible for study drug assignment kept the randomization table in a sealed envelope until scheduled unblinding. The Shionogi emergency center kept the emergency codes.

The investigator or the independent safety committee did not require unblinding. However, a patient experienced a portal vein thrombosis as a suspected unexpected serious adverse reaction. Since the pharmacovigilance division which was independent of the developmental divisions of the sponsor had to judge whether they reported it to the regulatory authorities, they required unblinding of this patient to the Shionogi emergency centre. The patient was revealed to be the 3-mg group; therefore, the information that this SAE occurred in the 3-mg group was notified to the regulatory authorities, all the investigators, and the IRBs of the medical institutions.

The person responsible for study drug assignment opened the randomization table after all data from CRFs were locked. Plasma drug concentrations were reported to the sponsor after the database was locked because the treatment assignment could be identified. Blinding was maintained during the study except for the above mentioned case for all the persons related the study except for the person responsible for study drug assignment.

Statistical methods

Analysis Population

- Full analysis set (FAS) included all randomized patients who received at least 1 study drug and had a measurement of platelet counts at baseline and at least 1 measurement of platelet counts after the initiation of study drug administration.
- Safety analysis population included all randomized patients who received at least 1 actual dose of the study drug. The population was analyzed according to the treatment that the patients actually received, rather than the treatment to which the patients were randomized.
- Per protocol set (PPS) included all randomized patients included in FAS and did not meet any of the following conditions:
    - Patients with any protocol inclusion or exclusion violations
    - Patients with insufficient treatment compliance of the study drug
    - Patients with violations of restrictions on concomitant therapy
- Pharmacokinetic concentration population included all patients who received at least 1 actual dose of S-888711 and had at least 1 measurement of plasma S- 888711 concentration. This population was used for the concentration listing and plasma concentration-time profile graphing.

Handling of Missing Data

Missing data was not imputed. All analyses were done using actual observations.

Analysis of primary efficacy endpoints

As the primary analysis, the proportion of patients who required no platelet transfusion prior to invasive procedure (ie, the primary efficacy endpoint) was calculated in each treatment group and its 95% confidence interval for incidence was calculated by using Clopper-Pearson method. The proportion was compared between the 3-mg group and the placebo group with Cochran-Mantel-Haenszel test with consideration of stratification factors (ie, platelet count at screening and planned primary invasive procedure). The relative risk of the 3-mg group compared with the placebo group and its 95% confidence interval were calculated. As a sensitive analysis, the same statistical analysis was performed for the PPS.

Statistical analysis of the primary efficacy endpoint:

- The proportion of patients who required no platelet transfusion prior to invasive procedure and its 95% confidence interval were calculated by each stratification factor, ie, platelet count at screening and planned primary invasive procedure in each treatment group.
- Subgroup analyses were performed for the following categories to evaluate the efficacy of S-888711 3 mg in those subgroups. The proportion of patients who required no platelet transfusion prior to invasive procedure was calculated by each category in each treatment group,

and each relative risk of the 3-mg group compared with the placebo group and its 95% confidence interval were calculated. The interaction between each subgroup and the treatment group was tested with Breslow-Day test.

- Performed invasive procedure (percutaneous RFA/MCT or other invasive procedures)
- Performed detailed invasive procedure (only for the proportion of patients who required no platelet transfusion prior to invasive procedure) (percutaneous RFA/MCT, laparoscopic RFA/MCT, EVL, EIS, TACE, TAE, or other invasive procedures)
- Baseline platelet count (< 35,000/μL, ≥ 35,000/μL to < 45,000/μL, or ≥ 45,000/μL)
- Child-Pugh (A or B)

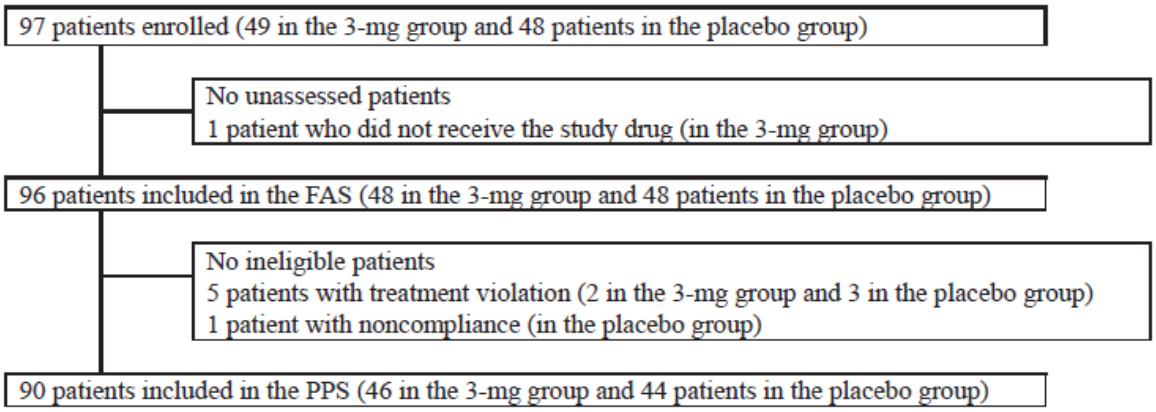
Secondary efficacy endpoints were analysed as follows:

- Proportion of patients requiring no platelet transfusion, frequency of platelet transfusion and dose (unit) transfused during the study
- Responder rate
- Duration of maintenance of increase in platelet count
- Time course of platelet count

Results

Participant flow

Figure 8: efficacy analysis population



Recruitment

Date of the first administration of the study drug to the first patient: October 17, 2013

Date of the final observation for the last patient: May 1, 2014

Conduct of the study

Amendments

The study protocol was amended once (see Table 5) for adding the list of example invasive procedures.

Table 5: Major changes in the study protocol

No. of version	Amendment date	Major changes	Rationale
1	August 26, 2013	-	-
2	September 6, 2013	Adding the list of example invasive procedures	Due to answer the request from the Japanese regulatory authority

Protocol Deviations

Table 6 shows a list of major deviations, excluding minor deviations (eg, missing value, deviation from specified schedule of the study assessment). Major deviations were found in 9 patients. The deviations were classified as the violation of study treatment and prohibited concomitant drug/therapy.

Table 6: list of major protocol deviations:

Institution	Patient ID	Type [a]	Deviation
		3	The patient received 1 tablet of the study drug at 12:50 on Day 1 but misguidedly received 1 tablet of the study drug at 18:50 on the same day (overdose).
		3	On Day 11, PEIT, planned invasive procedure, was cancelled and RFA was performed.
		3	On Day 11, EVL, planned invasive procedure, was cancelled and argon plasma coagulation was performed.
		4	Thoracentesis, a prohibited concomitant therapy, was performed on Day 25 to treat an SAE of pleural effusion (reported term, aggravation of pleural effusion) (emergency deviation).
		4	Gran Syringe 75, a prohibited concomitant drug, was used on Day 19 to treat an AE of pancytopenia (emergency deviation).
		4	Kenketu Nonthron 1500 for injection, a prohibited concomitant drug, was used from Day 15 to 17 to treat an AE of portal vein thrombosis (emergency deviation).
		4	Emergency EIS, a prohibited concomitant therapy, was performed from Day 21 until 22 to treat an SAE of oesophageal varices haemorrhage (reported term, esophageal varices ruptured) (emergency deviation).
		4	Percutaneous liver biopsy was performed with TACE.
		4	Thoracentesis was performed on Day 21 to treat an AE of pleural effusion (reported term, right pleural effusion caused by RFA).

Abbreviations: adverse event (AE), endoscopic injection sclerotherapy (EIS), endoscopic variceal ligation (EVL), percutaneous ethanol injection therapy (PEIT), radiofrequency ablation (RFA), serious adverse event (SAE), transcatheter arterial chemoembolization (TACE).

[a] Type of deviation: 1, GCP noncompliance; 2, violation of inclusion/exclusion criteria; 3, violation of study treatment; 4, violation of prohibited/restricted concomitant drug/therapy; 5, violation of withdrawal criteria.

[Note in translation: Gran Syringe and Kenketu Nonthron are brand names of filgrastim and freeze-dried concentrated human antithrombin III in Japan, respectively.]

Baseline data

Table 7: demographic characteristics (FAS):

		S-888711 3 mg N=48 n (%)	Placebo N=48 n (%)	Overall N=96 n (%)
Sex	Male	21 (43.8)	30 (62.5)	51 (53.1)
	Female	27 (56.3)	18 (37.5)	45 (46.9)
Age (years)	n	48	48	96
	Mean	68.9	66.8	67.8
	SD	6.6	10.2	8.6
	Min	51	40	40
	Median	70.5	65.5	67.0
	Max	81	88	88
Weight (kg)	n	48	48	96
	Mean	59.73	63.87	61.80
	SD	10.50	14.92	13.00
	Min	34.9	45.0	34.9
	Median	58.85	62.35	60.10
	Max	81.3	115.6	115.6
Ethnicity	Hispanic or Latino	0	0	0
	Not Hispanic or Latino	48 (100.0)	48 (100.0)	96 (100.0)
Race	American Indian or Alaska Native	0	0	0
	Asian	48 (100.0)	48 (100.0)	96 (100.0)
	Black or African American	0	0	0
	Native Hawaiian or Other Pacific Islander	0	0	0
	White	0	0	0
Medical history of chronic hepatitis B	Yes	4 (8.3)	8 (16.7)	12 (12.5)
	No	44 (91.7)	40 (83.3)	84 (87.5)
Medical history of chronic hepatitis C	Yes	39 (81.3)	32 (66.7)	71 (74.0)
	No	9 (18.8)	16 (33.3)	25 (26.0)
Medical history of alcoholic hepatitis	Yes	2 (4.2)	6 (12.5)	8 (8.3)
	No	46 (95.8)	42 (87.5)	88 (91.7)
Medical history of non-alcoholic hepatitis	Yes	3 (6.3)	4 (8.3)	7 (7.3)
	No	45 (93.8)	44 (91.7)	89 (92.7)
Medical history of autoimmune hepatitis	Yes	0	0	0
	No	48 (100.0)	48 (100.0)	96 (100.0)
History of transfusion	Yes	28 (58.3)	26 (54.2)	54 (56.3)
	No	20 (41.7)	22 (45.8)	42 (43.8)
Child-Pugh grade	A	26 (54.2)	22 (45.8)	48 (50.0)
	B	22 (45.8)	26 (54.2)	48 (50.0)
Planned surgery	RFA/MCT	20 (41.7)	21 (43.8)	41 (42.7)
	Other	28 (58.3)	27 (56.3)	55 (57.3)
Platelet count (*10^4/uL) at screening	< 3.5	9 (18.8)	9 (18.8)	18 (18.8)
	>= 3.5 to < 4.5	22 (45.8)	24 (50.0)	46 (47.9)
	>= 4.5	17 (35.4)	15 (31.3)	32 (33.3)
Baseline platelet count (*10^4/uL)	< 3.5	7 (14.6)	10 (20.8)	17 (17.7)
	>= 3.5 to < 4.5	26 (54.2)	25 (52.1)	51 (53.1)
	>= 4.5	15 (31.3)	13 (27.1)	28 (29.2)
	n	48	48	96
	Mean	4.09	3.99	4.04
	SD	0.63	0.69	0.66
	Min	2.3	2.3	2.3
	Median	4.25	4.20	4.20
	Max	4.9	5.5	5.5

Table 14.1.3.2 Other Baseline Characteristics
FAS

		S-888711 3 mg N=48 n (%)	Placebo N=48 n (%)	Overall N=96 n (%)
Performance status	Grade 0	43 (89.6)	45 (93.8)	88 (91.7)
	Grade 1	5 (10.4)	3 (6.3)	8 (8.3)
Gastroesophageal varix	Yes	42 (87.5)	41 (85.4)	83 (86.5)
	No	6 (12.5)	7 (14.6)	13 (13.5)
Splenomegaly	Yes	45 (93.8)	46 (95.8)	91 (94.8)
	No	3 (6.3)	2 (4.2)	5 (5.2)
Ascites	Yes	11 (22.9)	14 (29.2)	25 (26.0)
	No	37 (77.1)	34 (70.8)	71 (74.0)
WHO bleeding scale	Grade 0	42 (87.5)	42 (87.5)	84 (87.5)
	Grade 1	6 (12.5)	6 (12.5)	12 (12.5)

Numbers analysed

Please see section Statistical Methods.

Outcomes and estimation

Primary Endpoint

The primary endpoint was the proportion of patients who required no platelet transfusion prior to invasive procedure (hereafter referred to as the proportion of patients who required no preoperative platelet transfusion) and defined as the proportion of patients who received no platelet transfusion prior to the primary invasive procedure in respective analysis population.

The proportion of patients who required no preoperative platelet transfusion was 79.2% (38/48 patients) in the 3-mg group and 12.5% (6/48 patients) in the placebo group; the proportion in the 3-mg group was significantly greater than that in the placebo group (P <0.0001).

Table 8: summary of proportion of patients who required no platelet transfusion before surgery (FAS)

	S-888711 3 mg N=48	Placebo N=48
Proportion of patients who required no platelet transfusion	79.2% (38/48)	12.5% (6/48)
Exact 95% confidence interval	(65.0, 89.5)	(4.7, 25.2)
Comparison with placebo		
- P value from CMH test [a]	<.0001	
- Relative risk (95% confidence interval)	6.16 (2.92, 13.00)	
Stratified by planned surgery		
- RFA/MCT	70.0% (14/20)	14.3% (3/21)
- Other	85.7% (24/28)	11.1% (3/27)
Stratified by platelet count (*10^4/uL) at screening		
- < 3.5	55.6% (5/9)	0.0% (0/9)
- >= 3.5 to < 4.5	77.3% (17/22)	12.5% (3/24)
- >= 4.5	94.1% (16/17)	20.0% (3/15)

[a] Cochran-Mantel-Haenszel test with planned surgery and platelet count at screening as stratification factors. The patients who discontinued in the study before surgery are defined as treatment failure. Therefore, they are treated as patients who required platelet transfusion.

Table 9: Summary of proportion of patients who required no platelet transfusion before surgery in per protocol set (PPS)

	S-888711 3 mg N=46	Placebo N=44
Proportion of patients who required no platelet transfusion	78.3% (36/46)	11.4% (5/44)
Exact 95% confidence interval	(63.6, 89.1)	(3.8, 24.6)
Comparison with placebo		
- P value from CMH test [a]	<.0001	
- Relative risk (95% confidence interval)	6.78 (2.94, 15.59)	
Stratified by planned surgery		
- RFA/MCT	70.0% (14/20)	10.5% (2/19)
- Other	84.6% (22/26)	12.0% (3/25)
Stratified by platelet count (*10^4/uL) at screening		
- < 3.5	55.6% (5/9)	0.0% (0/8)
- >= 3.5 to < 4.5	76.2% (16/21)	12.5% (3/24)
- >= 4.5	93.8% (15/16)	16.7% (2/12)

[a] Cochran-Mantel-Haenszel test with planned surgery and platelet count at screening as stratification factors. The patients who discontinued in the study before surgery are defined as treatment failure. Therefore, they are treated as patients who required platelet transfusion.

Secondary Endpoints

Proportion of Patients Who Required No Platelet Transfusion during the Study

Table 10: summary of proportion of patients whjo required no platelet transfusion during the study (FAS)

	S-888711 3 mg N=48	Placebo N=48
Proportion of patients who required no platelet transfusion	79.2% (38/48)	12.5% (6/48)
Exact 95% confidence interval	(65.0, 89.5)	(4.7, 25.2)
Comparison with placebo		
- P value from CMH test [a]	<.0001	
- Relative risk (95% confidence interval)	6.16 (2.92, 13.00)	
Stratified by planned surgery		
- RFA/MCT	70.0% (14/20)	14.3% (3/21)
- Other	85.7% (24/28)	11.1% (3/27)
Stratified by platelet count (*10^4/uL) at screening		
- < 3.5	55.6% (5/9)	0.0% (0/9)
- >= 3.5 to < 4.5	77.3% (17/22)	12.5% (3/24)
- >= 4.5	94.1% (16/17)	20.0% (3/15)

[a] Cochran-Mantel-Haenszel test with planned surgery and platelet count at screening as stratification factors. The patients who discontinued in the study before surgery are defined as treatment failure. Therefore, they are treated as patients who required platelet transfusion.

Proportion of Responders

Table 11: summary of proportion of patients who met responder criteria at least once during the study (FAS):

	S-888711 3 mg N=48	Placebo N=48
Proportion of responders	77.1% (37/48)	6.3% (3/48)
Exact 95% confidence interval	(62.7, 88.0)	(1.3, 17.2)
Comparison with placebo		
- P value from CMH test [a]	<.0001	
- Relative risk (95% confidence interval)	11.91 (4.00, 35.44)	
Stratified by planned surgery		
- RFA/MCT	65.0% (13/20)	9.5% (2/21)
- Other	85.7% (24/28)	3.7% (1/27)
Stratified by platelet count (*10^4/uL) at screening		
- < 3.5	55.6% (5/9)	0.0% (0/9)
- >= 3.5 to < 4.5	77.3% (17/22)	4.2% (1/24)
- >= 4.5	88.2% (15/17)	13.3% (2/15)

[a] Cochran-Mantel-Haenszel test with planned surgery and platelet count at screening as stratification factors. The responder is defined as the patient whose platelet count achieved >=50,000/uL and increased >=20,000/uL from baseline.
The data of platelet counts observed after the first platelet transfusion are excluded from the analysis.

Table 12: summary of proportion of patients who met responder criteria at least once during the study by time point (excluded from the data after the first platelet transfusion)

Time Point	S-888711 3 mg N=48	Placebo N=48
Day 5	6.3% (3/48)	4.2% (2/48)
Day 6	4.2% (2/48)	4.2% (2/48)
Day 7	14.6% (7/48)	0.0% (0/48)
Day 8	43.8% (21/48)	4.2% (2/48)
Day 10	65.9% (29/44)	0.0% (0/41)
Day 12	82.1% (32/39)	0.0% (0/24)
Day 14	89.5% (34/38)	0.0% (0/6)
Day 17	71.1% (27/38)	0.0% (0/6)
Day 21	42.1% (16/38)	16.7% (1/6)
Day 28	15.8% (6/38)	16.7% (1/6)
Day 35	5.3% (2/38)	0.0% (0/6)

The responder is defined as the patient whose platelet count achieved >=50,000/uL and increased >=20,000/uL from baseline.
The data of platelet count observed after the first platelet transfusion are excluded from the analysis.

Duration of Maintenance of Increase in Platelet Count

Table 13: Summary of duration of increase in platelet count >= 50,000/uL (FAS)

		S-888711 3 mg		Placebo	
		With PT	Without PT	With PT	Without PT
Summary statistics	n	10	38	40	7
	Mean	11.2	21.7	5.1	18.1
	SD	8.0	6.5	6.2	10.8
	Min	0.0	5.7	0.0	4.2
	Median	10.3	22.1	3.3	18.5
	Max	23.0	33.5	22.3	34.8
Parameter estimates	LS mean (SE)	12.25 (1.89)	21.09 (0.99)	6.05 (0.96)	15.96 (2.31)
Treatment comparisons	vs. S-888711 3 mg without PT				
	- Difference of LS mean (SE)	---		15.04 (1.38)	5.13 (2.49)
	- 95% confidence interval	---		12.30, 17.78	0.19, 10.07
	- P value	---		<.0001	0.0420
P value for test of fixed effect	- Planned surgery	0.5131			
	- Baseline platelet count	<.0001			
	- Observation period	0.1896			
	- Group	<.0001			

PT: Platelet transfusion.

Table 14: summary of duration of increase in platelet count >= 70,000/uL (FAS)

		S-888711 3 mg		Placebo	
		With PT	Without PT	With PT	Without PT
Summary statistics	n	10	38	40	7
	Mean	2.3	8.2	0.2	2.3
	SD	3.4	6.8	0.5	5.4
	Min	0.0	0.0	0.0	0.0
	Median	0.3	7.7	0.0	0.0
	Max	8.6	26.2	2.0	14.4
Parameter estimates	LS mean (SE)	2.53 (1.44)	8.17 (0.75)	0.56 (0.73)	1.14 (1.75)
Treatment comparisons	vs. S-888711 3 mg without PT				
	- Difference of LS mean (SE)	---		7.61 (1.05)	7.02 (1.89)
	- 95% confidence interval	---		5.52, 9.69	3.27, 10.78
	- P value	---		<.0001	0.0004
P value for test of fixed effect	- Planned surgery	0.2804			
	- Baseline platelet count	0.0328			
	- Observation period	0.1044			
	- Group	<.0001			

PT: Platelet transfusion.

Time Course of Platelet Count

The mean (range) maximum platelet count in patients without platelet transfusion was 9.02 (5.9 to 14.5) × 10^4/μL and the mean (range) time to reach the maximum platelet count was 13.4 days (6 to 28 days) in the 3-mg group. The mean maximum platelet count in patients with platelet transfusion was 6.85 × 10^4/μL in the 3-mg group and 5.28 × 10^4/μL in the placebo group.

The mean changes in platelet count were 1.67 × 104/μL immediately after transfusion (on the day of transfusion), 1.34 × 10^4/μL 1 day after transfusion, and 0.70 × 10^4/μL 2 days after transfusion in the placebo group; increments in platelet count after transfusion were small and short in duration. All the 10 patients who were withdrawn from the study treatment (8 in the 3-mg group and 2 in the placebo group) met the criteria for withdrawal (platelet count ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline). The maximum platelet count in these patients was 14.0 × 10^4/μL in the 3-mg group and 7.3 × 10^4/μL in the placebo group, indicating no excessive increase.

