24 July 2025
EMA/CHMP/139482/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Romvimza

International non-proprietary name: vimseltinib

Procedure No. EMEA/H/C/006363/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Abbreviation	Definition
ADR	Adverse drug reaction
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
AUC0-inf	Area under the concentration-time curve from time-zero extrapolated to infinity
AUC_{0-t}	Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration
AUC0-xh	Area under the concentration-time curve from time-zero to x hour
BCRP	Breast cancer resistance protein
BCS	Biopharmaceutics Classification System
BIW	Biweekly, twice a week
BPI	Brief Pain Inventory
$C_{avg,ss}$	Average concentration during a dosing interval at steady state
CFU	Colony forming units
C_{max}	Maximum concentration observed
$C_{max,ss}$	Maximum concentration during a dosing interval at steady state
$C_{min,ss}$	Minimum concentration during a dosing interval at steady state
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/F	Apparent total body clearance
CNS	Central nervous system
COA	Clinical outcome assessment
CPK	Creatine phosphokinase
CQA	Critical quality attribute
CR	Complete response
CSF1	Colony-stimulating factor 1
CSF1R	Colony-stimulating factor 1 receptor
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCO	Data cutoff
DDI	Drug-drug interaction
DOR	Duration of response
DP-7005	Metabolite of vimseltinib
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
EQ-5D-5L VAS	EuroQoL 5 Dimension 5 Level Visual Analogue Scale
E-R	Exposure-response
EU	European Union
FDA	Food and Drug Administration
FIH	First-in-human
FLT3	FMS-like tyrosine kinase 3
FT-IR	Fourier transform infrared spectroscopy
GC	Gas chromatography
GLP	Good laboratory practice
hAME	Human absorption, metabolism, and excretion
HDPE	High density polyethylene
hERG	Human ether-à-go-go-related gene
HI	Hepatic impairment

IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP-MS	Inductively coupled plasma mass spectrometry
IRR	Independent radiological review
ISS	Integrated safety summary
KIT	Cellular homologue of the feline sarcoma viral oncogene v-kit
LS	Least squares
MAA	Marketing authorisation application
MAT	Mean absorption time
MCID	Minimal clinically important difference
MedDRA	Medical Dictionary for Regulatory Activities
MPR	Metabolite-to-parent ratio
MST	Malignant solid tumour
MTD	Maximum tolerated dose
NCM	Nonclassical monocytes
NDA	New drug application
NLT	Not less than
NMT	Not more than
NOAEL	No-observed-adverse-effect-level
NRS	Numeric rating scale
OCT2	Organic cation transporter 2
oPA	Oriented polyamide
ORR	Objective response rate
PBPK	Physiologically based pharmacokinetic
PDGFRA/B	Platelet-derived growth factor receptor alpha/beta
PF	Physical function
PGIC	Patient global impression of change
PGIS	Patient global impression of severity
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
PopPK	Population pharmacokinetic
PPI	Proton pump inhibitor
PR	Partial response
PRO	Patient-reported outcome
PROMIS-PF	Patient-reported Outcomes Measurement Information System-Physical Function
PT	Preferred term
PVC	Polyvinyl chloride
QC	Quality control
QD	Once daily
Q/F	Apparent inter-compartmental clearance
QoL	Quality of life
QTc	QT interval corrected for heart rate
QTcF	QT corrected by Fridericia's formula
RECIST v1.1	Response Evaluation Criteria in Solid Tumors version 1.1
REMS	Risk evaluation and mitigation strategy
RH	Relative humidity
ROM	Range of motion
rpm	rounds per minute
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
STD	Standard deviation
TAMC	Total aerobic microbial count
Tmax	Time of the maximum concentration

TEAE	Treatment-emergent adverse event
TGCT	Tenosynovial giant cell tumour
TKI	Tyrosine kinase inhibitors
TSE	Transmissible spongiform encephalopathy
TVS	Tumour volume score
TYMC	Total combined yeasts/moulds count
UPLC	Ultra performance liquid chromatography
USP	United States Pharmacopoeia
USP/NF	United States Pharmacopoeia/National Formulary
UV	Ultraviolet
Vc/F	Apparent central volume of distribution
Vp/F	Apparent peripheral volume of distribution
Vis	Visible
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Deciphera Pharmaceuticals (Netherlands) B.V. submitted on 29 June 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Romvimza, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 May 2023.