Table 15: Summary of maximum platelet count and maximum increase from bseline in platelet count (*10^4/uL) (FAS)

	Statistic	S-888711 3 mg		Placebo	
		With PT	Without PT	With PT	Without PT
Maximum platelet count	n	10	38	41	7
	Mean	6.85	9.02	5.28	6.67
	SD	1.61	2.21	1.08	1.68
	Min	4.6	5.9	2.9	5.5
	Median	6.80	8.70	5.20	6.20
	Max	9.6	14.5	7.5	10.2
Maximum increase from baseline in platelet count	n	10	38	41	7
	Mean	3.02	4.86	1.37	2.20
	SD	1.49	2.12	0.91	1.63
	Min	1.7	1.2	0.0	0.9
	Median	2.75	4.60	1.20	1.30
	Max	6.6	10.2	3.3	5.5
The time (day) to reach the maximum platelet count	n	---	38	---	7
	Mean	---	13.4	---	17.0
	SD	---	3.8	---	12.8
	Min	---	6	---	5
	Median	---	14.0	---	10.0
	Max	---	28	---	35

PT: Platelet transfusion

1/1

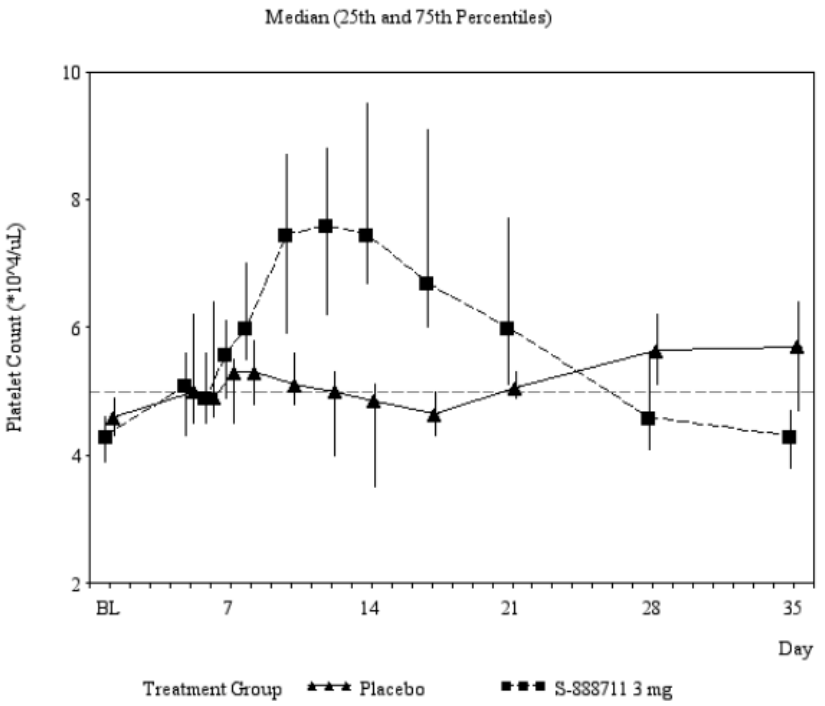


Figure 9: median (25th and 75th percentiles) platelet count in patients without platelet transfusion

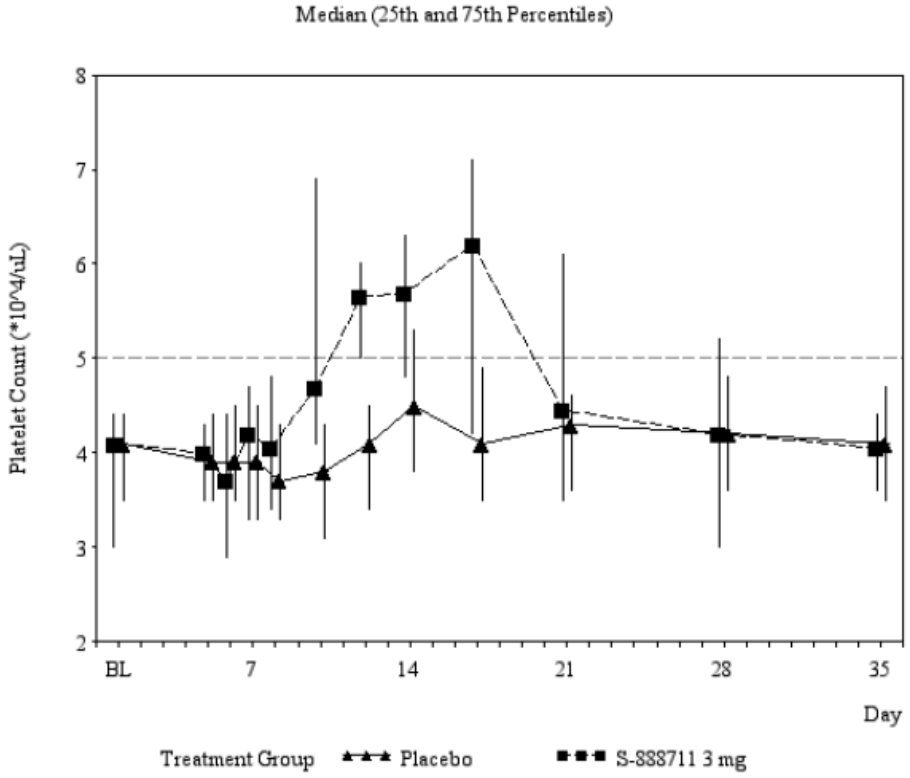


Figure 10: median (25th and 75% percentiles) platelet counts in patients with platelet transfusion

Study M0634

Study participants

Inclusion Criteria

Each subject was to meet the following criteria to be eligible for the study:

1. Able to understand the study and comply with all the study procedures

2. Willing to provide written informed consent prior to screening

3. Male or female

4. Eighteen years of age or older at the time of signing informed consent

5. CLD limited to Child-Pugh class A and class B disease

6. Platelet count < 50 × 10^9/L at baseline on Day 1 prior to randomization

7. Undergoing an elective invasive procedure that: was likely to require administration of platelets, was expected to be performed between Days 9 and 14, did not include laparotomy, thoracotomy, craniotomy, open-heart surgery, or organ resection, did not include partial organ resection.

8. Eastern Cooperative Oncology Group (ECOG) performance status (PS) grade of 0 or 1

9. In the opinion of the investigator, was able to meet the requirements of the study

10. Male subjects who were sterile or who agreed to use an appropriate method of contraception (including use of a condom with spermicide) from screening to completion of the posttreatment period

11. Female subjects who were not postmenopausal or surgically sterile had to agree to use a highly effective contraception (including contraceptive implant, injectable contraceptive, combination hormonal contraceptive [including vaginal rings], intrauterine contraceptive device, or vasectomized partner) from screening to completion of the posttreatment period. Barrier method with or without spermicide, double-barrier contraception and oral contraceptive pill were insufficient methods on their own

Exclusion Criteria

Subjects who met any of the following criteria were to be excluded from the study:

1. Any of the following diseases: hematopoietic tumour, aplastic anaemia, myelodysplastic syndrome, myelofibrosis, congenital thrombocytopenia, drug-induced thrombocytopenia, generalized infection requiring treatment except for viral liver disease, immune thrombocytopenia

2. Any solid malignant tumour if: the subject required systemic chemotherapy or radiotherapy for that malignant tumour during the study, the malignant tumour was associated with nodal metastasis, distant metastasis, or invasion of the surrounding organs.

3. History of splenectomy

4. History of liver transplantation

5. Any of the following at screening: hepatic encephalopathy uncontrolled by drugs, ascites uncontrolled by drugs

6. Portal vein tumor embolism

7. Known to be positive for the human immunodeficiency virus

8. Past or present thrombosis or prothrombotic condition (eg, cerebral infarction, myocardial infarction, angina pectoris, coronary artery stent placement, angioplasty, coronary artery bypass grafting, congestive heart failure [New York Heart Association Grade III/IV], arrhythmia known to increase the risk of thromboembolic events [eg, atrial fibrillation], pulmonary thromboembolism, deep vein thrombosis, or disseminated intravascular coagulation syndrome)

9. History or presence of any of the following diseases: cCongenital thrombotic disease (eg, antithrombin deficiency, protein C deficiency, protein S deficiency, or coagulation factor [Factor V Leiden] mutation), acquired thrombotic disease (eg, antiphospholipid antibody syndrome, paroxysmal nocturnal hemoglobinuria, hyperhomocysteinemia, or increased factor VIII), budd-Chiari syndrome

10. Portal vein thrombosis based on ultrasound, computed tomography (CT), or magnetic resonance imaging (MRI) within 28 days prior to randomization or a history of portal vein thrombosis

11. Absence of hepatopetal blood flow in the main trunk of the portal vein as demonstrated by Doppler ultrasonography within 28 days prior to randomization

12. Untreated gastro-oesophageal varices that were bleeding or required treatment based on upper gastrointestinal endoscopy within 180 days prior to randomization (except for subjects in whom the primary invasive procedure was for the treatment of gastro-oesophageal varices)

13. History or presence of disease associated with a risk of bleeding (eg, coagulation factor deficiency or von Willebrand factor deficiency)

14. Bleeding score at randomization $\geqslant$ Grade 2 according to the World Health Organization (WHO) Bleeding Scale

15. Any of the following drugs or therapies within 90 days prior to randomization: anticancer drugs except for transcatheter arterial chemoembolization (TACE) and lipiodolization, interferon preparations, radiation therapy, exsanguination, other TPO receptor agonist, any investigational agent

16. Any of the following invasive procedures within 90 days prior to randomization:

- Laparotomy, thoracotomy, craniotomy, or open-heart surgery
- Procedures involving any organ resection or any partial organ resection (tissue resection associated with an endoscopic examination was permitted)
- Partial splenic embolization

17. Any invasive procedure (except for the treatment of gastro-oesophageal varices) within 14 days prior to randomization

18. Blood transfusion (except for red blood cell products and albumin preparations) within 14 days prior to randomization

19. Subjects who had received lusutrombopag before

20. Pregnant or lactating females

21. Subjects with known or suspected ongoing, active alcohol or substance abuse; subjects with a recent history who the investigator felt were able to comply with the study procedures and medications were allowed to participate

22. Considered ineligible by the investigator for any other reason

Treatments

A 3-mg tablet of lusutrombopag or a matching placebo tablet was to be administered orally once daily. Study drug was to be administered for up to 7 days. Administration of the study drug on Day 2 was to be performed ≥ 12 hours after administration on Day 1.

On subsequent days, study drug was to be administered at the same time of the day to the extent possible. On Days 5, 6, and 7, the platelet count was to be measured before administration of study drug; if a subject met the administration stopping criterion (ie, platelet count ≥ 50 × 109/L with an increase of ≥ 20 × 109/L from baseline), no additional dose of study drug was to be administered.

Invasive Procedure

The planned invasive procedure was to be performed in the posttreatment period between Days 9 and 14. The need for the invasive procedure was to be reassessed in the event of the following:

- Platelet count ≥ 200 × 109/L
- Administration of an antithrombotic drug
- In the opinion of the investigator, the procedure was no longer in the subject's best interest because of an AE or other concern
- The subject requested cancellation of the invasive procedure after randomization

If any of the above criteria was met and the invasive procedure could not be performed between Days 9 and 14, it was permitted to be performed up to Day 35. If a subject did not undergo a procedure, all relevant follow-up assessments were to be performed and data collected up to Day 35. If the invasive procedure performed between Days 9 and 14 needed to be repeated, the same procedure could be performed after Day 15 at the discretion of the investigator.

Objectives

Primary Objective

To compare the efficacy of S-888711 with placebo for the treatment of thrombocytopenia in subjects with CLD who are undergoing elective invasive procedures.

Secondary Objectives

- To assess the safety and tolerability of S-888711 treatment compared with placebo
- To assess the platelet response following treatment with S-888711 compared with placebo
- To assess the pharmacodynamics (PD) and PK of S-888711

Outcomes/endpoints

Primary endpoint:

The primary endpoint was the proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure.

Secondary endpoints:

- Proportion of Subjects Who Required No Platelet Transfusion During the Study
- Proportion of Responders (A responder was defined as a subject who achieved a platelet count of ≥ 50 × 109/L with an increase of ≥ 20 × 109/L from baseline at any time during the study.)
- Duration of the Increase in Platelet Count
- Proportion of Subjects who Required Rescue Therapy
- Frequency of Platelet Transfusion and Dose Transfused During the Study
- Time Course of Platelet Count

Sample size

Two hundred subjects with CLD and thrombocytopenia who were scheduled to undergo elective invasive procedures were planned to be randomized to either of 2 treatment groups (100 subjects per group).

In the Phase 3 study (Study M0631) conducted in Japan, the proportion of subjects who required no platelet transfusion prior to the primary invasive procedure was 79.2% in the lusutrombopag 3-mg dose group and 12.5% in the placebo group. The difference in the proportion of subjects was 66.7% (95% CI: 51.9%, 81.5%). Based on these results, a target of a 50% difference between the lusutrombopag and placebo groups was selected for the current study. Assuming that the proportion of subjects who met the primary endpoint was 20% in the placebo group and 70% in the lusutrombopag group, 100 subjects per group provided 99% power to detect a difference of 50% between lusutrombopag and placebo groups at a 2-sided significance level of 0.05. For the safety analysis, 100 subjects per group assured that there was at least a 95% probability of detecting AEs with an incidence of 3% or more.subjects per group).

Randomisation

Method of Assigning Subjects to Treatment Groups

Subjects were to be randomized in a 1:1 ratio to receive either lusutrombopag 3 mg or placebo using the

IVRS/IWRS. Randomization was stratified by the primary invasive procedure and the platelet count at baseline as follows:

- Primary invasive procedure: liver ablation/coagulation or other invasive procedures
- Platelet count at baseline: < 35 × 109/L or ≥ 35 × 109/L

Blinding (masking)

The study was to be conducted in a double-blind manner using a placebo matching the active drug in appearance, labelling, and packaging. An IVRS/IWRS was to be used for central subject randomization and study drug assignment. The IVRS/IWRS was to assign study drug identifiers according to a randomization schedule. The randomization scheme and medication identification (Card No.) number schedule were generated by the IVRS/IWRS vendor.
All subjects, the investigator, and study site and Shionogi personnel were to be blinded to the treatment assigned at randomization until database lock. The randomization schedule was to be kept confidential and was not to be accessible to anyone until unblinding, except for the sponsor's drug supply management staff, IVRS/IWRS clinical coordinator(s), IVRS/IWRS vendor staff, unblinded statisticians on the DSMB, and Drug Safety personnel reporting suspected unexpected serious adverse reactions, as required by local regulation.
Unblinding at the investigator's request was to occur only in the event of an emergency or an AE where details of the treatment assigned were required to determine an appropriate course of therapy. Prior to unblinding, and if the situation allowed it, the investigator was to contact the sponsor in order to obtain additional information about the investigational product. If this was impractical, the investigator or qualified designee was to follow the process for obtaining the treatment assignment from the IVRS/IWRS system, and was to notify the sponsor of the unblinding as soon as possible without revealing the treatment assignment of that subject. The investigator was to document the subject identification number and the date and time of breaking the blind, as well as the reason the blind was broken.
Since treatment assignment could have been determined from plasma drug concentrations, these data were to be reported to the sponsor after database lock.

Statistical methods

Analysis Populations

- Intention-to-treat (ITT) Population: includes all randomized subjects. Subjects were analyzed according to the treatment to which they were randomized. This population was the primary population for the analysis of efficacy.
- Per-protocol (PP) Population: includes all randomized subjects who had nomajor protocol deviations pertaining to the efficacy evaluation. Deviations weredetermined prior to unblinding of the study data. This population was used in asensitivity analysis of the primary endpoint.
- Safety Population: includes all randomized subjects who received at least 1 dose of the study drug. This population was analyzed according to the treatment that subjects actually received, rather than the treatment to which they were randomized. This population was the primary population for the analysis of safety.

Primary Endpoint Analysis

The number and proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from the date of randomization through 7 days after the primary invasive procedure were summarized by treatment group, along with 95% confidence intervals

(CIs) calculated using the Clopper-Pearson method. The treatment groups were compared using the Cochran-Mantel-Haenszel (CMH) test, adjusted using the stratification factors of platelet count at randomization (< 35 × 109/L, ⩾ 35 × 109/L) and the planned primary invasive procedure (liver ablation/coagulation, other invasive procedure).
Differences in the primary endpoint and 95% CIs were also calculated using the Wald method.

Secondary Endpoint Analysis

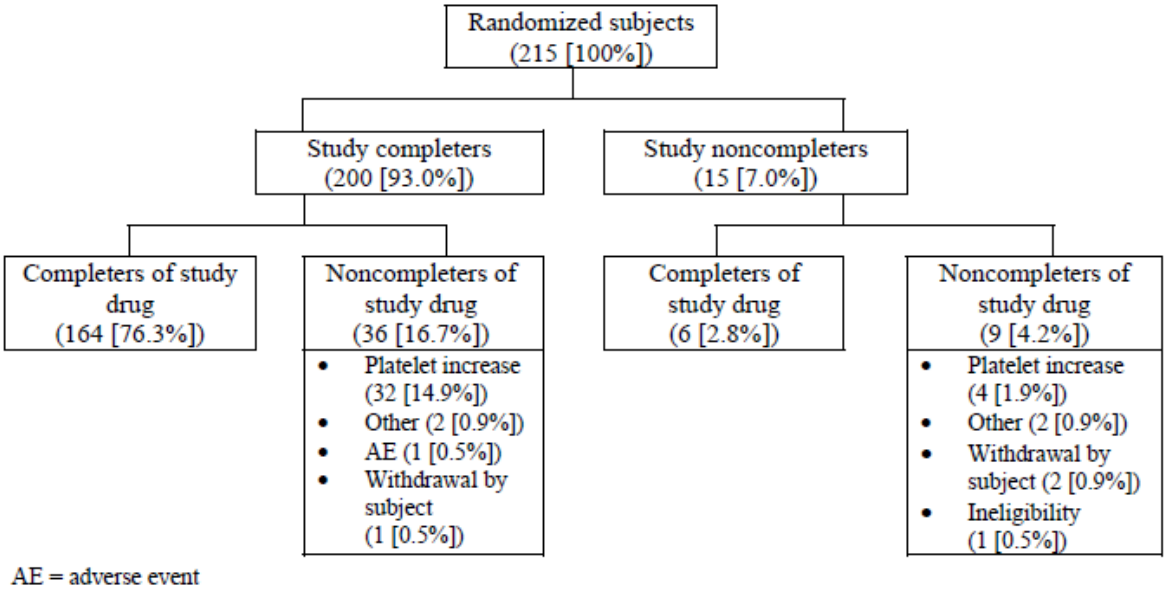
A gatekeeping procedure was employed for sequentially testing the important secondary endpoints, identified as the most clinically relevant endpoints. If the primary endpoint was statistically significant, the secondary endpoints were tested at the 0.05 level (2-sided) in sequence. Sequential testing for the secondary endpoints was conducted in the following order:

- The comparison between lusutrombopag and placebo of the number and proportion of subjects who required no platelet transfusion during the study (using the CMH test adjusted by the stratification factors)
- The comparison between lusutrombopag and placebo of the number and proportion of responders: subjects who achieved a platelet count of ⩾ 50 × 109/L, with an increase of ⩾ 20 × 109/L from baseline at any time during the study (using the CMH test adjusted by the stratification factors)
- The comparison between lusutrombopag and placebo of the duration of platelet count ⩾ 50 × 109/L (using the van Elteren test stratified with platelet transfusion during the study)
- The comparison between lusutrombopag without platelet transfusion and placebo with platelet transfusion of the duration of platelet count ⩾ 50 × 109/L (using the Wilcoxon rank sum test)

Results

Participant flow

Figure 11: disposition of subjects (all randomized subjects)



AE = adverse event

Subject disposition (all randomized subjects)

Disposition	Lusutrombopag 3 mg N = 108	Placebo N = 107	Overall N = 215
Subjects who completed the study [a]	98 (90.7)	102 (95.3)	200 (93.0)
Subjects who discontinued in the treatment period	1 (0.9)	1 (0.9)	2 (0.9)
Withdrawal by subject	1	1	2 [b]
Subjects who discontinued in the posttreatment period	9 (8.3)	4 (3.7)	13 (6.0)
Adverse event	3	1	4 [c]
Withdrawal by subject	3	2	5 [d]
Lost to follow up	1	1	2 [e]
Other	2	0	2 [f]

[a] Defined as completing both the treatment period and the posttreatment period.

[b] Subject in the lusutrombopag group and Subject 8KN001 in the placebo group.

[c] Subjects in the lusutrombopag group and Subject 8CG003 in the placebo group.

[d] Subjects in the lusutrombopag group and Subjects 8CG001 and 8HA002 in the placebo group.

[e] Subject in the lusutrombopag group and Subject 8EC013 in the placebo group.

[f] Subjects and in the lusutrombopag group.

Recruitment

15 Jun 2015 (first subject informed consent) and 19 Apr 2017 (last subject last observation)

Conduct of the study

Protocol Amendments

The study protocol was amended once, prior to submission to any IRBs/IECs and prior to enrollment of the first subject in the study.

Protocol Deviations

Table 10-2 Subjects Excluded from the Per-protocol Population (All Randomized Subjects)

Category of Exclusion	Primary Reason for Exclusion	Number of Subjects (%)		
		Lusutrombopag 3 mg N = 108	Placebo N = 107	Overall N = 215
Efficacy criteria	Noncompliance with preprocedure platelet transfusion instructions	8 (7.4) [a]	10 (9.3) [a]	18 (8.4) [a]
	Out of window of preprocedure platelet transfusion assessment	2 (1.9)	3 (2.8)	5 (2.3)
IMP compliance	Poor study drug administration: subject received less than 5 days of study drug but did not fulfill the stopping criterion for study drug	1 (0.9)	0	1 (0.5)
	No study drug administration	1 (0.9)	0	1 (0.5)
Eligibility and entry criteria	Child-Pugh class C	3 (2.8)	0	3 (1.4)
	Received other TPO receptor agonist	1 (0.9)	0	1 (0.5)
	Platelet count $> 50 \times 10^9$/L at baseline on Day 1 prior to randomization	1 (0.9)	1 (0.9)	2 (0.9)
Concomitant medication	Use of prohibited concomitant medications and therapies	0	4 (3.7)	4 (1.9)
Total number of excluded subjects [b]		17 (15.7)	18 (16.8)	35 (16.3)

IMP = investigational medicinal product; TPO = thrombopoietin

[a] Noncompliance with preprocedure platelet transfusion instructions includes 5 subjects in the lusutrombopag group, but 0 subjects in the placebo group who received a platelet transfusion but should not have and 3 subjects in the lusutrombopag group and 10 subjects in the placebo group who did not receive a platelet transfusion but should have.

[b] Subjects with more than 1 reason for exclusion from the PP Population were allocated a primary reason during the blind data review meeting.

Baseline data

Demographic and baseline characteristics (ITT population)

		Lusutrombopag 3 mg N = 108	Placebo N = 107	Overall N = 215
Sex (n [%])	Male	65 (60.2)	69 (64.5)	134 (62.3)
	Female	43 (39.8)	38 (35.5)	81 (37.7)
Age (years)	n	108	107	215
	Mean (SD)	55.2 (11.6)	56.1 (11.0)	55.7 (11.3)
	Range	19 to 81	19 to 83	19 to 83
Height (cm)	n	108	106	214
	Mean (SD)	168.32 (9.80)	168.29 (10.47)	168.31 (10.11)
	Range	146.0 to 193.0	142.2 to 189.0	142.2 to 193.0
	Missing (n [%])	0	1 (0.9)	1 (0.5)
Weight (kg)	n	108	106	214
	Mean (SD)	77.86 (17.77)	78.53 (19.22)	78.19 (18.46)
	Range	39.0 to 142.0	43.2 to 156.0	39.0 to 156.0
	Missing (n [%])	0	1 (0.9)	1 (0.5)
Ethnicity (n [%])	Hispanic or Latino	14 (13.0)	12 (11.2)	26 (12.1)
	Not Hispanic or Latino	93 (86.1)	95 (88.8)	188 (87.4)
	Unknown	1 (0.9)	0	1 (0.5)
	Not provided	0	0	0
Race (n [%])	American Indian or Alaska Native	2 (1.9)	0	2 (0.9)
	Asian	15 (13.9)	17 (15.9)	32 (14.9)
	Black or African American	1 (0.9)	0	1 (0.5)
	Native Hawaiian or Other Pacific Islander	0	0	0
	White	85 (78.7)	86 (80.4)	171 (79.5)

		Lusutrombopag 3 mg N = 108	Placebo N = 107	Overall N = 215
	Other	3 (2.8)	0	3 (1.4)
	Not provided	2 (1.9)	4 (3.7)	6 (2.8)
Medical history of CLD due to hepatitis B (n [%])	Yes	24 (22.2)	21 (19.6)	45 (20.9)
	No	84 (77.8)	86 (80.4)	170 (79.1)
Medical history of CLD due to hepatitis C (n [%])	Yes	51 (47.2)	51 (47.7)	102 (47.4)
	No	57 (52.8)	56 (52.3)	113 (52.6)
Medical history of CLD due to alcoholic hepatitis (n [%])	Yes	24 (22.2)	26 (24.3)	50 (23.3)
	No	84 (77.8)	81 (75.7)	165 (76.7)
Medical history of CLD due to nonalcoholic hepatitis (n [%])	Yes	12 (11.1)	15 (14.0)	27 (12.6)
	No	96 (88.9)	92 (86.0)	188 (87.4)
Medical history of CLD due to autoimmune hepatitis (n [%])	Yes	5 (4.6)	5 (4.7)	10 (4.7)
	No	103 (95.4)	102 (95.3)	205 (95.3)
History of any transfusion (n [%])	Yes	48 (44.4)	62 (57.9)	110 (51.2)
	No	60 (55.6)	45 (42.1)	105 (48.8)
Child-Pugh class (n [%])	A	72 (66.7)	63 (58.9)	135 (62.8)
	B	33 (30.6)	43 (40.2)	76 (35.3)
	C	3 (2.8)	0	3 (1.4)
	Missing	0	1 (0.9)	1 (0.5)
Planned invasive procedure (n [%])	Liver ablation/ coagulation	7 (6.5)	5 (4.7)	12 (5.6)
	Other	101 (93.5)	102 (95.3)	203 (94.4)
Baseline platelet count ($\times 10^9$/L)	n	107	106	213
	Mean (SD)	37.7 (9.0)	37.4 (7.8)	37.6 (8.4)
	Range	13 to 54	12 to 55	12 to 55
	< 35 (n [%])	36 (33.3)	38 (35.5)	74 (34.4)
	≥ 35 (n [%])	71 (65.7)	68 (63.6)	139 (64.7)
	Missing (n [%])	1 (0.9)	1 (0.9)	2 (0.9)
ECOG PS (n [%])	Grade 0	83 (76.9)	95 (88.8)	178 (82.8)
	Grade 1	25 (23.1)	12 (11.2)	37 (17.2)
Gastro-esophageal varices (n [%])	Yes	92 (85.2)	90 (84.1)	182 (84.7)
	No	15 (13.9)	14 (13.1)	29 (13.5)
	Missing	1 (0.9)	3 (2.8)	4 (1.9)
Splenomegaly (n [%])	Yes	95 (88.0)	95 (88.8)	190 (88.4)
	No	13 (12.0)	12 (11.2)	25 (11.6)
Ascites (n [%])	Yes	22 (20.4)	25 (23.4)	47 (21.9)
	No	86 (79.6)	82 (76.6)	168 (78.1)

		Lusutrombopag 3 mg N = 108	Placebo N = 107	Overall N = 215
WHO Bleeding Scale (n [%])	Grade 0	101 (93.5)	97 (90.7)	198 (92.1)
	Grade 1	6 (5.6)	10 (9.3)	16 (7.4)
	Missing	1 (0.9)	0	1 (0.5)

CLD = chronic liver disease; ECOG = Eastern Cooperative Oncology Group; PS = performance status; SD = standard deviation; WHO = World Health Organization

Primary invasive procedure (all randomised subjects)

	Lusutrombopag 3 mg N = 108	Placebo N = 107	Overall N = 215
Planned Primary Invasive Procedure			
Liver-related procedures	22 (20.4)	20 (18.7)	42 (19.5)
Percutaneous RFA/MCT	9 (8.3)	5 (4.7)	14 (6.5)
TACE	8 (7.4)	5 (4.7)	13 (6.0)
Liver biopsy	3 (2.8)	6 (5.6)	9 (4.2)
Liver-related other procedures	2 (1.9)	4 (3.7)	6 (2.8)
Gastrointestinal/endoscopy-related procedures	64 (59.3)	64 (59.8)	128 (59.5)
EVL	35 (32.4)	41 (38.3)	76 (35.3)
EIS	1 (0.9)	1 (0.9)	2 (0.9)
Gastrointestinal endoscopy (regardless of polypectomy or biopsy, except for EVL and EIS)	28 (25.9)	22 (20.6)	50 (23.3)
Other procedures	22 (20.4)	23 (21.5)	45 (20.9)
Dental extraction	14 (13.0)	16 (15.0)	30 (14.0)
Others	8 (7.4)	7 (6.5)	15 (7.0)
Performed Primary Invasive Procedure			
Liver-related procedures	20 (18.5)	20 (18.7)	40 (18.6)
Percutaneous RFA/MCT	4 (3.7)	1 (0.9)	5 (2.3)
TACE	11 (10.2)	9 (8.4)	20 (9.3)
Liver biopsy	3 (2.8)	6 (5.6)	9 (4.2)
Liver-related other procedures	2 (1.9)	4 (3.7)	6 (2.8)
Gastrointestinal/endoscopy-related procedures	61 (56.5)	60 (56.1)	121 (56.3)
EVL	32 (29.6)	29 (27.1)	61 (28.4)
EIS	1 (0.9)	1 (0.9)	2 (0.9)
Gastrointestinal endoscopy (regardless of polypectomy or biopsy, except for EVL and EIS)	28 (25.9)	30 (28.0)	58 (27.0)
Other procedures	21 (19.4)	18 (16.8)	39 (18.1)
Dental extraction	13 (12.0)	11 (10.3)	24 (11.2)
Others	8 (7.4)	7 (6.5)	15 (7.0)
Procedure not performed	6 (5.6)	9 (8.4)	15 (7.0)

EIS = endoscopic injection sclerotherapy; EVL = endoscopic variceal ligation; MCT = microwave coagulation therapy; RFA = radiofrequency ablation; TACE = transcatheter arterial chemoembolization.

Numbers analysed

Please see section Statistical Methods.

Outcomes and estimation

Summary of study drug exposure (safety population)

Duration of Exposure (Days)	Lusutrombopag 3 mg N = 107	Placebo N = 107	Overall N = 214
1	0	0	0
2	0	0	0
3	0	0	0
4	15 (14.0)	5 (4.7)	20 (9.3)
5	8 (7.5)	4 (3.7)	12 (5.6)
6	11 (10.3)	4 (3.7)	15 (7.0)
7	73 (68.2)	94 (87.9)	167 (78.0)

Primary Endpoint

The primary endpoint was the proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure.

Summary of the proportion of subjects who met the primary endpoint (ITT population)

	Lusutrombopag 3 mg N = 108	Placebo N = 107
Proportion of subjects who met the primary endpoint [a]	64.8% (70/108)	29.0% (31/107)
Exact 95% CI	(55.0, 73.8)	(20.6, 38.5)
Comparison with placebo		
Difference in proportion (95% CI)	36.7 (24.9, 48.5)	
p-value from CMH test	< 0.0001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel

[a] Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure. In addition to subjects who received platelet transfusion, subjects who did not undergo an invasive procedure regardless of the reason were considered as receiving platelet transfusion.

Summary of proportion of patients who met the primary endpoint (per protocol analysis) PP population

	S-888711 3 mg N=91	Placebo N=89
Proportion of patients who met the primary endpoint [a]	72.5% (66/91)	20.2% (18/89)
Exact 95% confidence interval	(62.2, 81.4)	(12.4, 30.1)
Comparison with placebo		
- Difference of proportion (95% confidence interval)	53.3 (42.1, 64.5)	
- P value from Cochran-Mantel-Haenszel test	<.0001	

[a] Proportion of patients who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary elective procedure. In addition to patients who received platelet transfusion, patients who did not receive an invasive procedure regardless of the reason were considered as receiving platelet transfusion.
Program :
Q:/SDD/project/s888711/m0634/production/analysis/programs/tlf/m0634_tab_14_2_1_2_s15145.sas
Output : Q:/SDD/project/s888711/m0634/production/analysis/tlf/E_SAR_M0634_TAB14_2_1_2.rtf
Generated on : 14JUL2017 00:55

Secondary endpoints

Proportion of Subjects Who Required No Platelet Transfusion During the Study

Summary of the proportion of subjects who required no platelet transfusion during the study (ITT popuation)

	Lusutrombopag 3 mg N = 108	**Placebo N = 107**
Proportion of subjects who required no platelet transfusion [a]	63.0% (68/108)	29.0% (31/107)
Exact 95% CI	(53.1, 72.1)	(20.6, 38.5)
Comparison with placebo		
Difference in proportion (95% CI)	34.8 (22.8, 46.8)	
p-value from CMH test	< 0.0001	

CI = confidence interval; CMH = Cochran-Mantel-Haenszel

[a] Proportion of subjects who required no platelet transfusion and underwent the invasive procedure during the study.

Proportion of Responders

A responder was defined as a subject who achieved a platelet count of $\geqslant 50 \times 10^9$/L with an increase of $\geqslant 20 \times 10^9$/L from baseline at any time during the study.

Duration of the Increase in Platelet Count

The duration of the increase in platelet count was defined as the number of days during which the platelet count was maintained as $\geqslant 50 \times 10^9$/L.

Summary of the duration of increase in platalet count ≥50 * 10^ 9/L (ITT population)

	Lusutrombopag 3 mg			Placebo		
	With PT N = 34	W/O PT N = 74	Total N = 108	With PT N = 73	W/O PT N = 34	Total N = 107
n	34	73	107	73	34	107
Median (25 to 75 percentile)	1.73 (0.00, 14.00)	19.21 (12.64, 28.00)	15.11 (6.59, 23.88)	0.00 (0.00, 5.04)	8.86 (0.00, 18.73)	0.98 (0.00, 9.22)
p-value	-	< 0.0001 [a]	0.0002 [b]	-	-	-

PT = platelet transfusion; W/O = without

[a] Comparison between lusutrombopag without platelet transfusion and placebo with platelet transfusion by Wilcoxon rank sum test.

[b] Comparison between lusutrombopag and placebo by van Elteren test stratified by platelet transfusion during the study.

Proportion of Subjects who Required Rescue Therapy

No subjects in the lusutrombopag group received rescue therapy for bleeding events compared to 2/107 subjects (1.9%) in the placebo group:

- one patient underwent polypectomy as the primary invasive procedure, received platelet transfusion as rescue therapy for large intestinal hemorrhage that started on Day 10.
- one patient underwent mastoidectomy plus tympanoplasty as the primary invasive procedure, received platelet transfusion and red blood cells as rescue therapy for ear hemorrhage that started on Day 12.

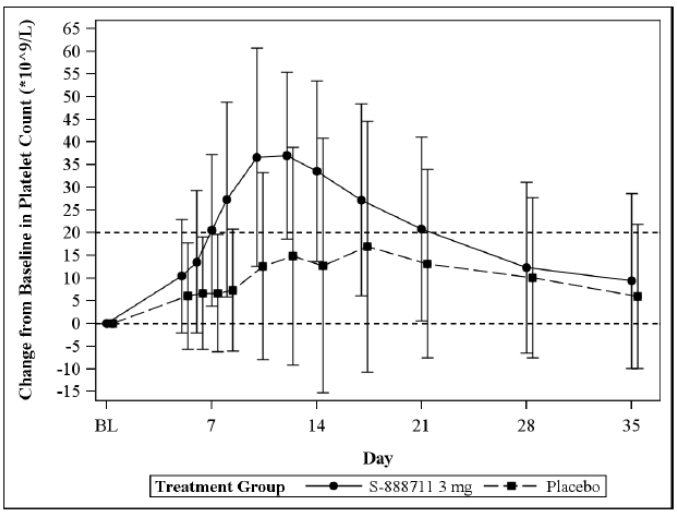
Frequency of Platelet Transfusion and Dose Transfused During the Study

Fewer subjects in the lusutrombopag group than in the placebo group received platelet transfusion during the study (34 [31.5%] vs. 73 [68.2%]).

Furthermore, in the lusutrombopag group, all of the subjects receiving platelet transfusion (n = 34) received only a single platelet transfusion. In the placebo group, 61/73 subjects received a single platelet transfusion; 12 subjects required multiple platelet transfusions, including 6 subjects who received 2 platelet transfusions , 5 subjects who received 3 platelet transfusions, and 1 subject who received 5 platelet transfusions.

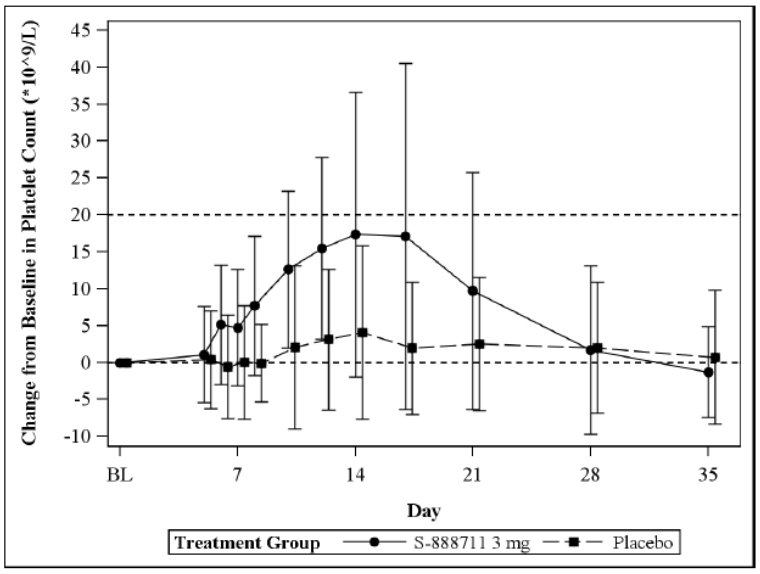
Time Course of Platelet Count

Figure 12: Mean (+/_ standard deviation) change from baseline in platelet count in subjects without platelet transfusion (ITT population)



N = 74 in the lusutrombopag group and N = 34 in the placebo group

Figure 13: Mean (+/- standr=ard deviation(change from baseline in platelet count in subjects with platelet transfusion (ITT population)



N = 34 in the lusutrombopag group and N = 73 in the placebo group

Trial M0633

Methods

The study was conducted in the following 3 groups (the A/B-1 group, the A/B-2 group, and the non-naive A/B group) (see Table 16). Patients who had received S-888711 previously were assigned to the non-naive A/B group. Patients who had not previously received S-888711 were enrolled in the A/B-1 group or the A/B-2 group. In each group, the study treatment was stopped as shown in the table below. This rule was termed “the platelet-related criteria for stopping the study treatment”. Of the A/B-1 and A/B-2 groups, the patient recruitment started with the A/B-1 group (Step 1). When the number of patients who had experienced platelet count of ⩾ 200,000/μL was less than 2 in the A/B-1 group, which consists of the target sample size of 45 patients (see Section 9.1.2), the A/B-2 group (Step 2) could be initiated.

Aside from the non-naive A/B group, patients treated in the A/B-1 group or the A/B-2 group could be retreated with S-888711 during the Post-treatment Period, provided platelet count was < 50,000/μL, an additional invasive procedure was determined to be necessary, and there was no portal vein thrombosis based on imaging evaluation performed between 3 and 10 days after the previous invasive procedure (see Section 9.4.1). The retreatment was initiated between Days 14 and 35 and continued up to 7 days with the original patient ID in the group in which the patient had been enrolled initially. The day of the initial retreatment was counted as Day 1 of the retreatment. The same study procedures followed during the Treatment Period and Post-treatment Period of the first treatment was repeated, and the additional invasive procedure was performed on Day 9 to 14 of the retreatment (the day of the initial retreatment was counted as Day 1 of the retreatment).

Table 16: Treatment groups:

Group	Step [a]	Child-Pugh Class/ History of S-888711	Method for Applying the Platelet Count-related Criteria for Stopping the Study Treatment	Target Sample Size
A/B-1	1	A or B/ No	The investigator or subinvestigator will stop the study treatment if platelet count ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline on Day 6 or if platelet count increase of > 40,000/μL from baseline on Day 5, Day 6, or Day 7.	45 [b]
A/B-2	2	A or B/ No	The investigator or subinvestigator will NOT stop the study treatment even if platelet count ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline. The investigator or subinvestigator will stop the study treatment if platelet count increase of > 40,000/μL from baseline on Day 5, Day 6, or Day 7.	45
Non-naive A/B	—	A or B/ Yes	The investigator or subinvestigator will stop the study treatment if platelet count ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline on Day 3, Day 5, Day 6, or Day 7 or if platelet count increase of > 40,000/μL from baseline on Day 3, Day 5, Day 6, or Day 7.	5

[a] Regarding the rule of proceeding to the next step, see Section 9.1.2.

[b] The need of additional patient recruitment was considered based on discussions with the independent safety committee and the medical officer in cases in which no proceeding to the next step was determined after completing the patient recruitment of the A/B-1 group or data of the A/B-1 group was determined not to meet the criterion for proceeding to the next step during the patient recruitment of the A/B-1 group.

The stopping criterion was applied on Day 6 only in Group A/B-1;

- not at all in the Group A/B-2 in which subjects were treated for a fixed 7 days;
- and on Days 3, 5, 6, and 7 in non-naive Group A/B.

In addition, study treatment was to be stopped if a platelet count increase of > 40,000/μL from baseline was observed on Days 5, 6, or 7 in Groups A/B-1 and A/B-2 or on Days 3, 5, 6 , or 7 in the non-naive Group A/B.

Study participants

Inclusion Criteria

Each patient had to meet the following criteria to be eligible for the study:

1. Patients who were able to understand the study and comply with all study procedures, and were willing to provide written informed consent prior to screening

2. Male or female patients aged 20 years or older at the time of signing the informed consent form

3. Thrombocytopenic patients due to CLD

4. Patients with a platelet count of < 50,000/μL at screening

5. Patients undergoing invasive procedures fulfilling the following criteria:

   – procedures expected to be completed between 9 and 14 days after the initiation of the study

treatment

- procedures which did not include any of the following: laparotomy, thoracotomy, craniotomy, open-heart surgery, organ resection, or partial organ resection (except for procedures comparable to tissue resection)

6. Patients with the Eastern Cooperative Oncology Group (ECOG) performance status grade 0 or 1

7. Patients who were able to stay in the hospital between the day before the invasive procedure and the 14 days after the initiation of the study treatment

8. Only for male patients, patients who were sterile or who agreed to use an appropriate method of contraception (including use of a condom with spermaticide) from enrolment until 3 months after the last dose of study drug

9. Only for female patients, patients who agreed to use the following contraception measures from enrolment until 3 months after the last dose of study drug except for female patients who were postmenopausal or who were surgically sterile: combined (oestrogen and progestogen containing) oral hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone releasing system, bilateral tubal occlusion, vasectomised partner, or sexual abstinence

Exclusion Criteria

Patients who met any of the following criteria were excluded from the study:

1. Patients with any of the following diseases: hematopoietic tumour, aplastic anaemia, myelodysplastic syndrome, myelofibrosis, congenital thrombocytopenia, drug-induced thrombocytopenia, generalized infection requiring treatment except for viral liver disease, immune thrombocytopenia

2. Patients with any of the following concomitant malignant tumours other than the treatment target of the primary invasive procedure in the study: malignant tumours which are not included in the categories of skin cancer (except for melanoma), intramucosal cancer, or carcinoma in situ, malignant tumours involving nodal metastasis, distant metastasis, invasion to the surrounding organ, malignant tumours requiring any treatment during the study

3. Patients who had undergone liver transplantation

4. Patients with any of the following at the screening examination: severe hepatic impairment (Child-Pugh class C), uncontrollable hepatic encephalopathy with drugs, uncontrollable ascites with drugs

5. Patients with portal vein tumour embolism

6. Patients with past or present thrombosis (eg, cerebral infarction, myocardial infarction, angina pectoris, pulmonary thromboembolism, deep vein thrombosis, disseminated intravascular coagulation syndrome)

7. Patients with a complication or with a history of any of the following diseases: congenital thrombotic disease (eg, antithrombin deficiency, protein C deficiency, protein S deficiency, coagulation factor [Factor V Leiden] mutation), acquired thrombotic disease (eg, antiphospholipid antibody syndrome, paroxysmal nocturnal haemoglobinuria, hyperhomocysteinemia, increased factor VIII), Budd-Chiari syndrome

8. Patients with portal vein thrombosis based on ultrasonography or imaging evaluation within 28 days prior to enrolment or with a history of portal vein thrombosis

9. Patients for whom no hepatopetal portal blood flow was demonstrated by Doppler ultrasonography within 28 days prior to enrolment

10. Patients who required antithrombotic drugs within 14 days prior to enrolment and thereafter

11. Patients with untreated gastroesophageal varices which were bleeding or found to require treatment based on upper gastrointestinal endoscopy within 180 days prior to enrolment (except for patients in whom the primary invasive procedure was for the treatment of gastroesophageal varices)

12. Patients with a complication or with a history of disease associated with a risk of bleeding (eg, coagulation factor deficiency, von Willebrand factor deficiency)

13. Patients with Grade 2 or more severe bleeding at screening according to the World Health Organization (WHO) Bleeding scale

14. Patients who had received any of the following drugs or therapies within 90 days prior to enrolment:

- anticancer drugs except for transcatheter arterial chemoembolization (TACE) and lipiodolization
- interferon preparations
- radiation therapy
- exsanguination

15. Patients who had received any of the following invasive procedures within 90 days prior to enrolment:

- procedures involving laparotomy, thoracotomy, craniotomy, or open-heart surgery
- procedures involving any organ resection or any partial organ resection
- partial splenic embolization

16. Patients who had received any invasive procedures (except for the treatment of gastroesophageal varices) within 14 days prior to enrolment

17. Patients who had received blood transfusions (except for red blood cell preparations and albumin preparations) within 14 days prior to enrolment

18. Female patients who were pregnant, possibly pregnant, or lactating

19. Patients who had received other investigational products within 90 days prior to enrolment

20. Patients who were considered ineligible for the study by the investigator or sub-investigator for any other reasons

Treatments

A 3-mg tablet of S-888711 was administered orally once daily. The duration of the study treatment was up to 7 days (Day 1 to 7). Administration of the study drug on Day 2 was performed at 12 hours or longer after administration on Day 1. The study drugs were administered at the same time of the days between Days 2 and 7 to the extent possible.

Rescue Therapy

The use of the following therapies was permitted only with the following restrictions.

- Platelet preparation

Platelet preparation was permitted only when bleeding-related AEs occurred regardless of platelet count.

- Antithrombotic

Antithrombotic drugs were allowed to be administered only when a platelet count was ⩾ 200,000/μL or thrombus formation was highly suspected.

Invasive Procedure

Planned invasive procedure was performed between Days 9 and 14. If patients met any of the following criteria, the need for the invasive procedure was re-assessed to ensure the safety of the patient:

1. Platelet count reached ⩾ 200,000/μL.

2. Antithrombotic drug was administered.

3. AEs, which led the investigator or sub-investigator to consider that the procedure should not be performed, occurred.

4. Other problems, which led the investigator or sub-investigator to consider that the procedure should not be performed, occurred.

5. A patient requested to cancel the procedure after the start of the study.

If the invasive procedure was not performed between Days 9 and 14 because any of criteria 1 to 4 above were met and the need for the additional invasive procedure was determined after Day 15, the procedure was allowed to be performed after Day 15. The additional invasive procedure was limited to the same primary invasive procedures as initially allowed.

In the patient retreated with S-888711 during the Post-treatment Period, the additional invasive procedure was performed between Days 9 and 14 of the retreatment.

Determination of the Need for Pre-operative Platelet Transfusion

The need for preoperative platelet transfusion prior to the initial invasive procedure (ie, the primary invasive procedure in the study for the patient) was determined based on platelet count measured after Day 8 and immediately before performing the invasive procedure (ie, within 2 days before the day of the invasive procedure). Preoperative platelet transfusion was performed only when the platelet count was < 50,000/μL. If patients retreated with S-888711 during the Post treatment Period underwent an additional invasive procedure, the need for preoperative platelet transfusion similarly was determined based on platelet count measured after Day 8 of the retreatment and immediately before performing the invasive procedure (ie, within 2 days before the day of the invasive procedure).

Objectives

Primary Objective

To assess the significance of platelet count measurement during administration of S-888711 to thrombocytopenic patients with CLD receiving S-888711 as a pre-treatment of invasive procedures

Secondary Objectives

- To evaluate the safety, PK, and efficacy of S-888711 in thrombocytopenic patients with CLD receiving S-888711 as a pre-treatment of invasive procedures
- To evaluate the safety, PK, and efficacy of S-888711 in thrombocytopenic patients with CLD receiving S-888711 among patients who have previously received S-888711

Outcomes/endpoints

Efficacy Variable

The efficacy endpoints were the proportion of patients who required no platelet transfusion:

- Proportion of Patients who Required No Platelet Transfusion Prior to the Initial Invasive Procedure
- Proportion of Patients who Required No Platelet Transfusion until 7 Days after the Primary

Invasive Procedure,

- Proportion of Patients who Required No Platelet Transfusion During the Study

Responder rate (ie, the proportion of patients for whom the platelet count reached ⩾ 50,000/μL with an increase of ⩾ 20,000/μL from baseline),

Duration of the increase in platelet count,

Time course of platelet count and frequency of platelet transfusion and

Dose (unit) transfused.

Sample size

The primary objective of the study was to assess the frequency of platelet count measurement during administration of S-888711, that is, to assess the time point of platelet count measurement when the withdrawal criterion (platelet count ⩾ 50,000/μL with an increase of ⩾ 20,000/μL from baseline during the study treatment) should be applied. The confirmatory phase 3 study (1304M0631) was conducted under the study treatment using the withdrawal criterion based on platelet counts measured on Day 5 to 7 in patients with Child-Pugh class A or B. The target sample size of Study 1304M0631 was 45 patients per group. Therefore, the target sample size of 45 patients per group (90 patients in total of A/B-1 and A/B-2 groups) is needed to assess the efficacy and the safety with the same precision as Study 1304M0631. In addition, for patients with Child-Pugh class A or B who have previously received S-888711, the target sample size of 5 patients was considered feasible.

Table 17: Summary of proportion of responders by time point (FAS)

Time Point	A/B-1 N=47	A/B-2 N=47	Non-naive A/B N=8
Day 3	---	---	0.0% (0/8)
Day 5	8.5% (4/47)	4.3% (2/46)	0.0% (0/8)
Day 6	6.4% (3/47)	8.5% (4/47)	0.0% (0/8)
Day 7	21.3% (10/47)	19.1% (9/47)	0.0% (0/8)
Day 8	44.7% (21/47)	38.3% (18/47)	37.5% (3/8)
Day 10	61.7% (29/47)	66.0% (31/47)	62.5% (5/8)
Day 12	76.6% (36/47)	74.5% (35/47)	75.0% (6/8)
Day 14	71.7% (33/46)	78.7% (37/47)	75.0% (6/8)
Day 17	60.9% (28/46)	63.0% (29/46)	37.5% (3/8)
Day 21	52.2% (24/46)	54.3% (25/46)	50.0% (4/8)
Day 28	13.0% (6/46)	10.9% (5/46)	12.5% (1/8)
Day 35	4.4% (2/45)	4.3% (2/46)	0.0% (0/8)

The responder is defined as the patient whose platelet count achieved >=50,000/uL and increased >=20,000/uL from baseline.
The patient with platelet transfusion is considered as non-responder at the time point after the first platelet transfusion.