Romvimza, was designated as an orphan medicinal product EU/3/19/2227 on 16 December 2019 in the following condition: Treatment of tenosynovial giant cell tumour, localised and diffuse type.

The applicant applied for the following indication: Romvimza is indicated for treatment of adult patients with tenosynovial giant cell tumour (TGCT) who are not amenable to surgery.

1.2. Legal basis and dossier content

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).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0084/2022 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Applicant's request(s) for consideration

1.5.1. New active Substance status

The applicant requested the active substance vimseltinib 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.

1.6. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
25 March 2021	EMA/SA/0000049171	Pierre Demolis, Olli Tenhunen

The Protocol assistance pertained to the following non-clinical and clinical aspects:

- Acceptability of the non-clinical development package, including characterisation of metabolites and approaches to address carcinogenic and reproductive toxicity potential, in support of marketing authorisation application (MAA)
- Adequacy of the proposed clinical pharmacology study plan and rationale for the dose regimen to be used in further clinical development and MAA
- Design elements and enrolment criteria for the multicentre, double-blinded placebo-controlled pivotal phase 3 trial
- Selection of ORR per RECIST (v1.1) at Week 25 as primary endpoint and of selected secondary endpoints (and related statistical considerations) as measures of efficacy for Phase 3.
- Adequacy of the proposed phase 3 trial as single pivotal trial and of the planned safety dataset (and associated analyses) for benefit/risk determination

1.7. Steps taken for the assessment of the product

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

Rapporteur: Martin Mengel Co-Rapporteur: Jean-Michel Race

The application was received by the EMA on	29 June 2024
The procedure started on	18 July 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	11 October 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	24 October 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	14 November 2024
The applicant submitted the responses to the CHMP consolidated List of	21 February 2025

Questions on	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	14 April 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	10 April 2025
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	25 April 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 June 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	04 July 2025
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 Romvimza on	24 July 2025
Furthermore, the CHMP adopted a report on new active substance (NAS) status of the active substance contained in the medicinal product	24 July 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Tenosynovial giant cell tumour (TGCT) is a rare, non-malignant neoplasm involving the synovium and tendon sheaths that typically presents in young and middle-aged adults (de St Aubain Somerhausen and van de Rijn, 2013). Symptoms often include pain, stiffness, swelling, and reduced range of motion (ROM) of the affected joint, which may result in marked functional limitation. Localized forms of TGCT usually allow total resection with excellent or good clinical results and show little recurrence. However, diffuse forms of the disease can be challenging to manage surgically and local control is uncertain (van der Heijden et al, 2023).

Diffuse TGCT carries a risk of multiple recurrences, and affected patients often have more extensive involvement and a poorer likelihood of success with surgery (Gouin and Noailles, 2017; Staals et al, 2016). Surgical resection may involve removal of major tendons, neurovascular structures, or limbs, leading to significant postsurgical morbidity. The aim of systemic therapy in the context of a non-lethal tumour which is not amenable to surgery could be to reduce the tumour in a dimension which allows successful resection (neo-adjuvant setting) and to preserve joint function and ameliorate patient quality of life.

2.1.2. Epidemiology

TGCT is a rare pathology affecting young subjects, 4th and 5th decades for the more frequent localized form and a little earlier (<40 years) for the diffuse form (Stacchiotti et al, 2023).