Randomisation

The study was conducted in the following 3 groups (the A/B-1 group, the A/B-2 group, and the non-naive A/B group) (see Table 16). Patients who had received S-888711 previously were assigned to the non-naive A/B group. Patients who had not previously received S-888711 were enrolled in the A/B-1 group or the A/B-2 group. In each group, the study treatment was stopped as shown in the table below. This rule was termed “the platelet-related criteria for stopping the study treatment”. Of the A/B-1 and A/B-2 groups, the patient recruitment started with the A/B-1 group (Step 1). When the number of patients who had experienced platelet count of ⩾ 200,000/μL was less than 2 in the A/B-1 group, which consists of the target sample size of 45 patients (see Section 9.1.2), the A/B-2 group (Step 2) could be initiated.

Blinding (masking)

Neither patients nor investigators were blinded towards the assigned treatment regimen.

Statistical methods

Analysis sets:

- Full analysis set (FAS) included all enrolled patients who received at least 1 study drug and had a measurement of platelet counts at baseline and at least 1 measurement of platelet counts after the initiation of study drug administration.
- Safety analysis population included all patients who received at least 1 dose of the study drug.
- PK concentration population included all patients who received at least 1 dose of S-888711 and had at least 1 measurement of plasma S-888711 concentration. This population was used for the concentration listing, calculation of summary statistics, and plasma concentration-time profile graphing.
- PK parameter population includes all patients with at least 1 pharmacokinetic parameter of S-888711 estimated appropriately. This population was used for S-888711 PK parameter listing and summary. This population was also used for the statistical analysis.

The FAS was used as the efficacy analysis population.

Efficacy Analysis:

Proportion of Patients who Required no Platelet Transfusion

The number and proportion of patients who required no platelet transfusion were summarized by treatment group, along with 95% confidence intervals (CIs) calculated using the Clopper-Pearson method. If patient was withdrawn from the study during the treatment period and did not undergo invasive procedure, the patient was to be considered as treatment failure, ie, the patient who required platelet transfusion.

Responder Rate

The number and proportion (with 95% CIs using the Clopper-Pearson method) of responders during the study and at each scheduled time point were calculated by treatment group. The patient was considered as non-responder if their platelet count met the responder criterion only after the first platelet transfusion.

Duration of the Increase in Platelet Count

The duration of the increase in platelet count was calculated based on scheduled time points. Details of the calculation are provided in the SAP (Appendix 16.1.9). Summary statistics for the duration of increased platelet count were calculated by treatment group in patients who received or did not receive platelet transfusions.

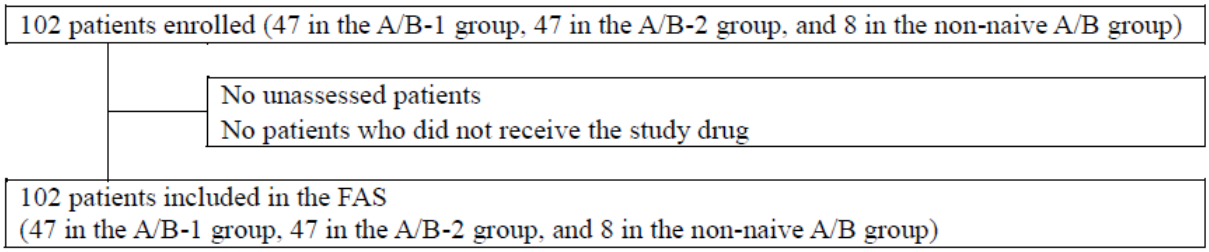
Time Course of Platelet Count

Summary statistics were provided for platelet count at each scheduled time point by treatment group. The change in platelet count from baseline, the percent change in platelet count from baseline, maximum platelet count and maximum change in platelet count for each patient were also summarized by treatment group. In addition, the number and proportion of patients with a decreased platelet count compared to baseline value at the end of the study were summarized by treatment group. For patients who required no platelet transfusion, the time point of the maximum platelet count was summarized by treatment group.

Results

Participant flow

Figure 14: efficacy analysis populations



Recruitment

16 October 2015 (date of the first subject consent) and 30 September 2016 (date of the final observation for the last patient)

Conduct of the study

Protocol Amendments

The study protocol was amended 4 times. The final protocol (5th version) was dated 20 May 2016.

Table 18: Major changes in the study protocol:

No. of Version	Amendment Date	Major Changes	Rationale
1	May 25, 2015	-	-
2	July 23, 2015	Change in a platelet count-related criterion for stopping the study treatment (ie, change in the criterion from the maximum platelet count of 200,000/μL to the maximum platelet count increase of 40,000/μL from baseline) Change in the study settings for patients with Child-Pugh class C and patients with Child-Pugh class A or B who have previously received S-888711 (ie, applying a responder criterion [platelet count of ≥ 50,000/μL with an increase of ≥ 20,000/μL from baseline] on any day during the study treatment in these groups) Adding the platelet measurement on Day 3 in patients with Child-Pugh class C	Based on discussion with the Japanese regulatory authority
3	August 26, 2015	Excluding patients with Child-Pugh class C from the study	Due to answer the request from the Japanese regulatory authority
4	March 4, 2016	Change in the planned study period (from May 2016 to July 2016)	Due to the need for recruiting planned number of patients
5	May 20, 2016	Change in the planned study period (from July 2016 to September 2016)	Due to the need for recruiting planned number of patients

Protocol Deviations

Table 19: List of major protocol deviations:

Treatment Group	Institution	Patient ID	Type[a]	Deviation
A/B-1			4	A prohibited concomitant therapy with TAI, an invasive procedure deviating from the primary invasive procedure, was performed at TACE on Day 11.
			4	Vitamin K, a restricted concomitant drug, was used at RFA on Day 11.
A/B-2			4	Vitamin K, a restricted concomitant drug, was used at additional RFA on Day 16.
			3	The patient forgot to take the study drug on Day 4.
			4	Ordamin and haptogrobin, prohibited concomitant drugs, were used for the treatment of BRTO on Day 13.
			4	A prohibited concomitant therapy with PEIT, an invasive procedure deviating from the primary invasive procedure, was performed at RFA on Day 9.
			4	Additional invasive procedure should have been performed after Day15 (if needed), but a concomitant therapy with PEIT, an invasive procedure, was performed on Day 12.
			4	Methotrexate, a prohibited concomitant drug was used for rheumatoid arthritis during study.
			4	A prohibited concomitant therapy with PEIT, an invasive procedure deviating from the primary invasive procedure, was performed at RFA on Day 13.

a 1, GCP noncompliance; 2, violation of inclusion/exclusion criteria; 3, violation of study treatment; 4, violation of prohibited/restricted concomitant drug/therapy; 5, violation of discontinuation criteria.

Baseline data

Table 20: demographic characteristics (FAS)

		A/B-1 N=47 n (%)	A/B-2 N=47 n (%)	Non-naive A/B N=8 n (%)
Sex	Male	26 (55.3)	26 (55.3)	4 (50.0)
	Female	21 (44.7)	21 (44.7)	4 (50.0)
Age (years)	n	47	47	8
	Mean	71.0	67.1	73.6
	SD	7.8	8.7	6.0
	Min	50	49	64
	Median	73.0	68.0	74.5
	Max	83	81	80
Height (cm)	n	47	47	8
	Mean	159.16	159.60	157.43
	SD	9.34	9.30	7.05
	Min	142.5	138.0	147.5
	Median	158.00	159.50	156.85
	Max	181.2	179.3	168.0
Weight (kg)	n	47	47	8
	Mean	61.05	62.95	59.49
	SD	11.17	13.31	8.96
	Min	39.5	41.1	47.8
	Median	58.60	60.70	57.15
	Max	86.5	93.4	73.7
BMI (kg/m^2)	n	47	47	8
	Mean	24.00	24.54	24.01
	SD	3.36	3.83	3.22
	Min	18.5	19.7	19.6
	Median	23.40	24.30	24.00
	Max	32.1	33.9	29.3
Ethnicity	Hispanic or Latino	0	0	0
	Not Hispanic or Latino	47 (100.0)	47 (100.0)	8 (100.0)
Race	American Indian or Alaska Native	0	0	0
	Asian	47 (100.0)	47 (100.0)	8 (100.0)
	Black or African American	0	0	0
	Native Hawaiian or Other Pacific Islander	0	0	0
	White	0	0	0
Medical history of CLD due to hepatitis B	Yes	5 (10.6)	4 (8.5)	0
	No	42 (89.4)	43 (91.5)	8 (100.0)
Medical history of CLD due to hepatitis C	Yes	31 (66.0)	32 (68.1)	4 (50.0)
	No	16 (34.0)	15 (31.9)	4 (50.0)
Medical history of CLD due to alcoholic hepatitis	Yes	10 (21.3)	4 (8.5)	3 (37.5)
	No	37 (78.7)	43 (91.5)	5 (62.5)
Medical history of CLD due to non-alcoholic hepatitis	Yes	0	6 (12.8)	0
	No	47 (100.0)	41 (87.2)	8 (100.0)
Medical history of CLD due to autoimmune hepatitis	Yes	1 (2.1)	1 (2.1)	0
	No	46 (97.9)	46 (97.9)	8 (100.0)

		A/B-1 N=47 n (%)	A/B-2 N=47 n (%)	Non-naive A/B N=8 n (%)
Medical history of CLD due to cholestatic hepatitis	Yes	0	1 (2.1)	0
	No	47 (100.0)	46 (97.9)	8 (100.0)
History of transfusion	Yes	27 (57.4)	25 (53.2)	6 (75.0)
	No	20 (42.6)	22 (46.8)	2 (25.0)
Child-Pugh grade	A	25 (53.2)	35 (74.5)	4 (50.0)
	B	22 (46.8)	12 (25.5)	4 (50.0)
Planned invasive procedure	RFA/MCT	17 (36.2)	15 (31.9)	2 (25.0)
	Other	30 (63.8)	32 (68.1)	6 (75.0)
	Not required	0	0	0
Baseline platelet count (*10^4/uL)	n	47	47	8
	Mean	3.98	3.89	3.85
	SD	0.88	0.72	0.56
	Min	2.1	2.4	3.1
	Median	4.00	3.90	3.90
	Max	5.3	5.4	4.7
	< 3.5	13 (27.7)	15 (31.9)	3 (37.5)
	>= 3.5	34 (72.3)	32 (68.1)	5 (62.5)

Table 21: Other baseline characteristics (FAS):

		A/B-1 N=47 n (%)	A/B-2 N=47 n (%)	Non-naive A/B N=8 n (%)
Performance status	Grade 0	37 (78.7)	41 (87.2)	7 (87.5)
	Grade 1	10 (21.3)	6 (12.8)	1 (12.5)
MELD score	n	47	47	8
	Mean	8.9	9.0	7.4
	SD	2.8	2.3	3.6
	Min	1	3	1
	Median	9.0	9.0	8.0
	Max	14	14	12
Gastroesophageal varix	Yes	34 (72.3)	36 (76.6)	7 (87.5)
	No	13 (27.7)	11 (23.4)	1 (12.5)
Splenomegaly	Yes	44 (93.6)	42 (89.4)	8 (100.0)
	No	3 (6.4)	5 (10.6)	0
	After splenectomy	0	0	0
Ascites	Yes	9 (19.1)	5 (10.6)	2 (25.0)
	No	38 (80.9)	42 (89.4)	6 (75.0)
WHO bleeding scale	Grade 0	39 (83.0)	43 (91.5)	8 (100.0)
	Grade 1	8 (17.0)	4 (8.5)	0
Thrombopoietin (pg/mL) at screening	n	47	47	8
	Mean	105.40	76.54	142.09
	SD	133.30	116.73	161.06
	Min	31.3	31.3	31.3
	Median	69.60	43.40	90.10
	Max	836.9	795.0	524.7

The non-naive A/B group consisted of patients who had previously received S-888711 in the following studies: 1 patient in Study 1017M0623 (at 1.5 mg), 3 patients in Study 1208M0626 (2 patients at 3 mg and 1 patient at 4 mg), 3 patients in Study 1304M0631 (at 3 mg), and 1 patient in this Study 1338M0633

(at 3 mg) (for details, see Section 11.2.1). One patient in this Study 1338M0633 was newly enrolled as a non-naive A/B patient with the different patient ID in the non-naive A/B group after the patient had completed the study in the A/B-1 group and the patient was counted in both groups.

Numbers analysed

Please see section Statistical Methods.

Outcomes and estimation

Proportion of Patients who Required No Platelet Transfusion Prior to the Initial Invasive Procedure

Table 22: summary of the proportion of patients who required no platelet transfusion prior to the invasive procedure (FAS)

	A/B-1 N=47	A/B-2 N=47	Non-naive A/B N=8
Proportion of patients who required no platelet transfusion	80.9% (38/47)	83.0% (39/47)	75.0% (6/8)
Exact 95% confidence interval	(66.7, 90.9)	(69.2, 92.4)	(34.9, 96.8)

Proportion of Patients who Required No Platelet Transfusion until 7 Days after the Primary Invasive Procedure

Table 14.2.1.2 Summary of Proportion of Patients who Required No Platelet Transfusion until for at Least 7 Days after the Primary Invasive Procedure
FAS

	A/B-1 N=47	A/B-2 N=47	Non-naive A/B N=8
Proportion of patients who required no platelet transfusion	80.9% (38/47)	83.0% (39/47)	75.0% (6/8)
Exact 95% confidence interval	(66.7, 90.9)	(69.2, 92.4)	(34.9, 96.8)
Performed invasive procedure			
- RFA/MCT	81.3% (13/16)	86.7% (13/15)	---
- Other	83.3% (25/30)	83.9% (26/31)	---
- Not required	0.0% (0/1)	0.0% (0/1)	---
Detailed performed invasive procedure			
- Percutaneous RFA/MCT	81.3% (13/16)	86.7% (13/15)	---
- Laparoscopic RFA/MCT	---	---	---
- EVL	100.0% (5/5)	88.9% (8/9)	---
- EIS	---	---	---
- TACE	72.2% (13/18)	85.7% (12/14)	---
- TAE	---	---	---
- Other	100.0% (7/7)	75.0% (6/8)	---
Baseline platelet count (*10^4/uL)			
- < 3.5	46.2% (6/13)	66.7% (10/15)	---
- >= 3.5	94.1% (32/34)	90.6% (29/32)	---
Child-Pugh grade			
- A	88.0% (22/25)	80.0% (28/35)	---
- B	72.7% (16/22)	91.7% (11/12)	---
Ascites			
- Yes	77.8% (7/9)	80.0% (4/5)	---
- No	81.6% (31/38)	83.3% (35/42)	---
MELD score [a]			
- < 9.0	88.9% (16/18)	85.7% (18/21)	---
- >= 9.0	75.9% (22/29)	80.8% (21/26)	---

[a] Median for the patients in A/B-1 and A/B-2 groups is used as the cutoff point.
The patients who discontinued the study before invasive procedure are defined as treatment failure. Therefore, they are treated as patients who required platelet transfusion.

Proportion of Patients who Required No Platelet Transfusion During the Study

The proportion of patients who required no platelet transfusion during the study was 78.7% (37/47 patients) in the A/B-1 group and 83.0% (39/47 patients) in the A/B-2 group; No meaningful difference was found between the A/B-1 and A/B-2 groups.

In the non-naive A/B group, the proportion of patients who required no platelet transfusion during the study was 75.0% (6/8 patients).

Proportion of Responders

A responder was defined as patient who achieved platelet count of ⩾ 50,000/μL with an increase of ⩾ 20,000/μL from baseline.

Table 23: summary of proportion of patients who met responder criteria at least once during the study (FAS)

	A/B-1 N=47	A/B-2 N=47	Non-naive A/B N=8
Proportion of responders	83.0% (39/47)	85.1% (40/47)	75.0% (6/8)
Exact 95% confidence interval	(69.2, 92.4)	(71.7, 93.8)	(34.9, 96.8)

The responder is defined as the patient whose platelet count achieved >=50,000/uL and increased >=20,000/uL from baseline.
The patient is considered as non-responder if the patient met the responder criteria only after platelet transfusion.

Duration of the Increase in Platelet Count

Table 24: summary of duration of increase in platelet count (FAS)

Criteria	Statistic	A/B-1		A/B-2		Non-naive A/B	
		With PT	Without PT	With PT	Without PT	With PT	Without PT
PLt >= 50,000/uL	n	9	34	7	37	2	6
	Mean	7.9	20.7	4.0	20.3	10.6	22.8
	SD	7.3	9.4	7.3	7.6	4.2	5.3
	Min	0.0	1.8	0.0	4.1	7.6	13.9
	Median	8.6	20.6	1.8	22.3	10.6	24.6
	Max	17.7	38.6	20.3	32.9	13.5	28.6
PLt >= 70,000/uL	n	9	34	7	37	2	6
	Mean	1.2	8.7	0.0	7.7	0.0	7.8
	SD	3.5	7.7	0.0	6.4	0.0	6.6
	Min	0.0	0.0	0.0	0.0	0.0	2.2
	Median	0.0	8.6	0.0	7.2	0.0	5.0
	Max	10.5	22.6	0.0	24.7	0.0	17.9
Responder criteria [a]	n	9	34	7	37	2	6
	Mean	5.1	12.8	1.2	13.3	9.8	14.3
	SD	6.7	6.8	1.1	5.8	3.4	7.2
	Min	0.0	0.0	0.0	3.7	7.4	5.9
	Median	0.6	11.6	1.0	13.1	9.8	14.3
	Max	15.1	26.6	2.9	26.0	12.2	21.4

Time Course of Platelet Count

The mean (range) maximum platelet count in patients without platelet transfusion was 9.26 (5.5 to 17.3) × 10^4/μL in the A/B-1 group and 8.54 (5.9 to 11.5) × 10^4/μL in the A/B-2 group. The mean (range) time to reach the maximum platelet count in patients without platelet transfusion was 14.53 (10.0 to 28.0) days in the A/B-1 group and 13.90 (10.0 to 28.0) days in the A/B-2 group. The mean maximum platelet count in patients with platelet transfusion was 5.97 × 10^4/μL in the A/B-1 group and 5.57 × 10^4/μL in the A/B-2 group. No meaningful difference was found between the A/B-1 and A/B-2 groups.

In the non-naive A/B group, the mean (range) maximum platelet count in patients without platelet transfusion was 8.45 (7.5 to 9.8) × 10^4/μL, the mean (range) time to reach the maximum platelet count in patients without platelet transfusion was 13.33 (12.0 to 14.0) days, and the mean maximum platelet

count in patients with platelet transfusion was 6.70 × 10^4/μL.

Table 25: summary of maximum platelet count and maximum increase from baseline in platelet count (*10^4?uL) (FAS)

	Statistic	A/B-1		A/B-2		Non-naive A/B	
		With PT	Without PT	With PT	Without PT	With PT	Without PT
Maximum platelet count	n	9	38	7	40	2	6
	Mean	5.97	9.26	5.57	8.54	6.70	8.45
	SD	1.49	2.85	0.84	1.64	0.28	1.06
	Min	4.5	5.5	4.3	5.9	6.5	7.5
	Median	5.80	8.95	5.70	8.10	6.70	8.10
	Max	9.3	17.3	7.0	11.5	6.9	9.8
Maximum increase from baseline in platelet count	n	9	38	7	40	2	6
	Mean	2.79	5.09	2.14	4.56	3.50	4.38
	SD	1.32	2.50	0.77	1.56	0.42	0.97
	Min	1.1	1.3	1.0	2.3	3.2	3.4
	Median	2.30	4.45	2.40	4.30	3.50	4.20
	Max	5.3	12.3	3.0	8.3	3.8	5.9
The time (day) to reach the maximum platelet count	n	---	38	---	40	---	6
	Mean	---	14.53	---	13.90	---	13.33
	SD	---	3.90	---	3.51	---	1.03
	Min	---	10.0	---	10.0	---	12.0
	Median	---	14.00	---	12.00	---	14.00
	Max	---	28.0	---	28.0	---	14.0

PT: Platelet transfusion.

Frequency of Platelet Transfusion and the Dose (Unit[s]) Transfused

Table 26: summary of patients with platelet transfusion (FAS)

	A/B-1 N=47 n (%)	A/B-2 N=47 n (%)	Non-naive A/B N=8 n (%)
Patients with platelet transfusion	9 (19.1)	7 (14.9)	2 (25.0)
Reason for use			
- Before invasive procedure and platelet count < 50,000/uL	9 (19.1)	7 (14.9)	2 (25.0)
- Adverse events related to bleeding	0 (0.0)	0 (0.0)	0 (0.0)
- Other	0 (0.0)	0 (0.0)	0 (0.0)
Frequency of platelet transfusion			
- 1	8 (17.0)	7 (14.9)	2 (25.0)
- 2	1 (2.1)	0 (0.0)	0 (0.0)
- 3	0 (0.0)	0 (0.0)	0 (0.0)
Average dose (unit) per platelet transfusion			
- n	9	7	2
- Mean	9.4	12.9	10.0
- SD	1.7	4.9	0.0
- Min	5	10	10
- Median	10.0	10.0	10.0
- Max	10	20	10

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27. Summary of efficacy for trial M0631

Title: A phase 3 study of S-888711 in thrombocytopenic patients with chronic liver disease		
Study identifier	**1304M0631**	
Design	A multicenter, randomized, double-blind, parallel-group, placebo-controlled study of lusutrombopag in thrombocytopenic patients with chronic liver disease as a pretreatment for invasive procedures.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment Period: 7 days, Post-treatment Period: 28 days. not applicable not applicable

Hypothesis	Superiority		
Treatments groups	Lusutrombopag		Lusutrombopag 3 mg up to 7 days; n=48
	Placebo		Placebo; n=48
Endpoints and definitions	Primary endpoint	**No Trans Proc**	Proportion of patients who required no platelet transfusion prior to invasive procedure
	Secondary endpoint	**No Trans Study**	Proportion of patients who required no platelet transfusion during the study
	Secondary endpoint	**Responder**	Proportion of Responders (a patient who achieved platelet count of ≥ 50,000/ěL with an increase of ≥ 20,000/ěL from baseline)
Database lock	<date>		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Lusutrombopag	Placebo
	Number of subject	48	48
	No Trans Proc	79.2% (38/48)	12.5% (6/48)
	95% confidence interval	65.0, 89.5	4.7, 25.2
	No Trans Study	79.2% (38/48)	12.5% (6/48)
	95% confidence interval	65.0, 89.5	4.7, 25.2
	Responder	77.1% (37/48)	6.3% (3/48)
	95% confidence interval	62.7, 88.0	1.3, 17.2
Effect estimate per	Primary	**No Trans Proc**	Lusutrombopag vs Placebo

comparison	endpoint	Relative risk	6.16
		95% confidence interval	2.92, 13.00
		P-value (CMH)	<.0001
	Secondary endpoint	**No Trans Study**	Lusutrombopag vs Placebo
		Relative risk	6.16
		95% confidence interval	2.92, 13.00
		P-value	<.0001
	Secondary endpoint	**Responder**	Lusutrombopag vs Placebo
		Relative risk	11.91
		95% confidence interval	4.00, 35.44
		P-value	<.0001

Table 28 Summary of efficacy for trial M0634

Title: A Phase 3 randomised, double-blind, placebo-controlled study to assess the safety and efficacy of S-888711 (lusutrombopag) for the treatment of thrombocytopenia in patients with chronic liver disease undergoing elective invasive procedures (L-PLUS 2)			
Study identifier	**1423M0634**		
Design	A multinational, randomized, double-blind, parallel-group, placebo-controlled study of lusutrombopag in thrombocytopenic patients with chronic liver disease undergoing elective invasive procedures.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Treatment Period: 7 days, Post-treatment Period: 28 days. not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Lusutrombopag		Lusutrombopag 3 mg up to 7 days; n=108
	Placebo		Placebo; n=107
Endpoints and definitions	Primary endpoint	**No Trans Proc No Rescue**	Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure

	Secondary endpoint	**No Trans Study**	Proportion of patients who required No platelet transfusion during the study
	Secondary endpoint	**Responder**	Proportion of Responders (a patient who achieved platelet count of ≥ 50,000/ěL with an increase of ≥ 20,000/ěL from baseline)
Database lock	<date>		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Lusutrombopag	Placebo
	Number of subject	108	107
	No Trans Proc No Rescue	64.8% (70/108)	29.0% (31/107)
	95% confidence interval	55.0, 73.8	20.6, 38.5
	No Trans Study	63.0% (68/108)	29.0% (31/107)
	95% confidence interval	53.1, 72.1	20.6, 38.5
	Responder	64.8% (70/108)	13.1% (14/107)
	95% confidence interval	55.0, 73.8	7.3, 21.0
Effect estimate per comparison	Primary endpoint	**No Trans Proc No Rescue**	Lusutrombopag vs Placebo
		Difference in proportion	36.7
		95% confidence interval	24.9, 48.5
		P-value (CMH)	< 0.0001
	Secondary endpoint	**No Trans Study**	Lusutrombopag vs Placebo

		Difference in proportion	34.8
		95% confidence interval	22.8, 46.8
		P-value	< 0.0001
	Secondary endpoint	**Responder**	Lusutrombopag vs Placebo
		Difference in proportion	52.5
		95% confidence interval	42.0, 62.9
		P-value	< 0.0001

Table 29. Summary of efficacy for trial M0633

Title: A Phase 3b Open-label Study of S-888711 in Thrombocytopenic Patients with Chronic Liver Disease		
Study identifier	**1338M0633**	
Design	A multicenter, open-label study in patients with thrombocytopenia and chronic liver disease undergoing elective invasive procedures.	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Treatment Period: 7 days, Post-treatment Period: 28 days. not applicable not applicable
Hypothesis	Primary Objective To assess the significance of platelet count measurement during administration of lusutrombopag to thrombocytopenic patients with CLD as a pretreatment for invasive procedures	
Treatments groups	Naïve **A/B-1**	Lusutrombopag 3 mg up to 7 days; The stopping criterion was applied on Day 6 only; n=47
	Naïve **A/B-2**	Lusutrombopag 3 mg fixed for 7 days; The stopping criterion was applied not at all; n=47
	Non-naive **A/B**	Lusutrombopag 3 mg up to 7 days; The stopping criterion was applied on days 3, 5, 6, and 7; n=8

Endpoints and definitions	Efficacy endpoint	**No Trans Proc**	Proportion of patients who required no platelet transfusion prior to invasive procedure
	Efficacy endpoint	**No Trans Study**	Proportion of patients who required no platelet transfusion during the study
	Efficacy endpoint	**Responder**	Proportion of Responders (a patient who achieved platelet count of ≥ 50,000/ěL with an increase of ≥ 20,000/ěL from baseline)
Database lock	<date>		

Results and Analysis

Analysis description	**Primary Analysis** (Summary statistics which include the number of patients, arithmetic mean, standard deviation (SD), median, minimum, and maximum were calculated for items observed in continuous values and the number and proportion of patients in each category were calculated for those observed in categories)			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	**Nad've A/B1**	**Nad've A/B2**	**Non-nad've A/B**
	Number of subject	47	47	8
	No Trans Proc	80.9% (38/47)	83.0% (39/47)	75.0% (6/8)
	95% confidence interval	66.7, 90.9	69.2, 92.4	34.9, 96.8
	No Trans Study	78.7% (37/47)	83.0% (39/47)	75.0% (6/8)
	95% confidence interval	64.3, 89.3	69.2, 92.4	34.9, 96.8
	Responder	83.0% (39/47)	85.1% (40/47)	75.0% (6/8)
	95% confidence interval	69.2, 92.4	71.7, 93.8	34.9, 96.8

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

Clinical studies in special populations

No special populations apart from patients with chronic liver disease were investigated.