The incidence of TGCT appears to be similar worldwide. In a review of a Scottish hospital case series, Monaghan et al. suggested an incidence of 20 cases of GCT-TS per million. Similarly, Ushijima et al. described an incidence of 25 cases per million in Kyushu, Japan. Diffuse TGCT and localized TGCT have an estimated annual incidence of 1.8 cases per million and 9.2 cases per million, respectively, in the United States (US). A more recent survey in Denmark provides an incidence of 4.4 per million for localized TGCT and 1.1 per million for diffuse TGCT, while in the Netherlands reports incidence rates per million patient-years of 34 for localized TGCT in the digits, 11 for localized disease in other extremities, and 5 for diffuse TGCT. The prevalence of TGCT in the European Union (EU), including localized disease and diffuse type disease, is estimated as 2 in 10,000.

2.1.3. Biologic features, aetiology and pathogenesis

The consensual etiopathogenesis was proposed by West et al.: there is a "landscape effect of tenosynovial giant cell tumour" caused by translocation of a small number of cells. TS-GCT and the more aggressive pigmented villonodular synovitis are essentially the same, comprising mono- and multinuclear cells; translocation involving locus 1p 13 is found in most TGCTs, in a small proportion of cells (2–16%) with hyperexpression of CSF1. These tumour cells recruit macrophages bearing CSF1-R receptor, differentiate into multinuclear cells and create the aggressive multinuclear "landscape" of TGCT. This biological understanding opens the way, for potential targeted therapies.

2.1.4. Clinical presentation, diagnosis

Tenosynovial giant cell tumour is a rare tumour arising from the synovium of joints, bursae, and tendon sheaths (de St Aubain Somerhausen and van de Rijn, 2013) caused by dysregulation of the CSF1 gene, which results in overproduction of CSF1 and recruitment of CSF1R-dependent inflammatory cells into the affected joint (van der Heijden et al, 2023; West et al, 2006). The lesion can either present as a single nodule (localized form) or as multiple nodules (diffuse form) along a synovial layer or tendon sheath.

2.1.5. Management

The recommended treatment of this neoplastic disease is mainly resection; however, it is fully acknowledged that in diffuse TGCT it is more difficult to eradicate the tumour by surgery only and even total or near total synovectomy is often not successful in the diffuse subtype of TGCT. For the time being, there is no authorised medicinal product in the EU for this disease. There is no universally accepted standard of care for patients with diffuse TGCT. Practically, despite a lack of hard evidence, once TGCT has been diagnosed, different situations can be distinguished:

- symptoms are absent or mild (primary disease or recurrence): as there is no systemic risk, and given present-day means of imaging surveillance progression can be monitored on radiological and clinical surveillance;
- symptomatic localized forms: maximal resection is recommended (van der Heijden et al, 2023);
- symptomatic diffuse articular forms:
    - first-line resection should be as complete as possible (combined arthroscopic and open surgery in the knee; arthroscopic or open surgery in the hip, according to extension and location). Isotopic synoviorthesis or external RT may be considered as adjuvants, especially when synovectomy was incomplete and in joints other than the knee.
    - in recurrence or rapid progression, when total resection is not feasible or would induce severe morbidity, options comprise subtotal resection with adjuvant therapy, or exclusive therapy. This includes systemic treatment by targeted therapy (off-label use of imatinib recommended by NCCN guidelines, or nilotinib) or radiation therapy (Gronchi et al, 2021; Stacchiotti et al, 2023).

Considering the severe morbidity that a patient can experience with diffuse TGCT in recurrence, (or rapid progression), when surgery is not appropriate (or unresectable disease) and when radiotherapy is not an option, a systemic therapy that provides a meaningful clinical benefit is highly needed.

With respect to a systemic treatment option pexidartinib, a product with a similar mechanism of action and significant severe hepatotoxicity, was approved in the US, but due to a negative benefit-risk balance not in the EU.

2.2. About the product

Mode of action: vimseltinib is a highly selective small molecule TKI that targets CSF1R. Vimseltinib has >100-fold selectivity for inhibition of CSF1R versus all other kinases tested and >500-fold selectivity for other closely related type III receptor tyrosine kinases (KIT, PDGFRA/B, and FLT3). *In vitro* enzyme and cell-based assays have shown that vimseltinib inhibited CSF1R autophosphorylation and signalling induced by CSF1

ligand binding, as well as cellular function and proliferation of cells expressing CSF1R. Vimseltinib also inhibited CSF1R expressing cells and blocked downstream signalling in preclinical models in vivo.

Pharmacological classification: not yet assigned

Claimed indication: Romvimza is indicated for treatment of adult patients with TGCT who are not amenable to surgery.

Final approved indication: Romvimza is indicated for treatment of adult patients with symptomatic tenosynovial giant cell tumour (TGCT) associated with clinically relevant physical function deterioration and in whom surgical options have been exhausted or would induce unacceptable morbidity or disability.

The recommended dose of Romvimza is 30 mg taken twice weekly at least 72 hours apart as long as benefit is observed or until unacceptable toxicity.

2.3. Type of application and aspects on development

The legal basis for this application refers to: Article 8.3 of Directive 2001/83/EC, as amended – complete and independent application.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as hard capsules containing 14 mg, 20 mg or 30 mg vimseltinib (as vimseltinib dihydrate).

Other ingredients are:

Capsule content: lactose monohydrate, crospovidone (E 1202) and magnesium stearate (E 470b).

Capsule shell: gelatine, titanium dioxide (E 171), brilliant blue FCF (E 133) (30 mg hard capsule), erythrosine (E 127) (30 mg hard capsule), sunset yellow FCF (E 110) (14 mg and 20 mg hard capsules) and tartrazine (E 102) (20 mg hard capsule).

Printing ink: shellac (E 904), propylene glycol (E 1520), potassium hydroxide (E 525) and black iron oxide (E 172).

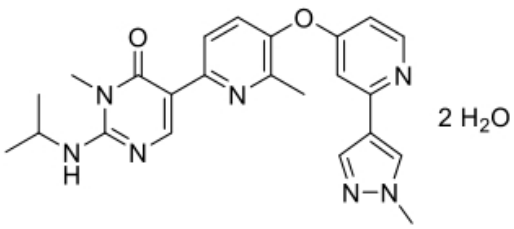
The product is available in oPA/aluminium foil/PVC film blisters with push through aluminium foil lidding as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of vimseltinib is 3-methyl-5-[6-methyl-5-[2-(1-methylpyrazol-4-yl)pyridin-4-yl]oxypyridin-2-yl]-2-(propan-2-ylamino)pyrimidin-4-one, dihydrate corresponding to the molecular formula $C_{23}H_{25}N_7O_2 \bullet 2H_2O$ ($C_{23}H_{29}N_7O_4$). It has a relative molecular mass of 467.52 g/mol and the following structure:

Figure 1. Active substance structure



The chemical structure of vimseltinib was elucidated by a combination of elemental analysis, infrared spectroscopy, UV/Vis spectrometry, nuclear magnetic resonance spectroscopy (^{1}H and ^{13}C NMR), single crystal X-ray analysis and mass spectroscopy. The solid-state properties of the active substance were studied by X-ray powder diffraction, differential scanning calorimetry, dynamic vapour sorption and laser diffraction.

The active substance vimseltinib is a white to off-white solid, which shows pH-dependent aqueous solubility. Vimseltinib is freely soluble in water under acidic conditions at pH 1 but is only very slightly soluble at pH 3 and above. Vimseltinib is slightly hygroscopic and has a non-chiral molecular structure.

Polymorphism has been observed for vimseltinib. It has been demonstrated that the manufacturing process consistently produces one form, and that the polymorphic form is stable throughout the retest period of the active substance. The polymorphic form is routinely controlled in the active substance specification.

2.4.2.2. Manufacture, characterisation and process controls

The active substance is manufactured by one manufacturing site. Satisfactory GMP documentation of the site has been provided.