Table 30: Numbers of Patients with Chronic Liver Disease by Age Group

	Age ≤ 64 (Number [% of total])	Age 65-74 (Number [% of total])	Age 75-84 (Number [% of total])	Age 85+ (Number [% of total])	Total
Controlled Trials [a]	231 (61.9)	96 (25.7)	43 (11.5)	3 (0.8)	373
Uncontrolled trials [b]	44 (28.0)	65 (41.4)	48 (30.6)	0	157

[a] ISS-1: Studies M0626, M0631, and M0634

[b] ISS-2: Studies M061B, M0623, M0625, and M0633. The data at retreatment were excluded.

Integrated Summary of Effectiveness for Lusutrombopag

The provided integrated analysis summarizes the efficacy of lusutrombopag in 2 pivotal Phase 3 studies: study 1304M0631 and study 1423M0634. These studies were multicenter, randomized, double-blind, placebo-controlled studies designed to assess the efficacy and safety of lusutrombopag 3 mg once daily for at least 4 days and up to 7 days for the treatment of thrombocytopenia in patients with chronic liver disease (CLD) who are undergoing elective invasive procedures. These studies were conducted under a similar study design and included 3 periods: a screening period up to 28 days, a treatment period of up to 7 days, and a posttreatment period of 28 days.

The Intent-to-treat (ITT) Population was defined as all randomized subjects and was the analysis population for the ISE. Subjects were analyzed according to the treatment to which they were randomized.

In principle, summary statistics, including the number, arithmetic mean, standard deviation (SD), median, and minimum and maximum values, were calculated for continuous variables. The number and proportion of subjects in each category were calculated for categorical variables.

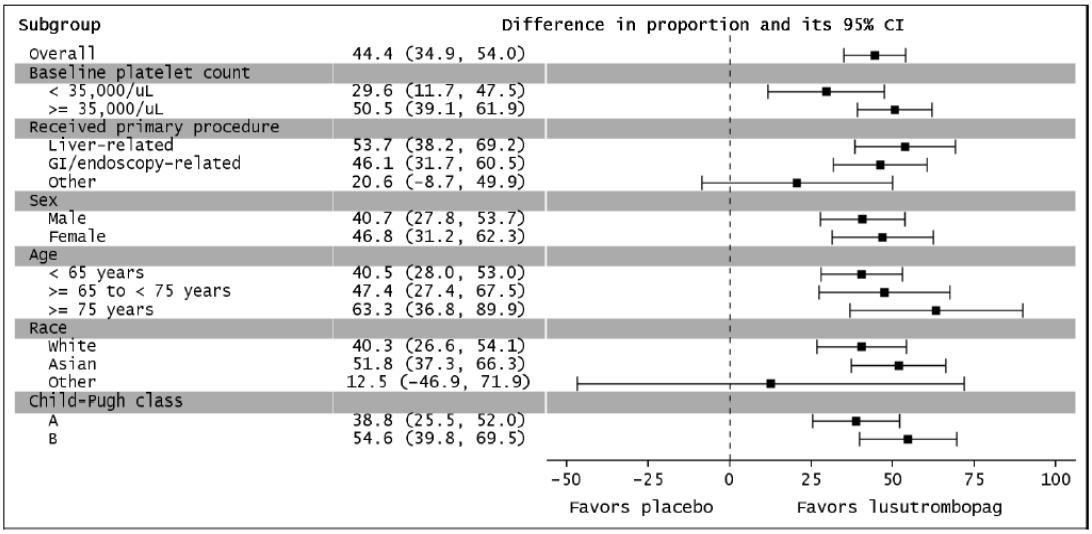
All analyses ware performed using SAS Version 9.2. Statistical tests were performed at a 2-sided significance level of 0.05. There was no adjustment for multiplicity.

There were 6 main objectives and related analyses, which were presented below:

1. Proportion of Subjects Who Required No Platelet Transfusion Prior to the Primary Invasive Procedure and No Rescue Therapy for Bleeding from Randomization Through 7 Days After the Primary Invasive Procedure
2. Proportion of Subjects Who Required No Platelet Transfusion Prior to the Primary Invasive Procedure
3. Proportion of Subjects Who Required No Platelet Transfusion During the Study
4. Proportion of Responders during the Study
5. Duration of the Increase in Platelet Count to at Least 50,000/ěL

6. Time Course of Platelet Count

Figure 15: Difference in Proportion of Subjects Who Required No Platelet Transfusion Prior to the Primary Invasive Procedure and No Rescue Therapy for Bleeding from Randomization Through 7 Days After the Primary Invasive Procedure (Pivotal Phase 3 Studies) Intent-to-treat Population



Across Studies M0631 and M0634, the proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary invasive procedure was significantly greater in the pooled lusutrombopag group (68.2% [107 of 157 subjects]) compared with the pooled placebo group (23.9% [37 of 155 subjects]) ($p < 0.0001$).

A similar trend was observed in each of the individual studies; however, a greater treatment difference for this endpoint was observed in Study M0631 (61.8%) compared with Study M0634 (36.6%). One reason that may account for this is the high number of protocol deviations related to platelet transfusions that favored the placebo group in Study M0634. Specifically, this would have an impact on the analysis using the ITT population, as the analysis included 3 subjects in the lusutrombopag group and 10 subjects in the placebo group who did not receive a platelet transfusion but should have (preprocedural platelet counts < 50,000/ěL), as well as 5 subjects in the lusutrombopag group, but 0 subjects in the placebo group who received a platelet transfusion but should not have (preprocedural platelet counts ≥ 50,000/ěL).

These effects were minimized in the analysis using the PP population, which excluded subjects with protocol deviations pertaining to platelet transfusions, and thus, relative to the ITT population, the proportion of subjects who met the primary endpoint increased in the lusutrombopag group and decreased in the placebo group, increasing the overall treatment effect (72.5% vs 20.2%; $p < 0.0001$).

There are noticeable differences in outcome defined as "Proportion of Subjects Who Required No Platelet Transfusion Prior to the Primary Invasive Procedure and No Rescue Therapy for Bleeding from Randomization Through 7 Days after Primary Invasive Procedure" between age groups (<65, ≥65 and <75, ≥75) and Child-Pugh classes. However, in light of the PK/PD analyses, the relatively low numbers of subjects in some categories is not considered clinically important. Furthermore, supplementary data from post-marketing and post- marketing surveillance are reassuring.

Table 31: summary of exposure: phase 3 studies MO631 and M0634 (ITT population)

	Study M0631		Study M0634		Overall	
	LUSU 3 mg N = 49	Placebo N = 48	LUSU 3 mg N = 108	Placebo N = 107	LUSU 3 mg N = 157	Placebo N = 155
Exposure	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Duration of exposure (days)						
- 0	1 (2.0)	0	1 (0.9)	0	2 (1.3)	0
- 1	0	0	0	0	0	0
- 2	0	0	0	0	0	0
- 3	0	0	0	0	0	0
- 4	3 (6.1)	2 (4.2)	15 (13.9)	5 (4.7)	18 (11.5)	7 (4.5)
- 5	1 (2.0)	0	8 (7.4)	4 (3.7)	9 (5.7)	4 (2.6)
- 6	4 (8.2)	0	11 (10.2)	4 (3.7)	15 (9.6)	4 (2.6)
- 7	40 (81.6)	46 (95.8)	73 (67.6)	94 (87.9)	113 (72.0)	140 (90.3)
Subjects who discontinued the study drug	9 (18.4)	2 (4.2)	35 (32.4)	10 (9.3) [b]	44 (28.0)	12 (7.7) [b]
Reason for discontinuation of study drug						
- Platelet increase [a]	8 (16.3)	2 (4.2)	30 (27.8)	6 (5.6)	38 (24.2)	8 (5.2)
- Ineligibility	0	0	1 (0.9)	0	1 (0.6)	0
- Adverse event	0	0	0	1 (0.9)	0	1 (0.6)
- Withdrawal by subject	0	0	2 (1.9)	1 (0.9)	2 (1.3)	1 (0.6)
- Other	1 (2.0)	0	2 (1.9)	2 (1.9)	3 (1.9)	2 (1.3)

LUSU = lusutrombopag

[a] Protocol-specified responder criterion met (ie, increase in platelet count to ≥ 50,000/μL, with an increase of ≥ 20,000/μL from baseline).

[b] Includes subjects who permanently discontinued study drug before Day 7, but does not include subjects who completed dosing on Day 7 but had < 7 days of exposure due to a missed dose of study drug (for any reason).

Source: ISE Table 1.3

Characteristic		Study M0631		Study M0634		Overall	
		LUSU 3 mg N=49 n (%)	Placebo N=48 n (%)	LUSU 3 mg N=108 n (%)	Placebo N=107 n (%)	LUSU 3 mg N=157 n (%)	Placebo N=155 n (%)
WHO bleeding scale	Grade 0	43 (87.8)	42 (87.5)	101 (93.5)	97 (90.7)	144 (91.7)	139 (89.7)
	Grade 1	6 (12.2)	6 (12.5)	6 (5.6)	10 (9.3)	12 (7.6)	16 (10.3)
Baseline platelet count (*10^4/uL) [b]	n	49	48	107	106	156	154
	Mean	4.12	3.99	3.77	3.74	3.88	3.82
	SD	0.67	0.69	0.90	0.78	0.85	0.76
	Min	2.3	2.3	1.3	1.2	1.3	1.2
	Median	4.30	4.20	3.90	3.70	4.05	3.80
	Max	5.9	5.5	5.4	5.5	5.9	5.5
	< 3.5	7 (14.3)	10 (20.8)	36 (33.3)	38 (35.5)	43 (27.4)	48 (31.0)
	>= 3.5	42 (85.7)	38 (79.2)	71 (65.7)	68 (63.6)	113 (72.0)	106 (68.4)
Splenomegaly	Yes	46 (93.9)	46 (95.8)	95 (88.0)	95 (88.8)	141 (89.8)	141 (91.0)
	No	3 (6.1)	2 (4.2)	13 (12.0)	12 (11.2)	16 (10.2)	14 (9.0)
Ascites	Yes	11 (22.4)	14 (29.2)	22 (20.4)	25 (23.4)	33 (21.0)	39 (25.2)
	No	38 (77.6)	34 (70.8)	86 (79.6)	82 (76.6)	124 (79.0)	116 (74.8)
Hepatic encephalopathy	None/No encephalopathy	35 (71.4)	37 (77.1)	89 (82.4)	88 (82.2)	124 (79.0)	125 (80.6)
	Grade I to II/Encephalopathy controlled medically	14 (28.6)	11 (22.9)	19 (17.6)	19 (17.8)	33 (21.0)	30 (19.4)
	Grade III to IV/Encephalopathy poorly controlled	0	0	0	0	0	0

CLD = chronic liver disease; LUSU = lusutrombopag; Max = maximum; Min = minimum; SD = standard deviation; WHO = World Health Organization
[a] Including whole blood, red blood cells, platelets, other transfusion, or transfusion type unspecified.
[b] The value observed on Day 1 before the initial dose of study drug. If this value was missing, the most recent value obtained prior to Day 1 within the 7 preceding days was used.
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Table 2.1.1 Proportion of Subjects Who Required No Platelet Transfusion Prior to the Primary Invasive Procedure and No Rescue Therapy for Bleeding from Randomization Through 7 Days After the Primary Invasive Procedure (Pivotal Phase 3 Studies)
Intent-to-treat Population

	Study M0631		Study M0634		Overall	
	LUSU 3 mg N=49	Placebo N=48	LUSU 3 mg N=108	Placebo N=107	LUSU 3 mg N=157	Placebo N=155
Proportion of subjects [a]	75.5% (37/49)	12.5% (6/48)	64.8% (70/108)	29.0% (31/107)	68.2% (107/157)	23.9% (37/155)
Exact 95% confidence interval	(61.1, 86.7)	(4.7, 25.2)	(55.0, 73.8)	(20.6, 38.5)	(60.3, 75.4)	(17.4, 31.4)
Comparison with placebo [b]						
- Difference of proportion (95% confidence interval)	61.8 (46.4, 77.2)		36.6 (24.6, 48.5)		44.4 (34.9, 54.0)	
- P value	<.0001		<.0001		<.0001	

LUSU = lusutrombopag
[a] Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy (including platelet transfusion) for bleeding from randomization through 7 days after the primary invasive procedure. In addition to subjects who received platelet transfusion, subjects who did not receive an invasive procedure regardless of the reason were considered as receiving platelet transfusion.
[b] Cochran-Mantel-Haenszel test with baseline platelet count as stratum. In the analysis for pooled data, study was added as a stratum. The p value and confidence interval were calculated using Wald method.
Program : Q:\SDD\project\s888711\ise\production\analysis\programs\tlf\ise_tab_2_1_1_s15145.sas
Output : Q:\SDD\project\s888711\ise\production\analysis\tlf\E_SAR_ISE_TAB2_1_1.rtf
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Table 2.2 Proportion of Subjects Who Required No Platelet Transfusion Prior to the Primary Invasive Procedure (Pivotal Phase 3 Studies)
Intent-to-treat Population

	Study M0631		Study M0634		Overall	
	LUSU 3 mg N=49	Placebo N=48	LUSU 3 mg N=108	Placebo N=107	LUSU 3 mg N=157	Placebo N=155
Proportion of subjects [a]	77.6% (38/49)	12.5% (6/48)	64.8% (70/108)	29.9% (32/107)	68.8% (108/157)	24.5% (38/155)
Exact 95% confidence interval	(63.4, 88.2)	(4.7, 25.2)	(55.0, 73.8)	(21.4, 39.5)	(60.9, 75.9)	(18.0, 32.1)
Comparison with placebo [b]						
- Difference of proportion (95% confidence interval)	63.8 (48.7, 78.9)		35.6 (23.6, 47.6)		44.4 (34.8, 53.9)	
- P value	<.0001		<.0001		<.0001	

LUSU = lusutrombopag
[a] Proportion of subjects who required no platelet transfusion prior to the primary invasive procedure. In addition to subjects who received platelet transfusion, subjects who did not receive an invasive procedure regardless of the reason were considered as receiving platelet transfusion.
[b] Cochran-Mantel-Haenszel test with baseline platelet count as stratum. In the analysis for pooled data, study was added as a stratum. The p value and confidence interval were calculated using Wald method.
Program : Q:\SDD\project\s888711\ise\production\analysis\programs\tlf\ise_tab_2_2_s15145.sas
Output : Q:\SDD\project\s888711\ise\production\analysis\tlf\E_SAR_ISE_TAB2_2.rtf
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This side by side comparison of the two pivotal trials reveals that in the Japanese study M0631, a substantially higher percentage of subjects could reach the endpoint 'no transfusion before primary invasive procedure and no rescue therapy for bleeding through 7 days after the invasive procedure'; ie. 75.5% vs. 64,8%. This outcome measure was defined as the primary endpoint for multinational pivotal trial M0634 and calculated post hoc for trial M0631.

The endpoint 'no transfusion before primary invasive procedure', which served as the primary endpoint in M0631 and a secondary endpoint in M0634, could be reached by 77.6% of patients in this study but only 64.8% of patients in the multinational trial M0634.

In all Japanese trials, an effect of about 80% with regard to this outcome measure was observed, regardless if the dose of lusutrombopag was 2, 2.5, 3 or 4 mg administered up to 7 days. The effect observed in the multinational pivotal trial did noticeably differ from this trend. As dose finding was undertaken in Japanese subjects only, it is of concern that the selected dose of 3 mg could be underperforming in Caucasian patients. The applicant was asked to comment on this and to submit efficacy results stratified by weight groups for the two pivotal trials, i.e. 40-<50kg, 50-<60kg, 60-<70kg etc. In an analysis of pooled data from Studies M0631 and M0634, subjects above ≥ 100 kg body weight were grouped together, and those below 100 kg were grouped by body weight quartiles (from minimum body weight to < 100). The applicant chose these cuts so as to have a meaningful number of subjects in each dose group: use of the smaller 10-kg cuts suggested would have led to very low numbers in weight groups and thus made drawing conclusions more difficult. The minimum weight in the <100 kg group was

34.9 kg, Q1 was 58.9, median = 69.0, and Q3 = 80.1. Reassuringly, differences in body weight did not lead to clinically relevant differences in platelet responses in these cut-off strata.

Conversely, the percentage of responders before day 7 was 16.3% in the Japanese trial and at 27.8% nearly double that figure in the multinational trial M0634. The applicant was asked to comment on that discrepancy with regard to efficacy outcomes in Japanese and Caucasian patients. A noticeably higher proportion of subjects in the international trial M0634 did not need a full 7 day course of lusutrombopag but met the stopping /responder criterion in comparison to the Japanese trial M0631. Demographic characteristics were very comparable between the two studies, apart from race and bodyweight.

Clinical studies in special populations

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled Trials	96/373	43/373	3/373
Non Controlled Trials	65/157	48/157	0

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Dose-finding was done in three phase II trials in patients with chronic liver disease, Child-Pugh Class A or B and severe thrombocytopenia planned to undergo percutaneous liver ablation. Open-label, non-controlled trials M0623 and M0625 evaluated lusutrombopag at doses of 0.25, 0.5, 1, 1.5, or 2 mg for up to 7 days (M0623) and at doses of 2.5, 3, or 4 mg for up to 7 days (M0625). In trial M0623 it was observed that doses below 2 mg did not show an appreciable impact on platelet counts. In trial M0625, the investigated doses of 2.5 mg (n=6), 3 mg (n=7) and 4 mg (n=8) lead to efficacy responses in these limited patient numbers.

The double-blind, parallel-group, placebo (n=15) controlled trial M0626 investigated doses of 2 mg (n=15), 3 mg (n=16) and 4 mg (n=15) of lusutrombopag administered for up to 7 days. The primary endpoint was defined as avoidance of pre-procedural platelet transfusion. In this small trial, efficacy was not unequivocally separated by lusutrombopag dose level, although a trend to a higher platelet response and a longer duration of this response could be observed for the 3 and 4 mg dose. Comparable robust efficacy over placebo was noted for both the 3 and 4 mg dose. However, due to safety considerations and the desire to avoid excessive platelet count increases with potential thrombotic complications, the 3 mg dose was finally carried forward into the phase III trials.

Two pivotal, double-blind, randomized clinical trials investigated the superiority of 3 mg lusutrombopag administered daily for up to 7 days over placebo. In these trials, invasive procedures other than liver ablation were allowed, but excluded any of the following situations: laparotomy, thoracotomy, craniotomy, open-heart surgery, organ resection, or partial organ resection. Trial M0631 enrolled 97 Japanese subjects and trial M0634 enrolled 215 subjects mainly of Caucasian background.

Sample size targets for trials M0631 and M0634 were chosen to obtain adequate power to meet the primary objective but also to have adequate sensitivity to detect common (incidence >3%) safety events (e.g. thrombotic events). Randomized treatment assignment in studies M0631 and M0634 was stratified by type of primary invasive procedure and baseline platelet count.

According to the main exclusion criteria in the phase III studies, patients with past or present thrombosis (e.g., cerebral infarction, myocardial infarction, angina pectoris, pulmonary thromboembolism, deep vein thrombosis, disseminated intravascular coagulation syndrome) were not enrolled. However, this large group of patients should not be excluded from treatment and a detailed statement in section 4.4 of the SmPC covers all at risk groups and is deemed sufficient to alert the treating physician to a potentially increased risk of thrombotic or thromboembolic events.

The primary endpoint was defined as the proportion of subjects who received no pre-procedural platelet transfusion in trial M0631 and as the proportion of subjects who required no platelet transfusion prior to the primary invasive procedure and no rescue therapy for bleeding from randomization through 7 days after the primary elective procedure in study M0634. In addition, a number of informative and clinically relevant secondary endpoints were collected (i.e. proportion of subjects who received no platelet transfusion during the study; number of days during which the platelet count was ≥ 50,000/ěL; time course of platelet count; number of platelet transfusions).

In terms of statistical analysis both trials were planned in a similar fashion. However, slight differences between the two trials regarding the specification of the analysis populations and the way that missing data were handled were noticed. This may have contributed to differences between treatment effect estimates obtained for the two studies. The primary efficacy analysis in either of the two trials was performed using the Cochran-Mantel-Haenszel test which takes into account the predefined stratification factors. Confidence intervals of platelet transfusion rates per treatment arm were estimated using the Clopper-Pearson exact confidence intervals which have been shown to provide conservative control of the coverage probability even for stratified designs. Finally, the applicant provided updated estimates of the confidence intervals for differences in transfusion rates between treatment arms using a procedure which has been shown to provide improved coverage probability compared to the originally planned procedure. Corresponding estimates are very close to those obtained originally. Consequently effect size estimates and corresponding confidence intervals can be considered robust with respect to the underlying statistical assumptions.

In all of these trials, lusutrombopag administration was titrated until the responder criterion = stopping criterion (platelet count ≥50.000 and increase over baseline of ≥20.000) was met or up to a maximum of 7 days. Platelet count on Day 5 to 7 had to be measured before the administration on respective days, and if the responder criterion was met, treatment was stopped. Hence not all subjects received a full course of 7 tablets during these trials.

The phase IIIb, multicentre, open-label study M0633 in Japanese subjects with CLD and severe thrombocytopenia endeavoured to investigate the safety and feasibility of a fixed 7 day duration of treatment (arms A/B-1, n=47; A/B-2, n=47) and effects of retreatment with lusutrombopag (arm A/B, n=8). The stopping criterion was applied on Day 6 only in Group A/B-1; not at all in the Group A/B-2 in which subjects were treated for a fixed 7 days; and on Days 3, 5, 6, and 7 in non-naive Group A/B.

Trial M0633 was conducted for the purpose of investigating whether a fixed 7 day treatment regimen would provide comparable safety and efficacy as the variable length treatment with platelet monitoring established in previous studies. For this purpose, however, a type of non-inferiority/equivalence comparison would have been ideal. The design of study M0633, however, was not set up to permit conclusions of a comparative nature. Most importantly the number of subjects having received a different dose than foreseen with the treatment regimen established in previous studies is small.

In all clinical trials pertaining to dose-finding and efficacy, subjects with chronic liver disease and severe thrombocytopenia were enroled, however, patients with splenectomy, concomitant interferon therapy or Child-Pugh Class C were consistently excluded.

Efficacy data and additional analyses

The primary efficacy endpoint in phase III trial M0631 (no transfusion before primary invasive procedure) could be reached by 79.2% (CI 65.0, 89.5%) of patients receiving lusutrombopag and 12.5% (CI 4.7, 25.2%) of placebo recipients in the FAS. In the multinational trial M0634, 64.8% (CI 53.1, 72.1%) of patients in the lusutrombopag group and 29.9% (CI 20.6, 38.5%) in the placebo group in the FAS met this endpoint, which was defined as a secondary efficacy outcome.

The primary efficacy endpoint in phase III trial M0634 (no transfusion before primary invasive procedure and no rescue therapy for bleeding through 7 days after the invasive procedure) could be reached by 64.8% (CI 55.0, 73.8%) of subjects in the lusutrombopag group compared to 29.0% (CI 20.6, 38.5%) in the placebo group in the FAS. A substantial number of protocol deviations with regards to platelet transfusions occurred in trial M0634. In 18 instances, the rules with regards to platelet transfusions were disregarded. However, the analysis in the PP population supported a clear beneficial effect of lusutrombopag, as 72.5% (CI 62.2, 81.4%) of subjects in the verum vs. 20.2% (CI 12.4, 30.1%) of subjects in the placebo group met the primary endpoint. In trial M0631, 75.5% (CI 61.1, 86.7%) of the lusutrombopag subjects and 12.5% (CI 4.7, 25.2%) of placebo subjects met this post hoc calculated endpoint. This outcome measure is considered to be even more clinically relevant than the primary endpoint used in M0631 (proportion of patients who did not need a transfusion before the primary invasive procedure), because this endpoint demonstrates the continued protection against bleeding events during the healing period.

Results obtained for the secondary endpoints support the clinical efficacy of lusutrombopag and illustrate the size of the increase of platelet counts, the duration of this effect as well as the dramatic reduction in need for platelet transfusions.

Surgical intervention was scheduled in the Post-treatment period between Days 9 and 14. An analysis, whether the time between end of treatment (between Days 4 and 7) may have had any influence on the efficacy and/or safety of the treatment is missing. The applicant was requested to provide additional analysis (for all Phase 3 trials) of the amount of time between end of dosing and surgical intervention (distribution, summary statistics, pooled and separate by treatment group, stratification factor) and potential association with treatment outcome (platelet counts before procedure, primary and secondary outcomes). In the submitted analysis there appeared to be an appreciable interaction between effect of treatment and time between last dose of treatment and date of surgical intervention for subjects treated with Lusutrombopag Shionogi. Response rates for subjects receiving interventions on Day 3 appear lower than for subjects with longer intervals between end of treatment and intervention, which is compatible with the notion that platelet production under treatment reaches its peak more than 3 days after treatment. No corresponding effect is observed for subjects in the placebo group, which would be expected under the assumption of randomly fluctuating platelet counts under placebo treatment. In conclusion, an interval of 2 or 3 days between the end of dosing and the invasive procedure is suboptimal and should be avoided. However, data provided by the Applicant illustrated that nearly all of those patients who successfully avoided a platelet transfusion prior and after their invasive procedure in each pivotal trial achieved the desired platelet count at day 9 after start of dosing. In combination with the recommendation to check the platelet count before undertaking the elective procedure, this is considered sufficient justification to support the statement in section 4.2 of the SmPC in this regard.

The efficacy outcomes from trial M0633 are comparable to those of trial M0631, with 80.9% of subjects in arm A/B-1, 83.0% in A/B-2 and 75% in non-naive A/B requiring no platelet transfusions prior to the invasive procedure. However, the applicant was asked to describe in detail the efficacy and safety outcomes of those patients who received 7 days of lusutrombopag therapy in arms A/B-1 and A/B2 but should have stopped if the safety criterion from the two pivotal trials, i.e. a rise of platelet counts above 50.000 with an increase of 20.000 were applied on day 5, 6 and 7, as such an in depth analysis of the

pertinent issue was missing. From the additional data submitted it appears that there may be an increase in response rate with increasing cumulative exposure.

It is acknowledged that the majority of subjects in clinical studies M0631 and M0634 received 7 days of treatment (73%, 113 out of 155), consequently only a minority of subjects who would be exposed to a higher dose under a treatment regimen without monitoring. In Study M0633 the number of subjects who received a larger dose compared to a treatment regimen with monitoring is limited (i.e. 20) rendering a comparative safety analysis whether such patients are exposed to a higher risk of safety events difficult. No association between the maximum platelet count and the duration of treatment (with or without stopping) is apparent. The presented data indicate a slightly improved efficacy of lusutrombopag at a fixed 7-day treatment regimen. Conversely, comparative assessment of safety data is uncertain due to the sparsity of data. However, it is considered that the data presented do not implicate a substantial safety issue with regard to a 7-day treatment with lusutrombopag without the application of a stopping criterion. Furthermore additional monitoring for vulnerable patients (bodyweight <45kg, Child Pugh C) is advised in the SmPC.

2.5.4. Conclusions on the clinical efficacy

In conclusion, short-term treatment with lusutrombopag could be an effective new treatment option in patients with chronic liver disease and severe thrombocytopenia prior to elective invasive procedures.

With regards to the proposed indication, the applicant has amended the wording in order to clearly reflect that only patients with severe thrombocytopenia were included into the clinical trials. The exclusion criteria with regards to the invasive procedures undertaken in the pivotal trials are clearly reflected in section 4.4 of the SmPC.

The available data pertaining to patients with the most severe liver disease (Child-Pugh Class C) are limited. However, efficacy of lusutrombopag in patients with Child Pugh class C disease is likely to be comparable to patients with a lesser grade of liver disease. This notion is supported by the evaluation of efficacy in those patients who were included into the clinical development programme or identified in post marketing surveillance data from Japan. The warning statements introduced into section 4.4. of the SmPC are considered adequate to manage the potential risks in patients with Child Pugh class C liver disease by additional monitoring for early signs of worsening or new onset hepatic encephalopathy, ascites, and thrombotic or bleeding tendency through monitoring of liver function tests, tests used for assessing clotting status and through imaging of portal vasculature. Additionally, section 4.4. of the SmPC was amended with specific guidance for platelet count monitoring. The inclusion of Child Pugh C in the indication and the proposed PASS will ensure further data collection in a systematic way in these patients and avoid the highly likely off-label use in this vulnerable population.

2.6. Clinical safety

The applicant submitted a pooled safety analysis for three different data sets: three randomized double blind placebo controlled trials (ISS-1: one Phase 2b and two Phase 3), four open-label trials (ISS-2: one Phase 1, one phase 2, one phase 3) and all studies including a lusutrombopag 3 mg group (ISS-3). Other safety findings are presented by study.

Separately a summary of the safety of two studies in ITP patients has been presented. Post marketing data from Japan have been included in the dossier.

Patient exposure

653 adult subjects were exposed to lusutrombopag among 20 clinical trials (317 subjects were healthy volunteers, dose: 0.1-50 mg). 285 were receiving a dose of 3 mg for up to 7 days (including 273 who underwent an invasive procedure).

343 subjects were included into controlled randomized studies receiving a dose of 3 mg of lusutrombopag or placebo (173/170). 108 subjects participating in uncontrolled studies received a treatment dose of 3 mg lusutrombopag.

Patient exposure (cut off) in M0623, M0626, M0627, M0631, M0633 and M0634 Studies.

	Patients enrolled	Patients exposed	Patients exposed to the proposed dose range (3 mg)	Patients exposed to the proposed dose range or higher (≥3 mg)
Placebo-controlled	202	202	171	186
Active -controlled	N.A.	N.A.	N.A.	N.A.
Open studies	163	162	114	122
Post marketing	N.A.	N.A.	N.A.	N.A.
Compassionate use	N.A.	N.A.	N.A.	N.A.

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Due to the application of a stopping criterion in most of the clinical studies, a lower proportion of subjects received 7 days of treatment in the lusutrombopag group than in the placebo group (73.1% versus 91.2%).

The number of patients with Child-Pugh class A liver disease was higher in the lusutrombopag group than in the placebo group (62.0% versus 55.3%, respectively). The cause for the difference in allocation was explained by the applicant and the type and incidence of AEs in Child Pugh-Class A patients were compared to Child Pugh Class B patients. The slight imbalance in Child Pugh Class A versus B between treatment and placebo group does not seem to have major influence on the safety outcome.

A comparison of AEs in patients receiving lusutrombopag vs placebo was presented separately for subjects with Child-Pugh class B and Child-Pugh class A.

Only one study (M0627) enrolled patients with Child-Pugh class C liver disorder at screening. Up to 15 patients were planned. However, enrollment of eligible patients was difficult, with only 5 patients enrolled.

Adverse events

The applicant presented overall incidences of adverse events for the pooled safety analysis of the controlled studies that comprises data from three randomized double blind placebo-controlled trials (one Phase 2b and two Phase 3). In the pooled analysis, 112 (65.5%) of 171 patients treated with lusutrombopag 3 mg and 115 (67.5%) of 170 patients in the placebo group had one or more adverse events. 13 (7.6%) patients in the lusutrombopag 3 mg group and 14 (8.2%) patients in the placebo group were reported to have treatment-related AEs. 9 (5.3%) patients in the lusutrombopag group and 12 (7.1%) patients in the placebo group had serious adverse events (fatal and nonfatal), including 2 subjects

(1.2%) in the lusutrombopag group and 1 (0.6%) in the placebo group who had serious adverse events that were considered treatment-related.

Table 32: overview of adverse events (controlled studies Safety analysis population)

Subjects with	Study M0626				Studies M0631 and M0634		Overall	
	LUSU 2 mg N=15 n (%)	LUSU 3 mg N=16 n (%)	LUSU 4 mg N=15 n (%)	Placebo N=15 n (%)	LUSU 3 mg N=155 n (%)	Placebo N=155 n (%)	LUSU 3 mg N=171 n (%)	Placebo N=170 n (%)
At least 1 AE	15 (100.0)	16 (100.0)	14 (93.3)	15 (100.0)	96 (61.9)	100 (64.5)	112 (65.5)	115 (67.6)
At least 1 AE with an outcome of death	1 (6.7)	0	0	0	3 (1.9)	0	3 (1.8)	0
At least 1 serious AE	3 (20.0)	1 (6.3)	0	1 (6.7)	8 (5.2)	11 (7.1)	9 (5.3)	12 (7.1)
At least 1 AE leading to withdrawal of study drug	0	0	0	0	0	1 (0.6)	0	1 (0.6)
At least 1 treatment-related AE	5 (33.3)	3 (18.8)	3 (20.0)	0	10 (6.5)	14 (9.0)	13 (7.6)	14 (8.2)
At least 1 treatment-related serious AE	0	0	0	0	2 (1.3)	1 (0.6)	2 (1.2)	1 (0.6)

AE = adverse event; LUSU = lusutrombopag
Includes only treatment-emergent adverse events.
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The most frequently reported treatment-emergent adverse events (TEAE) in at least 5% of subjects in the pooled lusutrombopag or placebo treatment group were procedural pain (19.3% lusutrombopag versus 17.1% placebo), postoperative fever (16.4% versus 20.0%), procedural hypertension (16.4% versus 15.3%), increased AST (12.9% versus 11.8%), increased ALT (8.8% versus 5.9%), decreased oxygen saturation (5.3% versus 6.5%) and increased blood bilirubin (5.3% versus 2.4%). Except procedural pain (19.3% lusutrombopag versus 17.1% placebo), increased ALT (8.8% versus 5.9%) and increased blood bilirubin (5.3% versus 2.4%), no adverse event was reported at a ≥ 2% difference in the total lusutrombopag group than in the placebo group.

Table 33: Adverse events with incidence ≥ 5% in either overall treatement group by preferred term (controlled studies)

Preferred Term	Study M0626				Studies M0631 and M0634		Overall	
	LUSU 2 mg N=15 n (%)	LUSU 3 mg N=16 n (%)	LUSU 4 mg N=15 n (%)	Placebo N=15 n (%)	LUSU 3 mg N=155 n (%)	Placebo N=155 n (%)	LUSU 3 mg N=171 n (%)	Placebo N=170 n (%)
Postoperative fever	10 (66.7)	9 (56.3)	7 (46.7)	6 (40.0)	19 (12.3)	28 (18.1)	28 (16.4)	34 (20.0)
Procedural pain	8 (53.3)	8 (50.0)	9 (60.0)	7 (46.7)	25 (16.1)	22 (14.2)	33 (19.3)	29 (17.1)
Procedural hypertension	10 (66.7)	8 (50.0)	6 (40.0)	8 (53.3)	20 (12.9)	18 (11.6)	28 (16.4)	26 (15.3)
Aspartate aminotransferase increased	10 (66.7)	10 (62.5)	9 (60.0)	3 (20.0)	12 (7.7)	17 (11.0)	22 (12.9)	20 (11.8)
Alanine aminotransferase increased	8 (53.3)	6 (37.5)	5 (33.3)	0	9 (5.8)	10 (6.5)	15 (8.8)	10 (5.9)
Oxygen saturation decreased	4 (26.7)	6 (37.5)	5 (33.3)	4 (26.7)	3 (1.9)	7 (4.5)	9 (5.3)	11 (6.5)
Fibrin degradation products increased	2 (13.3)	5 (31.3)	1 (6.7)	4 (26.7)	2 (1.3)	6 (3.9)	7 (4.1)	10 (5.9)
Fibrin D dimer increased	3 (20.0)	5 (31.3)	3 (20.0)	5 (33.3)	1 (0.6)	5 (3.2)	6 (3.5)	10 (5.9)
Procedural nausea	1 (6.7)	0	3 (20.0)	2 (13.3)	6 (3.9)	8 (5.2)	6 (3.5)	10 (5.9)
Ascites	2 (13.3)	0	2 (13.3)	2 (13.3)	6 (3.9)	7 (4.5)	6 (3.5)	9 (5.3)
Blood bilirubin increased	4 (26.7)	4 (25.0)	0	0	5 (3.2)	4 (2.6)	9 (5.3)	4 (2.4)

LUSU = lusutrombopag
Includes only treatment-emergent adverse events.
Adverse events were coded using MedDRA Version 18.0.
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Most of the AEs were considered unrelated to the study drug. The most frequently reported treatment-related AEs in the lusutrombopag group were nausea (1.8% lusutrombopag versus 1.2% placebo) and headache (1.8% versus none). Higher incidence for placebo in treatment associated AEs were noted for diarrhoea (0.6% lusutrombopag versus 1.2% placebo), abdominal pain (none versus 1.8%), fatigue (none versus 1.2%), vomiting (none versus 1.2%), increased AST (none versus 1.2%) and increased International normalised ratio (none versus 1.2%).

Table 34: Treatment related adverse events with incidence ≥ 1% in either overall treatment group by preferred term (controlled studies) (safety analysis population)

Preferred Term	Study M0626				Studies M0631 and M0634		Overall	
	LUSU 2 mg N = 15 n (%)	LUSU 3 mg N = 16 n (%)	LUSU 4 mg N = 15 n (%)	Placebo N = 15 n (%)	LUSU 3 mg N = 155 n (%)	Placebo N = 155 n (%)	LUSU 3 mg N = 171 n (%)	Placebo N = 170 n (%)
Nausea	0	0	0	0	3 (1.9)	2 (1.3)	3 (1.8)	2 (1.2)
Headache	1 (6.7)	0	0	0	3 (1.9)	0	3 (1.8)	0
Diarrhoea	0	0	0	0	1 (0.6)	2 (1.3)	1 (0.6)	2 (1.2)
Abdominal pain	0	0	0	0	0	3 (1.9)	0	3 (1.8)
Vomiting	0	0	0	0	0	2 (1.3)	0	2 (1.2)
Fatigue	0	0	0	0	0	2 (1.3)	0	2 (1.2)
Aspartate aminotransferase increased	0	0	0	0	0	2 (1.3)	0	2 (1.2)
International normalised ratio increased	0	0	0	0	0	2 (1.3)	0	2 (1.2)

LUSU = lusutrombopag

Includes only treatment-emergent adverse events.

Adverse events were coded using MedDRA Version 18.0.

Source: ISS Table 3.1.2.4.1

The reported TEAEs are considered to be consistent with the nature of the invasive procedures and the underlying medical condition of the study population. It is of note, that fewer subjects in both treatment groups had adverse events before the invasive procedure (lusutrombopag, 26.1%; placebo, 35.0%) than after the procedure (lusutrombopag, 60.6%; placebo, 62.5%). Adverse events with onset before the invasive procedure reported for more than 1 subject in the lusutrombopag group were limited to procedural pain and procedural hypertension (each in 1.2% of subjects in the lusutrombopag group vs 0 subjects in the placebo group).

Common adverse events with onset after the invasive procedure in the lusutrombopag group were procedural pain (lusutrombopag, 20.0%; placebo, 18.1%), postoperative fever (lusutrombopag, 17.0%; placebo, 21.3%), procedural hypertension (lusutrombopag, 17.0%; placebo, 16.3%), increased AST (lusutrombopag, 13.3%; placebo, 11.3%), increased ALT (lusutrombopag, 9.1%; placebo, 6.3%), and decreased oxygen saturation (lusutrombopag, 5.5%; placebo, 6.9%). Apart from increased blood bilirubin (lusutrombopag, 4.8%; placebo, 1.0%), the incidence of adverse events occurring after the procedure was similar in the lusutrombopag and placebo groups or lower in the lusutrombopag group than in the placebo group.

In the pooled analysis, the incidence of TEAEs is deemed comparable between the lusutrombopag and placebo group. However, in study M0626 a higher incidence of increased ALT (62.5% in the lusutrombopag 3 mg group versus 20% in placebo) and increased AST (37.5% versus none) was noted in subjects treated with lusutrombopag. The Applicant investigated age, Child Pugh score and number of liver cancers of all patients in study M0626 but no apparent correlation with the events of altered liver parameters could be determined. The Applicant provided additional data presenting the number and proportion of subjects who showed an increase in liver enzymes (AST, ALT, ALP) on day 8, day 14/17 and day 35. In study M0626, the proportion of subjects with increased AST >1.5x ULN was slightly higher at baseline, day 8, day 35 and at the time of the last observation in the lusutrompobag 3 mg group compared to placebo. A comparable tendency for increased AST in lusutrombopag-treated subjects was also observed in the pooled anaylsis of the controlled studies M0631 and M0634. However, a significantly higher incidence of increased ALT values >1.5x ULN was observed in lusutrombopag-treated subjects compared to placebo-treated subjects (50% lusutrombopag versus 26.7% placebo) at day 17.

However, in the analysis showing increased liver parameters as change from baseline, the proportion of subjects with increased AST and ALT values >1.5x baseline was comparable between lusutrombopag and placebo group with the exception of one subject in the lusutrombopag group who showed an increased ALT value >1.5x baseline at day 8. In the combined analysis of the studies M0631 and M0634, the proportions of subjects with increased AST and ALT values >1.5x baseline at day 8 were higher for

lusutrombopag-treated patients than for placebo-treated patients (3.2% lusutrombopag versus 0.6% placebo). The proportion of subjects with increased AST and ALT values >3x baseline was low across all controlled studies and comparable between the lusutrombopag and placebo group. Thus, the results did not indicate a greater tendency for an increase of liver enzymes from baseline in patients treated with lusutrombopag than for patients treated with placebo in study M0626. The results obtained in study M0626 were comparable with the results obtained from the pooled analysis of the controlled studies M0631 and M0634. Although the provided analysis does not satisfactorily explain the reported higher incidence of adverse events of increased liver parameters in patients treated with lusutrombopag compared to placebo in study M0626, no safety concerns related to hepatotoxicity arise from these data. In addition, the imbalance of liver parameter changes in the phase II trial M026 could very well have arisen due to chance with regard to the low numbers enrolled into each treatment arm.

A higher incidence of TEAEs has been observed in the studies conducted in Japan (M0626, M0631) in comparison to the multinational study (M0634). Different types of invasive procedures seem to affect the incidence of adverse events. A larger percentage of patients in the multinational study underwent less invasive procedures (e.g. gastrointestinal/endoscopy-related procedures: 57 % in the treatment group, liver related procedures: 18.7 %). Adverse events have been specified depending on the invasive procedure. The difference in the incidence of AEs in Asian and White subjects could not fully be explained by the differences of invasive procedures. However the incidence of AEs is comparable in the lusutrombopag and placebo group and does therefore seem to be unrelated to the treatment. Although weight is an influential covariate on PK and exposure may have been higher in Japanese subjects, no dose-related trends were noted across the Phase 2 studies in subjects with CLD.

Bleeding Events

In the pooled controlled studies (M0626, M0631, and M0634), 3.0% of lusutrombopag-treated subjects and 7.5% of placebo-treated subjects had bleeding events before the procedure, and 6.7% and 10.6%, respectively, had bleeding-related events after the procedure. The most frequent bleeding-related events were procedural haemorrhage (lusutrombopag, 3.0%; placebo, 1.3%), subcutaneous hemorrhage (1.8% and 0.6%, respectively), purpura (1.2% and none, respectively), and post-procedural hemorrhage (1.2% and 1.9%, respectively).

The applicant presented overall incidences of adverse events for the pooled safety analysis of the uncontrolled studies which comprises four open-label studies. In the pooled analysis, 16 (100%) of 16 patients in the lusutrombopag 0.25 – 1 mg group, 23 (95.8%) of 24 patients in the lusutrombopag 1.5 – 2.5 mg, 98 (90.7%) of 108 patients in the lusutrombopag 3 mg group and 8 (100%) of 8 patients in the lusutrombopag 4 mg group had at least one adverse event. 3 (18.8%) patients in the lusutrombopag 0.25- to 1-mg group, 2 (8.3%) patients in the 1.5- to 2.5-mg group, 6 (5.6%) patients in the 3 mg group and none in the 4 mg lusutrombopag group were reported to have treatment-related AEs. No treatment-related adverse event was experienced by more than one subject (0.9%) for any preferred term. 1 (6.3%) subject in the lusutrombopag 0.25- to 1-mg group, 2 (8.3%) in the 1.5- to 2.5-mg group, 5 (4.6%) in the 3 mg group, and 1 (12.5%) in the 4 mg group had serious adverse events (fatal and nonfatal), of which only 1 subject (0.9%) in the 3 mg group had a serious adverse event that was considered treatment-related.

Table 35: overview of treatment-emergent adverse events (uncontrolled studies) Safety analysis population

Subjects with	LUSU 0.25 to 1 mg N=16 n (%)	LUSU 1.5 to 2.5 mg N=24 n (%)	LUSU 3 mg N=108 n (%)	LUSU 4 mg N=8 n (%)
At least 1 AE	16 (100.0)	23 (95.8)	98 (90.7)	8 (100.0)
At least 1 AE with an outcome of death	1 (6.3)	0	0	0
At least 1 serious AE	1 (6.3)	2 (8.3)	5 (4.6)	1 (12.5)
At least 1 AE leading to withdrawal of study drug	0	0	0	0
At least 1 treatment-related AE	3 (18.8)	2 (8.3)	6 (5.6)	0
At least 1 treatment-related serious AE	0	0	1 (0.9)	0

AE = adverse event; LUSU = lusutrombopag
Includes only treatment-emergent adverse events.
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The most common adverse events in the pooled lusutrombopag 3 mg group (>10%) were procedural hypertension (38.0%), postoperative fever (35.2%), procedural pain (28.7%), increased AST (24.1%), increased ALT (15.7%), constipation (11.1%), increased blood pressure and pyrexia (10.2% each). The AEs reported in the uncontrolled studies are considered to be consistent with the study population and the nature of the invasive procedures and reveal a similar pattern to that reported in the controlled studies.