Vimseltinib is synthesised in four main steps using well defined starting materials with acceptable specifications. The manufacturing process is adequately described in the dossier and a detailed description of each synthetic step is provided. Adequate in-process controls are applied during the synthesis. The manufacturing process has been developed using a combination of conventional univariate studies and elements of Quality by Design, namely design of experiments (DoE), but no design space is claimed.

Potential and actual impurities are discussed with regards to their origin, and characterised. The control of impurities is supported by fate and purge studies. Based on these studies, six impurities have been included in the active substance specification as specified impurities. The provided information sufficiently demonstrates the ability of the process to remove relevant impurities to or below acceptable limits.

A major objection was initially raised regarding the information provided on the evaluation of potentially genotoxic impurities. In response, a mutagenicity assessment was conducted for all actual and potential impurities (including from intermediates, starting material and precursors as well as process impurities) in line with the requirements set out in ICH M7. The control strategy for (potentially) genotoxic impurities is acceptable. The major objection is resolved.

Solvents used in the manufacturing process for the active substance may contain traces of Class I solvents. The control strategy for residual solvents used in active substance manufacturing process is considered acceptable and in compliance with EU guidance (Annex I: Specifications for class 1 and class 2 residual solvents in active substances, CPMP/QWP/450/03, EMEA/CVMP/511/03).

Relevant elemental impurities are routinely controlled in the active substance specification.

The commercial manufacturing process for the active substance has been developed in parallel with the clinical development program. Changes introduced have been presented in sufficient detail and have been justified. The active substance used in initial toxicological and clinical studies was manufactured by a manufacturer different from the one proposed for marketing. Changes introduced to optimise the synthetic process have been presented in sufficient detail and have been justified. Overall, the purity of the active substance improved as a result of the development work.

The active substance is packaged in bags which comply with EC Regulation (EU) 10/2011, as amended.

2.4.2.3. Specification

The active substance specification includes tests for description, identity (FT-IR, UPLC), assay (UPLC), impurities (UPLC), residual solvents (GC), particle size distribution (laser diffraction), residual related substance (UPLC), residue on ignition (Ph. Eur.), solid form confirmation (XRPD), elemental impurities (ICP-MS), water content (Karl Fischer), microbial purity (Ph. Eur.) and absence of E. Coli (Ph. Eur.).

The specification for the active substance is acceptable and in line with the requirements set out in ICH Q6A. 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. Three specified impurities are controlled at the qualification threshold of NMT 0.15%. The limits are acceptable. The limit for any unspecified impurity in the active substance (NMT 0.10%) and the limit for total impurities (NMT 1.3%), respectively, is acceptable.

The proposed limits for residual solvents are set in line with ICH Q3C (Option 1). The limit (NMT 120 ppm) for the residual solvent isopropyl amine (class 2) is acceptable.

The limit for particle size distribution of the active is adequately justified.

The analytical methods used have been adequately described and non-compendial methods 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 from 3 commercial-scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch. Batch results have also been provided for various batches used in toxicological and clinical studies, and for stability studies. Overall, it can be concluded that the purity of the active substance has improved through the development process.

2.4.2.4. Stability

Stability data from three commercial-scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 36 months under long term conditions (25ºC / 60% RH) and for up to six months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. The analytical methods used were the same as for release and are stability indicating. All tested parameters were within the specifications and no significant trends were observed. Particle size distribution of the active substance showed no significant change.

Photostability testing following the ICH guideline Q1B was performed on one batch. All results were within specification. The active substance is not photosensitive.

Results from forced degradation studies have been presented. Samples were tested in the solid state as well as in solution/suspension. Samples were exposed to heat, light, aqueous acidic, aqueous basic and oxidative conditions. Degradation was observed under acidic conditions at elevated temperatures (10.79% degradation after 5 days in 0.1N HCl at 80°C). Some degradation was also observed under basic conditions at elevated temperatures (3.86% degradation after 5 days in 0.1N NaOH at 80 °C). No degradation was observed under thermal stress conditions (80°C for 14 day). An increase in assay was observed due to water loss from the samples. Minimal or no degradation was observed under oxidative or photolytic conditions.