Table 36: adverse events with incidence ≥5% in the pooled lusutrombopag 3 mg group by preferred term (uncontrolled studies) Safety analysis population

Preferred Term	LUSU 0.25 to 1 mg N=16 n (%)	LUSU 1.5 to 2.5 mg N=24 n (%)	LUSU 3 mg N=108 n (%)	LUSU 4 mg N=8 n (%)
Procedural hypertension	3 (18.8)	7 (29.2)	41 (38.0)	3 (37.5)
Postoperative fever	0	1 (4.2)	38 (35.2)	0
Procedural pain	0	0	31 (28.7)	0
Aspartate aminotransferase increased	8 (50.0)	10 (41.7)	26 (24.1)	6 (75.0)
Alanine aminotransferase increased	5 (31.3)	9 (37.5)	17 (15.7)	5 (62.5)
Constipation	0	3 (12.5)	12 (11.1)	2 (25.0)
Blood pressure increased	4 (25.0)	5 (20.8)	11 (10.2)	1 (12.5)
Pyrexia	6 (37.5)	10 (41.7)	11 (10.2)	6 (75.0)
Oxygen saturation decreased	3 (18.8)	7 (29.2)	8 (7.4)	2 (25.0)
C-reactive protein increased	0	2 (8.3)	7 (6.5)	1 (12.5)
Malaise	4 (25.0)	2 (8.3)	7 (6.5)	1 (12.5)
Post procedural discomfort	0	0	7 (6.5)	0
Headache	0	3 (12.5)	6 (5.6)	1 (12.5)
Procedural nausea	0	0	6 (5.6)	0
Procedural vomiting	0	0	6 (5.6)	0

LUSU = lusutrombopag
Includes only treatment-emergent adverse events.
Adverse events were coded using MedDRA Version 18.0.
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The most frequently adverse events reported in **phase 1 studies** excluding thrombocytopenic subjects with chronic liver disease were: feeling hot (7 subjects), increased platelet counts (13 subjects) and increased ALT (4 subjects in the lusutrombopag group and 2 subjects in the placebo group). The rate of treatment-related adverse events was low across the phase 1 studies and does not raise any safety concerns.

Splenectomised patients were excluded from all studies. Since the spleen plays an important role in platelet storage, the safety profile of lusutrombopag might be different in patients who underwent a splenectomy.

The applicant evaluated adverse events of portal vein thrombosis and rash. Headache and nausea were also judged as being related to study treatment and occurred more frequently in the lusutrombopag arm compared to placebo (1.8% lusutrombopag versus 0% placebo for headache and 1.8% lusutrombopag versus 1.2% placebo for nausea).

Adverse events of special interest

Thrombotic adverse events

In the controlled studies the incidence of thrombotic/thromboembolic events was almost equally distributed between the pooled placebo (4 subjects [2.4%]) and lusutrombopag 3 mg group (3 subjects [1.8%]). Thrombotic AEs were reported for 1 subject in the 2 mg group and 2 subjects in the 4 mg group. In the uncontrolled studies, thrombotic adverse events were reported for 1 subject (4.2%) in the lusutrombopag 1.5- to 2.5-mg group and 3 subjects (2.8%) in the 3-mg group. 2 thrombotic events were reported in study M0627. Except one event (cardiac ventricular thrombosis) which was found by a routine CT scan, all other thrombotic adverse events were found by imaging studies 3 to 10 days after the invasive procedure as specified in the protocol. No dose-related increase in the incidence of thrombotic events was noted in Study M0626. The majority of the subjects who experienced a thrombotic adverse event had platelet counts < 100 000/µl. One subject in the lusutrombopag 3 mg group and one subject in the lusutrombopag 4 mg group had platelet counts slightly above 100 000/µl. Only one subject in the placebo group showed a platelet count > 150 000/µl but still < 200 000/µl. Thus, no apparent relationship between thrombotic events and increased platelet counts was shown. Nevertheless, thrombotic events are a known risk among patients with liver cirrhosis and the prevalence increases with the severity of the underlying hepatic disease. The risk of thrombotic events may be increased in these patients when they undergo an invasive procedure. However, it might be possible that any elevation of platelet counts increases the risk in patients who have a predisposition to thromboembolic events. Several cases of portal vein thrombosis have been observed post-marketing in Japan.

Worsening liver function

Worsening liver function was defined retrospectively across the clinical development program as [(AST ≥ 3 times the upper limit of normal [× ULN] or ALT ≥ 3 × ULN) + total bilirubin ≥ 2 × ULN] on the same date, including:

- Change in AST, ALT, and/or total bilirubin reported as an adverse event by the investigator
- Change in AST, ALT, and/or total bilirubin identified on retrospective analysis by the sponsor, but not reported as an adverse event by the investigator

The incidence of the adverse event of worsening liver function was higher in the pooled placebo (8 subjects [4.7%]) group than in the lusutrombopag group (4 subjects [2.3%]). No dose-related trends increase in the incidence of worsening liver function was noted in Phase 2b Study M0626. In the uncontrolled studies abnormal liver function was reported for 5 patients (31.3%) in the lusutrombopag 0.25- to 1-mg group, 1 (4.2%) patient in the 1.5- to 2.5-mg group, 2 (1.9%) patients in the 3-mg group, and none in the 4-mg group. In phase 1 studies 8 subjects were reported with altered liver function. The event of hepatobiliary laboratory abnormalities was reversible and temporary. One subject (0.6%) in the lusutrombopag 3 mg group and 3 subjects (1.8%) in the placebo group had still altered laboratory values after the last observation on day 35.

Serious adverse event / deaths / other significant events

Deaths

Five patients treated with once-daily doses of lusutrombopag ranging from 0.5 to 3 mg for up to 7 days died across the clinical development program of lusutrombopag. Four deaths were reported in controlled studies (Study M0626 and M0634) and one death in an uncontrolled study (M0623). Two of the five subjects died after procedural complications. The maximum platelet count in these 2 subjects was 111,000/ěL. The non-procedural events with an outcome of death of the remaining three subjects were upper gastrointestinal haemorrhage, hepatic cirrhosis, multi-organ failure and cardiac arrest. The maximum platelet count in these 3 subjects was 79,000/ěL.

Table 3 Adverse Events with an Outcome of Death (All Studies)

(Study)	Lusutrombopag Dose (Day of Last Dose)	Adverse Event with Outcome of Death: No. of Days after Last Dose of Lusutrombopag: Onset of Event (Death)	Adverse Event with Outcome of Death: Preferred Term (Reported Term)
Controlled Studies			
(M0626)	2 mg (Day 7)	28 (28)	Upper gastrointestinal haemorrhage (upper gastrointestinal hemorrhage)
(M0634)	3 mg (Day 7)	20 [a] (21)	Multi-organ failure (multiple organ system failure), Cardiac arrest (death - cardiac arrest)
(M0634)	3 mg (Day 7)	15 (16)	Hepatic cirrhosis (decompensated liver cirrhosis)
(M0634)	3 mg (Day 6)	8 (18)	Vessel perforation (punctured terminal branch of internal mamary *[sic]* artery)
Uncontrolled Studies			
(M0623)	0.5 mg (Day 7)	4 (28)	Procedural complication (pleural hemorrhage due to injury to intercostal artery) Haemothorax/pleural haemorrhage [b] (pleural hemorrhage due to injury to intercostal artery)

[a] Acute renal failure first reported 13 days after the last dose; acute hepatic failure first reported 19 days after the last dose.

[b] Haemothorax based on MedDRA Version 18.0/pleural haemorrhage based on MedDRA Version 14.0.

Source: Study M0623 Translated Listing 16.2.10; ISS Listings 1.1.1 and 1.1.2

While none of the deaths were judged as being related to study drug by the investigators, the difference of five deaths in the lusutrombopag group and zero deaths in the placebo group is remarkable. It should be noted that three of five deaths occurred in the multinational phase 3 study (M0634) in the indicated dose of 3 mg lusutrombopag. It has been clearly shown that there is no obvious pattern in co-morbidities, co-medications or other risk factors that increased the likelihood of death with lusutrombopag treatment in this population. One patient with Child Pugh B liver disease died due to hepatic decompensation in the posttreatment period of study M0634. This patient experienced a rapid progression of the underlying disease. hTe medical history and the fatal outcome of this patient have been provided. The patient´s medical history included chronic viral hepatitis C and hepatic cirrhosis. In the medical death certificate completed by the treating physician it has been stated that the liver decompensation stage of this patient has been known since 2010 and thus the interval between the onset of pathological process and death was approximately 7 years. Additionally, the applicant provided a figure showing that liver function parameters (Alk phosphatase, ALT, AST and Bilirubin) were stable until day 15 (day of invasive procedure) and started to increase after day 15 whereas platelet counts started to decrease. Thus, no causal relationship of decompensated liver cirrhosis and lusutrombopag has been observed. Furthermore, one of 7 patients (14%) with Child-Pugh class C who were exposed to study drug has died (please refer to section safety in special populations).

All deaths occurred in the posttreatment period (13-28 days after last drug administration) of the study and could be attributable to the underlying medical condition or the procedural complications. Nevertheless, three out of five deaths were associated with bleeding events including the non-procedural event of upper gastrointestinal haemorrhage and two procedural complications where the subjects died

10 and 14 days after the complication. The posttreatment platelet counts of two subjects (treated with 2 and 3 mg lusutrombopag, respectively) remained above the pre-treatment values and above the margin of 50x109/L suggesting no correlation between platelet counts and the haemorrhagic event leading to the outcome of death. One Subject received platelet transfusion on day 10 and day 11. However, since this patient has been treated with 0.5 mg lusutrombopag, lack of efficacy seems comprehensible. Thus, no safety concerns related to therapeutic failure or a rebound effect after treatment discontinuation arise from these data.

The potential long-term toxicity of lusutrombopag was addressed by providing a summary of TEAE of two studies (M0621 and M0622) conducted in 20 patients with ITP who were treated with up to 2 mg lusutrombopag up to 387 days. The adverse event of bone marrow fibrosis has been reported in one subject on day 279. This is far from the intended 7-day treatment scheme and no safety concerns have been raised from the supportive studies.

Serious adverse events

In the pooled analysis of the controlled studies, 7 (4.1%) subjects treated with lusutrombopag 3 mg and 12 (7.1%) subjects treated with placebo had one or more serious nonfatal adverse events. In the uncontrolled studies, 8 (5.1%) subjects treated with lusutrombopag had one or more serious nonfatal adverse event. No SAEs were reported in the phase 1 studies.

The incidence of SAEs was low and similar between the lusutrombopag and placebo group. In the total pooled analysis, sinus node dysfunction (2 patients) and portal vein thrombosis (3 patients) were the only preferred terms reported for > 1 subject in the lusutrombopag 3 mg group. All other SAEs were reported in a single patient each. Except the thrombotic adverse events in the lusutrombopag 3 mg group and one event in the placebo group which were considered as related by the investigator all other serious adverse events were considered unrelated to the investigational product. The moderate treatment-related SAE of dehydration, hypokalemia, nausea and vomiting in the placebo group led to discontinuation of study drug administration. Treatment-related thrombotic SAEs were portal vein thrombosis in 3 subjects and cardiac ventricular thrombosis in 1 subject. All related SAEs resolved after drug discontinuation or corrective treatment. For a detailed evaluation of thrombotic events see section “adverse events of special interest”. In general, reported SAEs are considered to be consistent with the underlying medical condition of the study population and the nature of the invasive procedures.

Additionally, in the Phase 1/Phase 2 study (Study M0627) in subjects with Child-Pugh class C liver disease treated with lusutrombopag 3 mg (Study M0627), there was 1 nonfatal serious adverse event (decreased neutrophil count).

Laboratory findings

Hematological and biochemical parameters, coagulation status, vital signs (blood pressure and pulse rate) and ECG were evaluated. There were some minor changes in haematology parameters in subjects treated with Lusutrombopag Shionogi. Only slight differences between the placebo and Lusutrombopag Shionogi treatment groups for WBC and RBC could be observed.

There were minor changes in the biochemical laboratory parameters in subjects treated with Lusutrombopag Shionogi. AST, ALT and ALP values (mean change from baseline) showed an increase at day 14 in several patients. The increase of liver enzymes was higher in the Lusutrombopag Shionogi group than in the placebo group. This rise was reversible and has already decreased in most of the patients by the day of last observation (d35). The applicant provided additional tables presenting the number and proportion of subjects who showed an increase in liver enzymes (AST, ALT, ALP) on day 8, day 14/17 and day 35. The results of the submitted tables did not indicate a greater tendency for an increase of liver enzymes from baseline in patients treated with lusutrombopag than for patients treated

with placebo.For all other parameters and vital signs, no relevant changes have been observed after the treatment with Lusutrombopag Shionogi.

Due to the fact that protein binding of S-888711 was higher than 99.9%, there might be an increased risk related to the possibility of achieving uncontrollably high drug concentration in patients with hypoalbuminemia. This especially applies to principal findings such as increase in the activity of AST, ALT and ALP and prolongation of PT and APTT, as the risk of liver toxicity seems to be underestimated. Additional data were provided showing that in patients with hypoalbuminemia treatment with lusutrombopag is not associated with any greater risk of hepatic abnormalities than placebo. However, data were available for the relatively low proportion of subjects with low albumin at baseline.

Safety in special populations

Subgroup analyses of adverse events were performed on sex, age, race, liver function, invasive procedure and duration of treatment with regard to application of the stopping criterion. However, lusutrombopag effectiveness and safety was analysed in different rather small subgroups of age (<65, ≥65 and <75, ≥ 75), races (White vs Asian) and Child-Pugh classes. During evaluation, the Applicant argued that the experience in the clinical efficacy and safety studies is, however, supplemented by the pharmacokinetic/pharmacodynamic studies and analyses, including study M0627, a PK study in thrombocytopenic subjects with Child-Pugh class C liver disease and especially the population PK and population PK/PD analyses. In the light of the PK/PD analyses, the relatively low numbers of subjects in some categories is not considered clinically important.

Intrinsic factors

The incidence of adverse events was higher in females than in males in controlled studies. However the incidence of adverse events in females was also higher in the placebo group, therefore it does not give rise to concern. AEs in elderly ≥ 75 years of age increased in a higher proportion in the lusutrombopag group than in the placebo group. This finding was further elaborated by the applicant. The applicant argued that the low number of patients has to be considered and the small differences are often driven by one or two events. This finding could also be expected due to increased comorbidity and concomitant medication. Only procedural hypertension was reported at an incidence of >10% higher than in the placebo group. The applicant's arguments are acknowledged.

Lusutrombopag 3 mg administered orally once daily for up to 7 days appeared to be safe and well tolerated by thrombocytopenic subjects with CLD with Child-Pugh classes A and B who were undergoing an elective invasive procedure. However due to the limited number of patients suffering from Child-Pugh class C liver disease included in the studies no final conclusion on the safety of Lusutrombopag Shionogi in Child-Pugh class C patients can be drawn. During evaluation, the applicant provided additional post-marketing data and a thorough discussion regarding the safety profile of lusutrombopag in patients suffering from Child Pugh class C liver disease. The available safety database consists of the data from 8 subjects who have been treated with the intended dose of 3 mg lusutrombopag in the clinical development program and additional postmarketing surveillance data of 10 subjects. One of these eight subjects with Child Pugh class C liver disease died due to multiorgan failure considered probably secondary to sepsis caused by *C.difficile* infection and cardiac arrest 21 days after the last administration of lusutrombopag. The death was considered not related to the study drug since bacterial infection is a common complication in the course of cirrhosis and worsening of clinical and biochemical parameters in bacterial infection generally correlate with the severity of the liver disease.

The applicant provided additional literature showing that patients suffering from Child Pugh class C liver disease have a higher risk of bacterial infection and the mortality rate was approximately 5-fold higher in those patients compared to those without an infection. The provided post-marketing surveillance data

reported two additional deaths in patients with severe hepatic impairment. One subject died due to spontaneous bacterial peritonitis and one subject experienced serious hepatic cirrhosis and died due to intra-abdominal haemorrhage. The reported deaths seem to be consistent with the underlying medical condition of these patients and that there is no causal relationship between the reported outcomes of death and lusutrombopag treatment.

Among the 8 subjects in the clinical development program, acute kidney injury and anaemia were the only adverse events that have been reported in two subjects. All other adverse events were reported in single subjects. Additionally, during the clinical development program it has been observed that the incidence of adverse events was higher in patients with Child Pugh class B liver disease compared to those patients with less hepatic impairment (Child Pugh class A). It might be expected that the incidence of AEs further increase in patients suffering from Child Pugh class C liver disease. However, since no difference has been observed between the lusutrombopag and placebo group for each subgroup (Child Pugh class A and B), the incidence of AEs is likely to be higher due to the increased comorbidity and the underlying medical condition of this population.

Extrinsic factors:

Invasive Procedure

In the pooled controlled studies (M0626, M0631, and M0634), the incidence of adverse events was similar for lusutrombopag and for placebo in all invasive procedure subgroups. The incidence of adverse events was highest in subjects undergoing liver-related procedures in both the lusutrombopag and placebo groups. In the lusutrombopag group, ≥ 1 adverse event was reported for 83.6% of subjects undergoing liver-related procedures, 56.3% of subjects undergoing gastrointestinal/endoscopy-related procedures, and 42.9% undergoing other procedures. Corresponding percentages in the placebo group were 77.9%, 66.2%, and 55.6%. Adverse events in the System Organ Class of “Investigations” and “Injury, poisoning, and procedural complications” occurred with higher incidences in the subgroup undergoing liver-related procedures, but the incidences in lusutrombopag and placebo groups were similar.

Immunological events

No information has been given on the immunogenicity of Lusutrombopag Shionogi. Due to the fact that Lusutrombopag Shionogi represents a small molecule, no immunological reaction is to be expected.

Safety related to drug-drug interactions and other interactions

Coadministration of Lusutrombopag Shionogi with cyclosporine increased systemic exposure to lusutrombopag, and had an effect on the PK of lusutrombopag by P-gp and BCRP inhibition. Results of study M061E suggest that there was also a slight effect when coadministrated with cyclosporine on heart rate and QTc.

Discontinuation due to adverse events

Across the clinical development program, two lusutrombopag-treated healthy male subjects (Phase 1 study M0613) and one placebo-treated subject (Phase 3 study M0634) discontinued the study drug prematurely due to adverse events. One subject in the placebo group was withdrawn due to AEs of dehydration, hypokalemia, nausea and vomiting. The two healthy subjects in the lusutrombopag group were discontinued due to AEs of gastroenteritis and increased platelet count (>500,000/µl).

All reported AEs leading to withdrawal resolved after discontinuation of the investigational product. No withdrawal of study drug administration due to AEs has been reported for the indicated dose of 3 mg lusutrombopag. Overall, the rate of study drug discontinuation due to adverse events was very low across

the clinical development program and does not raise any safety concerns. In the pooled analysis of the controlled studies, four subjects discontinued study participation in the posttreatment period due to adverse events. Each of these reported adverse events had an outcome of death. More detailed justification and clarification of the backgrounds leading to the outcome of deaths has been provided by the Applicant (see section deaths).

2.6.1. Discussion on clinical safety

653 adult subjects were exposed to lusutrombopag in 20 clinical trials (317 subjects were healthy volunteers, dose: 0.1-50 mg). 285 were receiving a dose of 3 mg for up to 7 days (including 273 who underwent an invasive procedure). 343 subjects were included into controlled randomized studies receiving a dose of 3 mg of lusutrombopag or placebo (173/170). 108 subjects participating in uncontrolled studies received a treatment dose of 3 mg lusutrombopag. The number of subjects exposed to lusutrombopag seems adequate for the evaluation of the safety of Lusutrombopag Shionogi.

The rate of study drug discontinuations and discontinuations in the post-treatment period of the study due to AEs was very low and did not raise any safety concerns.

The most frequently reported related AEs were nausea (1.8% lusutrombopag, 1.2% placebo), headache (1.8%, none), portal vein thrombosis and rash.

The most frequently reported TEAEs were representative for the invasive procedures and the underlying medical condition of the study population. In the pooled analysis of the controlled studies, the most common TEAEs (>10%) were procedural pain (19.3% lusutrombopag, 17.1% placebo), postoperative fever (16.4%, 20.0%), procedural hypertension (16.4%, 15.3%) and increased AST (12.9%, 11.8%). Except for procedural pain (19.3% lusutrombopag, 17.1% placebo), increased ALT (8.8%, 5.9%) and increased blood bilirubin (5.3%, 2.4%), no adverse event was reported at a ≥ 2% difference in the total lusutrombopag group than in the placebo group. The majority of TEAEs occurred after the invasive procedure (60.6% lusutrombopag, 62.5% placebo). In the pooled analysis, no substantial differences were noted between the lusutrombopag and the placebo group.

AST, ALT and ALP values (mean change from baseline) showed an increase at day 14 in several patients. The increase of liver enzymes was higher in the Lusutrombopag Shionogi group than in the placebo group. This rise was reversible and has already decreased in most of the patients by the day of last observation (d35). The applicant states that there is no difference between 3 mg lusutrombopag and placebo, on average, for ALT, AST, ALP and Bilirubin. However, in study M0626 increased AST and ALT were reported more frequently in the lusutrombopag group compared to placebo (62.5% lusutrombopag, 20% placebo). Age, Child Pugh score and number of liver cancers of all patients in study M0626 have been investigated but no apparent correlation with the events of altered liver parameters could be determined. The Applicant provided additional tables presenting the number and proportion of subjects who showed an increase in liver enzymes (AST, ALT, ALP) on day 8, day 14/17 and day 35. The results did not indicate a greater tendency for an increase of liver enzymes from baseline in patients treated with lusutrombopag than for patients treated with placebo in study M0626. The results obtained in study M0626 were comparable with the results obtained from the pooled analysis of the controlled studies M0631 and M0634. Although the provided analysis does not satisfactorily explain the reported higher incidence of adverse events of increased liver parameters in patients treated with lusutrombopag compared to placebo in study M0626, no safety concerns related to hepatotoxicity arise from these data. In addition, the imbalance of liver parameter changes in the phase II trial M026 could very well have arisen due to chance with regard to the low numbers enrolled into each treatment arm.

A higher incidence of TEAEs has been observed in studies conducted in Japan (M0626 and M0631) compared to the multinational study (M0634). As a reason, the applicant mentions “more invasive procedures” in Asian subjects. Adverse events have been specified depending on the invasive procedure. The difference in the incidence of AEs in Asian and White subjects could not fully be explained by the differences of invasive procedures. However, the incidence of AEs is comparable in the lusutrombopag and placebo group and does therefore seem to be unrelated to the treatment. The reported TEAEs in the uncontrolled studies revealed a similar pattern to the controlled studies. No safety concerns arise from the submitted phase 1 studies.

The applicant has adequately captured the adverse events of special interest including thromboembolic events and worsening of liver function. The incidence of thromboembolic events was low and almost equally distributed between the lusutrombopag (1.8%) and placebo (2.4%) group. Thrombotic events were not associated with increased platelet counts > 200.000/µl. However, it might be possible that any substantial elevation of platelet numbers increases the risk in patients with chronic liver disease who have a procoagulant predisposition. This risk is appropriately reflected in section 4.4 and 4.8 of the SmPC. The incidence of irreversible changes of liver function parameters was low in lusutrombopag-treated patients.

The overall incidence of nonfatal SAEs was low across the clinical development program. The majority of SAEs were assessed as unrelated to the study medication. Three thromboembolic events in the lusutrombopag 3-mg group were judged as being related to the drug. This risk is adequately handled in section 4.4 and 4.8 of the SmPC. For a detailed evaluation of thromboembolic events see “adverse events of special interest”. The residual reported SAEs are considered to be consistent with the underlying disease of the study population and the nature of the invasive procedure and do not raise any particular concern.

Five deaths occurred in patients treated with lusutrombopag doses ranging from 0.5 to 3 mg across the development programme. Two of the five subjects died after procedural complications. The remaining three subjects died due to upper gastrointestinal haemorrhage, hepatic cirrhosis, multi-organ failure and cardiac arrest. Although three of five deaths occurred in the multinational phase 3 study (M0634), there was no obvious pattern in co-morbidities, co-medications or other risk factors that increased the likelihood of death with lusutrombopag treatment in this population. One patient with Child Pugh class B liver disease died due to hepatic decompensation in the posttreatment period of study M0634. Since this patient experienced a rapid progression of the underlying disease, the medical history and the fatal outcome of this patient has been discussed more thoroughly by the applicant. In the medical death certificate completed by the treating physician it has been stated that the liver decompensation stage of this patient has been known since 2010 and thus the interval between the onset of pathological process and death was approximately 7 years. There is no causal relationship between liver decompensation and lusutrombopag. Moreover, three deaths including the procedural complications and the upper gastrointestinal hemorrhage were associated with bleeding events. The list of platelet counts for each subject with an outcome of death associated with a bleeding event showed that the posttreatment platelet counts of two subjects (treated with 2 and 3 mg lusutrombopag, respectively) remained above the pretreatment values and above the margin of $50x10^9$/L suggesting no correlation between platelet counts and the haemorrhagic event leading to the outcome of death. One Subject received platelet transfusion on day 10 and day 11. However, since this patient has been treated with 0.5 mg lusutrombopag, lack of efficacy seems comprehensible. Thus, no safety concerns related to therapeutic failure or a rebound effect after treatment discontinuation arise from these data.

Co-medication with interferon preparations and splenectomy were defined as exclusion criteria across the entire clinical development program. Since this may have an impact on the safety profile of lusutrombopag, a warning has been added in section 4.4 of the SmPC.

Although lusutrombopag is intended to be administered for short-term use (7 days), a potential long term toxicity including potential increased risk of bone marrow fibrosis cannot be fully excluded for patients suffering from CLD and thrombocytopenia. However, data from supportive studies in ITP patients treated with up to 2 mg lusutrombopag for up to 387 days did not give raise to further safety concerns.

Due to the application of a stopping criterion in most of the clinical studies, a lower proportion of subjects received 7 days of treatment in the lusutrombopag group than in the placebo group (73.1% versus 91.2%). In the SmPC, a fixed 7 day administration is proposed and no stopping criterion has been foreseen for the treatment with lusutrombopag.
The presented data indicate a slightly improved efficacy of lusutrombopag at a fixed 7-day treatment regimen. Conversely, comparative assessment of safety data is uncertain due to the sparsity of data. However, it is considered that data presented do not implicate a substantial safety issue with regard to a 7-day treatment with lusutrombopag without the application of a stopping criterion. For patients at risk (i.e. low bodyweight, PK interactions, Child Pugh class C) further monitoring is advised in the SmPC.

Some subjects were included in more than one clinical study or received lusutrombopag in 2 treatment groups within the same study. Data observed at retreatment have been excluded from the pooled analysis. Due to the very sparse set of data available, the fact, that there is limited data in retreatment with lusutrombopag has been reflected in section 4.4 of the SmPC.

There is a limited number of patients suffering from Child-Pugh class C liver disease included in the studies. The Applicant provided additional post-marketing data and a thorough discussion regarding the safety profile of lusutrombopag in patients suffering from Child Pugh class C liver disease. It might be expected that the incidence of AEs and the rates of deaths are likely to be higher due to the increased comorbidity and the underlying medical condition of this population. In addition to the death reported during the clinical development program, two deaths have been reported in the provided post-marketing surveillance data in patients suffering from Child Pugh class C liver disease. The applicant thoroughly justified and clarified the backgrounds leading to the outcome of death. Two of three subjects died due to bacterial infection. Since bacterial infection is a common and life-threating complication of cirrhosis, the reported deaths seem to be consistent with the underlying medical condition of these patients. Although the provided safety database is limited in patients with Child Pugh class C liver disease, there is an unmet medical need in this subgroup of patients. The warning statement is considered adequate to further improve the safety in Child Pugh C patients by additional monitoring. Additionally, a PASS will be conducted by the applicant which will collect safety data for lusutrombopag in patients with Child Pugh C liver disease in a systematic manner.

2.6.2. Conclusions on the clinical safety

Lusutrombopag 3 mg administered orally once daily for up to 7 days was shown to be safe and well tolerated by thrombocytopenic subjects with CLD with Child-Pugh classes A and B who were undergoing an elective invasive procedure.

However, only 8 patients with Child-Pugh class C received lusutrombopag and one of these patients has died during the clinical development program. It might be expected that the incidence of AEs and the rates of deaths are likely to be higher due to the increased comorbidity and the underlying medical condition of this population. In addition to the death reported during the clinical development program, two deaths have been reported in the provided post-marketing surveillance data in patients suffering from Child Pugh class C liver disease. Although the provided safety database is limited in patients with Child Pugh class C liver disease, there is an unmet medical need in this subgroup of patients. The warning statement in the SmPC is considered adequate to further improve the safety in Child Pugh C patients by

additional monitoring. Additionally, a PASS will be conducted by the applicant which will collect safety data for lusutrombopag in patients with Child Pugh C liver disease in a systematic manner.

2.7. Risk Management Plan

Safety concerns

Summary of Safety Concerns	
Important Identified Risks	Thrombotic/thromboembolic complications
Important Potential Risks	None
Missing Information	Pregnant and lactating women Patients with Child-Pugh class C liver disease Patients with a history of splenectomy Patients receiving concomitant interferon preparations Repeated use for invasive procedures Safety in patients requiring highly invasive procedures Off label use in long term treatment

Pharmacovigilance plan

Study **Status**	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 3 - Required additional pharmacovigilance activities				
Hepatic safety of Lusotrombopag Shionogi in patients with Child Pugh Class C liver disease Planned	To assess the hepatic safety of Lusotrombopag Shionogi used in patents with Child Pugh class C liver disease To assess the level of platelet increase achieved following Lusotrombopag Shionogi use in patients with Child Pugh class C liver disease	Missing information in Patients with Child Pugh class C liver disease	Study protocol finalised Feasibility study initiated Feasibility study report to PRAC Study initiation Interim reports on patient accrual Final study report	3 months after EC decision (Q2 2019) Q2/3 2019 Q3 2020 Q4 2020 Provided in each PSUR 30 Dec 2025

The PRAC, having considered the data submitted, is of the opinion that the proposed post-authorisation PhV development plan could be sufficient to identify and characterise the risks of the product, provided a study protocol is submitted for review within 3 months after EC decision.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Thrombotic/Thromboembolic Complications	Routine risk minimisation measures: *SmPC Section 4.4 and 4.8* *PL Section 2 and 4* *No other risk minimisation measures applicable*	Routine Pharmacovigilance activities
Use in Pregnant or lactating Women	Routine risk minimisation measures: *SmPC Section 4.6* *PL Section 2*	Routine Pharmacovigilance activities
Use in Patients with Child-Pugh Class C Liver Disease	Routine risk minimisation measures: *SmPC Section 4.2, 4.4 and 5.2* *PL Section 2*	Routine Pharmacovigilance activities including specific questions on CP C class on follow up forms PASS to study impact of Lusotrombopag Shionogi on platelets and LFT values
Use in patients with a history of splenectomy	Routine risk minimisation measures: *SmPC Section 4.4* *PL Section 2*	Routine Pharmacovigilance activities
Use in patients concomitantly receiving interferon preparations	Routine risk minimisation measures: *SmPC Section 4.4* *PL Section 2*	Routine Pharmacovigilance activities
Repeated use for invasive procedures	Routine risk minimisation measures: *SmPC Section 5.1*	Routine Pharmacovigilance activities
Safety in patients requiring highly invasive procedures	Routine risk minimisation measures: *SmPC Section 4.4*	Routine Pharmacovigilance activities
Off label use in long term treatment	Routine risk minimisation measures: *SmPC Section 4.2*	Routine Pharmacovigilance activities

Conclusion

The CHMP and PRAC considered that the risk management plan version 2.0 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the IBD to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request an alignment of the PSUR cycle with the international birth date (IBD). The IBD is 28.09.2015.

2.9. New Active Substance

The CHMP, based on the available data, considers lusutrombopag to be a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lusutrombopag Shionogi (lusutrombopag) is included in the additional monitoring list as it is a new active substance.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Lusutrombopag is proposed for the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures.

3.1.2. Available therapies and unmet medical need

At present, the only treatment option for patients with chronic liver disease and with a bleeding risk due to severe thrombocytopenia prior to invasive procedures is the administration of platelet transfusions. There are no licensed pharmaceutical alternatives available in the EU. Although two different TPO receptor agonists are on the market, Revolade (eltrombopag) and Nplate (romiplostim), these are

licensed for treatment of ITP, thrombocytopenia associated with hepatitis C infection preventing antiviral therapy and acquired severe aplastic anaemia (Revolade) and ITP (Nplate).

It is possible for patients who receive repeated transfusions to become refractory and not achieve a sufficiently increased platelet count post transfusion. The indication for platelet transfusions is depending on the invasiveness of the procedure as well as the severity of the thrombocytopenia.

The prevalence of thrombocytopenia in patients with chronic hepatitis has been reported to be only 6%, but occurs in up to 78% of patients with cirrhosis. Moderate thrombocytopenia and severe thrombocytopenia are observed in approximately 13% and 1%, respectively, of cirrhotic patients (Thrombocytopenia in chronic liver disease, Markus Peck-Radosavljevic, Liver International. 2017;37:778–793). Literature on the prevalence and incidence of cirrhosis is scarce. However, available data suggest that about 0.1% of the European population is affected by cirrhosis, corresponding to 14-26 new cases per 100,000 inhabitants per year or an estimated 170,000 deaths per year (The Burden of Liver Disease in Europe; M. Blachier; EASL 2013).

3.1.3. Main clinical studies

The dossier of lusutrombopag contains two pivotal clinical trials (M0631, M0634) and an additional phase IIIb clinical trial (M0633).

Both pivotal trials were randomized, double-blind, multi-centre studies that enrolled patients suffering from chronic liver disease with Child-Pugh class A or B severity and thrombocytopenia below 50.000/µL planned to undergo elective invasive procedures, e.g. liver ablation, endoscopic variceal ligation etc. Trial M0631 enrolled 96 Japanese subjects, while trial M0634 enrolled 215 mainly Caucasian subjects and randomized them 1:1 to lusutrombopag 3mg per day or placebo up to 7 days. Both trials applied a stopping criterion on day 5, 6 and 7 before administration of the study medication. If the platelet count was ≥50.000 and showed an increase of ≥20.000 over baseline on any of these days, the treatment was terminated. This stopping criterion was introduced to prevent an excessive increase in platelet counts, which is associated with a heightened risk for thromboembolic events. Thus, a proportion of subjects in each trial received less than a 7 day regimen with lusutrombopag (or placebo).

The phase IIIb trial M0633 was an open-label, parallel-group trial in Japanese subjects with CLD and severe thrombocytopenia planned to undergo an elective procedure. This study endeavoured to investigate the impact of a less strict or no stopping criterion in two arms, respectively (A/B-1, n=47; A/B-2, n=47) and repeated treatment with lusutrombopag in a third arm (n=8).

3.2. Favourable effects

The primary efficacy endpoint in phase III trial M0631 (i.e. no transfusion before primary invasive procedure) could be reached by 79.2% (CI 65.0, 89.5%) of patients receiving lusutrombopag and 12.5% (CI 4.7, 25.2%) of placebo recipients in the FAS. In the multinational trial M0634, 64.8% (CI 53.1, 72.1%) of patients in the lusutrombopag group and 29.9% (CI 20.6, 38.5%) in the placebo group in the FAS met this endpoint, which was defined as a secondary efficacy outcome.

The primary efficacy endpoint in phase III trial M0634 (i.e. no transfusion before primary invasive procedure and no rescue therapy for bleeding through 7 days after the invasive procedure) could be reached by 64.8% (CI 55.0, 73.8%) of subjects in the lusutrombopag group compared to 29.0% (CI 20.6, 38.5%) in the placebo group in the FAS.

In trial M0631, 75.5% (CI 61.1, 86.7%) of the lusutrombopag subjects and 12.5% (CI 4.7, 25.2%) of placebo subjects met the post hoc calculated endpoint (i.e. the avoidance of platelets pre-procedurally as well as no need for rescue therapy for bleeding during 7 days after the procedure). This outcome measure

is considered to be even more clinically relevant than the primary endpoint used in M0631 (proportion of patients who did not need a transfusion before the primary invasive procedure), because this endpoint demonstrates the continued protection against bleeding events during the healing period.

The efficacy outcomes from trial M0633 are comparable to those of trial M0631, with 80.9% (CI 66.7, 90.9%) of subjects in arm A/B-1, 83.0% (CI 69.2, 92.4%) in A/B-2 and 75% (CI 34.9, 96.8%) in non-naïve A/B requiring no platelet transfusions prior to the invasive procedure.

3.3. Uncertainties and limitations about favourable effects

Considering that lusutrombopag is excreted mainly via the feces; the impact on the PK of lusutrombopag is likely therefore there is an uncertainty with regards to the use of Lusutrombopag Shionogi in patients with severe hepatic impairment (Child-Pugh class C). For Child-Pugh class A and B only modest differences in PK were observed. Unfortunately only very few subjects with Child-Pugh class C were available for evaluation. The PK/PD modelling seems to indicate that no clinically significant differences are to be expected on platelet increase of lusutrombopag in patients with different severity of hepatic impairment. Nonetheless, a warning statement has been added in section 4.4. of the SmPC concerning close monitoring for early signs of worsening and platelet counts monitoring in Child Pugh Class C subjects in order to ensure safety in this subgroup of patients with an unmet medical need. This has also been added as missing information in the RMP.

Patients with past or present thrombosis (e.g., cerebral infarction, myocardial infarction, angina pectoris, pulmonary thromboembolism, deep vein thrombosis, disseminated intravascular coagulation syndrome) were not enrolled into the clinical trials. However, it is not warranted to exclude all patients with any thromboembolic event from the indication. An appropriate statement in section 4.4 of the SmPC covers all at risk groups and is deemed sufficient to alert the treating physician to a potentially increased risk of thrombotic or thromboembolic events. This has also been added as an important identified risk in the RMP.

Concerning the severity of the planned invasive procedure, only interventions with a mild to moderate bleeding risk were allowed during the clinical investigation programme. Major surgery like laparotomy, thoracotomy, craniotomy, open-heart surgery or organ resection was excluded in all clinical trial protocols. This is reflected accordingly in section 4.4. of the SmPC.

In all clinical trials pertaining to dose-finding and efficacy, subjects with splenectomy or concomitant interferon therapy were consistently excluded and not all observed outcomes can be readily extrapolated to those patients. Appropriate statements to this effect have been included in scetion 4.4. of the SmPC.

A trend to higher peak platelet counts in patients with very low body weight <45 kg was observed. Therefore, additional platelet monitoring is considered warranted for this subpopulation and a warning has been added accordingly in the SmPC.

3.4. Unfavourable effects

653 adult subjects were exposed to lusutrombopag in the course of 20 clinical trials (317 subjects were healthy volunteers, dose: 0.1-50 mg). The most frequently reported TEAEs were representative of the invasive procedures and the underlying medical condition of the study population.

In the pooled analysis of the controlled studies, the most common TEAEs (>10%) were procedural pain (19.3% lusutrombopag, 17.1% placebo), postoperative fever (16.4%, 20.0%), procedural hypertension (16.4%, 15.3%) and increased AST (12.9%, 11.8%). Except procedural pain (19.3% lusutrombopag, 17.1% placebo), increased ALT (8.8%, 5.9%) and increased blood bilirubin (5.3%, 2.4%), no adverse event was reported at a ≥ 2% difference in the total lusutrombopag group than in the placebo group. The

majority of TEAEs occurred after the invasive procedure (60.6% lusutrombopag, 62.5% placebo). No substantial differences were noted between the lusutrombopag and the placebo group. The reported TEAEs in the uncontrolled studies revealed a similar pattern to the controlled studies.

Thromboembolic events and worsening of liver function are adverse events of special interest. Three thromboembolic events in the lusutrombopag 3-mg group were judged as being related to the drug. The incidence of thromboembolic events was low and almost equally distributed between the lusutrombopag (1.8%) and placebo (2.4%) group. Thrombotic events were not associated with increased platelet counts. The incidence of persistent worsening of liver function was low. One subject in the lusutrombopag 3 mg group and 3 subjects in the placebo group had still altered laboratory values after the last observation on day 35. A warning is reflected in section 4.4. of the SmPC.

Five patients treated with lusutrombopag ranging from 0.5 to 3 mg and none treated with placebo died across the development programme of lusutrombopag. Two of the five subjects died after procedural complications. The remaining three subjects died due to upper gastrointestinal haemorrhage, hepatic cirrhosis, multi-organ failure and cardiac arrest. All reported deaths were judged as being unrelated to the drug.

3.5. Uncertainties and limitations about unfavourable effects

Although the provided safety database is limited with regard to patients with Child Pugh class C liver disease, there is an unmet medical need in this subgroup of patients. The warning statement in the SmPC is considered adequate to manage the potential risks in patients with Child Pugh class C liver disease by additional monitoring for early signs of worsening or new onset hepatic encephalopathy, ascites, and thrombotic or bleeding tendency through monitoring of liver function tests, tests used for assessing clotting status and through imaging of portal vasculature. Additionally, a PASS will be conducted by the Applicant, which will collect safety data for lusutrombopag in patients with Child Pugh C liver disease in a systematic manner.

In Study M0626 increased AST and ALT were reported more frequently in the lusutrombopag group compared to placebo (62.5% lusutrombopag, 20% placebo). The applicant provided additional tables presenting the number and proportion of subjects who showed an increase in liver enzymes (AST, ALT, ALP) on day 8, day 14/17 and day 35. The results did not indicate a greater tendency for an increase of liver enzymes from baseline in patients treated with lusutrombopag than for patients treated with placebo in study M0626. The results obtained in study M0626 were comparable with the results obtained from the pooled analysis of the controlled studies M0631 and M0634. Although the provided analysis does not satisfactorily explain the reported higher incidence of adverse events of increased liver parameters in patients treated with lusutrombopag compared to placebo in study M0626, no safety concerns related to hepatotoxicity arise from these data. In addition, the imbalance of liver parameter changes in the phase II trial M026 could very well have arisen due to chance with regard to the low numbers enrolled into each treatment arm.

With regards to duration of treatment, the presented data indicate a slightly improved efficacy of lusutrombopag at a fixed 7-day treatment regimen. Conversely, comparative assessment of safety data is uncertain due to the sparsity of data. However, it is considered that data presented do not implicate a substantial safety issue with regard to a 7-day treatment with lusutrombopag without the application of a stopping criterion. For patients at risk further monitoring is advised in section 4.4. of the SmPC.

3.6. Effects Table

Table 37: Effects Table for Lusutrombopag Shionogi in the treatment of thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures.

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
Pivotal trial M0631 (Japan)			**Lusutrombopag Shionogi 3mg N=48**	**Placebo N=48**	Double-blind, randomized, multi-centre trial	Efficacy Section
No platelets Before procedure	Proportion of patients who required no platelet transfusion prior to invasive procedure	%	79.2% (38/48) 95% CI: 65.0, 89.5	12.5% (6/48) 95% CI 4.7, 25.2		
No platelets during study (35 days)	Proportion of patients who required no platelet transfusion during the study	%	79.2% (38/48) 95% CI 65.0, 89.5	12.5% (6/48) 95% CI 4.7, 25.2		
Responders	Proportion of Responders (a patient who achieved platelet count of ⩾ 50.000/ µL with an increase of ⩾ 20.000/µL from baseline)	%	77.1% (37/48) 95% CI 62.7, 88.0	6.3% (3/48) 95% CI 1.3, 17.2		
Pivotal trial M0634 (Multinational)			**Lusutrombopag Shionogi 3mg N=108**	**Placebo N=107**	Double-blind, randomized, multi-centre trial; 18 protocol deviations with regard to platelet transfusions	Efficacy Section
No platelets before procedure and no rescue for bleeding until day 7 post procedure	Proportion of subjects who required no platelet transfusion prior to the invasive procedure and no rescue bleeding from randomization through 7 days after the procedure	%	64.8% (70/108) 95% CI 55.0, 73.8	29.0% (31/107) 95% CI 20.6, 38.5		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
No platelets during study (35 days)	Proportion of patients who required no platelet transfusion during the study	%	63.0% (68/108) 95% CI 53.1, 72.1	29.0% (31/107) 95% CI 20.6, 38.5		
Responders	Proportion of Responders (a patient who achieved platelet count of ⩾ 50.000/ µL with an increase of ⩾ 20.000/ µL from baseline)	%	64.8% (70/108) 95% CI 55.0, 73.8	13.1% (14/107) 95% CI 7.3, 21.0		
Unfavourable Effects						
AESIs	Randomized, placebo controlled trials	Phase IIb: **M0626** (Arm receiving Lusutrombopag Shionogi 3 mg only) Phase III: **M0631; M0634** N=341				Safety Section
		Lusutrombopag Shionogi 3 mg N=171		Placebo N=170		
Thrombotic events		1.8% (3/171)	2.4% (4/170)			
Worsening of Liver function		2.3% (4/171)	4.7% (8/170)			
Deaths		1.8% (3/171)	0% (0/170)			

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The efficacy of lusutrombopag in raising platelet levels sufficiently to avoid platelet transfusions was clearly demonstrated across the six phase II and phase III trials. Up to 80% of patients with CLD and severe thrombocytopenia were able to forego pre-procedural transfusions, and nearly the same proportion could avoid platelets during the whole study period of 35 days. A clinically even more relevant outcome, the avoidance of platelets pre-procedurally as well as no need for rescue therapy for bleeding during 7 days after the procedure, could be met by 64.8% and 75.5% of patients on lusutrombopag in the pivotal trials M0634 (primary endpoint) and M0631 (calculated post hoc), respectively. This is in contrast to only 29% and 12.5% of patients who require no platelets during the study period in the placebo groups of trial M0634 and M0631. Because no major issues with regard to methodology were noticed for either study, estimates of a positive treatment effect difference (following the ITT principle) can be considered reliable and statistically significant. The notion that lusutrombopag is an effective treatment modality is further supported by compatible results on secondary endpoints, as well as sensitivity analyses based on the per-protocol population.

An increase in platelet counts was apparent after 5-6 days of treatment, with a peak of about 12-14 days after initiation of lusutrombopag. Platelet levels returned to baseline after approximately 28 days, thus affording patients' protection against bleeding events during and after the planned invasive procedure, i.e. during the healing process. In contrast, transfused platelets have a short lifespan and their effect usually disappears after 3 to 4 days at the latest. This kinetic could be readily observed in the placebo patients receiving transfusions.

The ability to avoid platelet transfusions, which have to be administered under medical supervision and which are associated with other transfusion reactions is considered an important benefit for this gravely ill population. Platelet concentrates account for near 10% of all labile blood components but are responsible for more than 25% of the reported adverse events (Garraud et al. Blood Transfus 2016; 14: 109-22).

The observed unfavourable effects were generally consistent with the multi-morbidity of the investigated population and the nature of the invasive procedure and no substantial imbalance with regards to the nature and severity of adverse events observed in the placebo group was apparent. The vast majority of TEAEs were reversible, and in the clinical phase II and III trials with the 3mg dose, there were no treatment withdrawals due to unwanted effects.

Uncertainties in subpopulations that have not been well characterised (e.g. body weight below 45kg) or were excluded from the study population (e.g. patients with splenectomy) can be addressed with additional safety precautions in the Summary of Product Characteristics.

3.7.2. Balance of benefits and risks

Lusutrombopag was administered orally once daily for up to 7 days in 6 phase II and phase III trials. Its ability to elevate platelet counts and thus lower the bleeding risk during and after invasive procedures, as substantiated by the avoidance of platelet transfusions preprocedurally as well as rescue medication for bleeding until 7 days after the intervention, could be able to outweigh the observed unfavourable effects. These effects consist mostly of events related to the morbidity of the patient population and the invasiveness of the procedure, e.g. pain, fever, hypertension and elevation of liver enzymes.

The proposed fixed 7-day dosing regimen is supported by limited data only. Additional platelet monitoring at least once approximately 5 days after the first lusutrombopag dose is advised and reflected in the SmPC for the different subsets of patients at higher risk, i.e, patients with Child Pugh C liver disease and patients with body weight ≤45 kg. Appropriate measures such as discontinuation of lusutrombopag should be taken, if the platelet count reaches ≥50,000/µL as a result of a 20,000/µL increase from baseline..

The available data pertaining to patients with the most severe liver disease (Child-Pugh Class C) are limited. However, efficacy of lusutrombopag in patients with Child Pugh class C disease is likely to be comparable to patients with a lesser grade of liver disease. This notion is supported by the evaluation of efficacy in those patients who were included into the clinical development programme or identified in post marketing surveillance data from Japan. There is an unmet medical need in this subgroup of patients. The warning statement is considered adequate to manage the potential risks in Child Pugh C patients by additional monitoring for early signs of worsening or new onset hepatic encephalopathy, ascites, and thrombotic or bleeding tendency, through monitoring of liver function tests, tests used for assessing clotting status and through imaging of portal vasculature. Additionally, a PASS will be conducted by the Applicant which will collect safety data for lusutrombopag in patients with Child Pugh C liver disease in a systematic manner.

3.8. Conclusions

The overall B/R of Lusutrombopag Shionogi is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Lusutrombopag Shionogi is favourable in the following indication:

Lusutrombopag Shionogi is indicated for the treatment of severe thrombocytopenia in adult patients with chronic liver disease undergoing invasive procedures (see section 5.1).

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that lusutrombopag is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.