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. The active substance does not require any special storage conditions.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Romvimza finished product is presented as a hard gelatine capsule. Romvimza is available in three strengths, containing 14 mg, 20 mg, or 30 mg vimseltinib (as vimseltinib dihydrate). The 14 mg hard capsule is size 4 (with a length of 14 mm), has a white opaque body and orange opaque cap, and is imprinted in black with "DCV14". The 20 mg hard capsule is size 2 (with a length of 18 mm), has a white opaque body and yellow opaque cap and is imprinted in black with "DCV20". The 30 mg hard capsule is size 1 (with a length of 19 mm), has a white opaque body and light blue opaque cap, and is imprinted in black with "DCV30". The three strengths are sufficiently distinguishable by size of the capsule, colour of the cap and by the imprinting.

The aim of formulation development was to develop an immediate release capsule dosage form of vimseltinib for oral administration.

The active substance is used in the stable polymorphic form. The active substance is classified as a BCS Class 2 substance with low solubility and high permeability. Solubility of the active substance is pH dependent, with higher solubility under acidic conditions (pH 1 to 3).

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards, with the exception of the colourants used in the capsule, which comply with Commission Regulation (EU) No 231/2012 for food additives. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report. The black iron oxide in the printing ink complies with the NF. Lactose monohydrate and the azo colouring agent sunset yellow FCF (E 110) are excipients with known physiological effect and are thus also listed in section 2 of the SmPC.

Pharmaceutical development has been sufficiently described. A summary describing the development of the formulation, including the definition of a quality target product profile (Table 1) as well as the identification of quality attributes which are critical for the proposed formulation was provided (CQAs: description, identification, assay, degradation products, uniformity of dosage units, water content, dissolution and microbial limits). The critical quality attributes were selected to ensure the quality of the product and are controlled as part of the finished product specification.

Table 1. Finished product QTPP

Product Attribute	Target Profile
Route of Administration	Oral
Dosage Strength	30 mg, 20 mg, 14 mg, 10 mg
Dosage Form	Powder Filled Hard Gelatin Capsule
Dosage Regimen	30 mg: 1 x 30 mg capsule (or) 3 x 10 mg capsules 20 mg: 1 x 20 mg capsule (or) 2 x 10 mg capsules 14 mg: 1 x 14 mg capsule All capsule strengths are intended for bi-weekly administration
Requirements to Assure Patient Safety and Efficacy at Release and during Shelf Life	Assay remains NLT 95.0% of label claim at release and NLT 94.0% label claim during shelf-life. Limits for degradation product established in accordance with ICH Guidance for Industry Uniformity of dosage units meets pharmacopeial limits. *In vitro* dissolution profile is indicative of immediate release product. Microbial limits are controlled in accordance to ICH Guidance Q6A Water content is at acceptable levels as to not have a significant impact on other critical quality attributes
Container Closure System	Container closure system is sufficiently protective to assure product quality throughout the shelf life. Vimseltinib capsules are packaged in oPA/Alu/PVC blister with Alu lidding.
Product Shelf life and Storage Conditions	At least 24 months shelf life at room temperature

Compatibility of the active substance with the chosen excipients was demonstrated. The development of the formulation from early development phases to the commercial formulation has been sufficiently described. Initially, a capsule formulation in the strength of 50 mg was developed which was then optimised to a strength of 10 mg and 2 mg, respectively to support dosing in clinical studies. The three product strengths proposed for marketing (14 mg, 20 mg and 30 mg) contain the same relative amounts of excipients as the 10 mg strength used in clinical trials (capsule fill blend containing 10.84% w/w active substance). The only differences are the fill weight as well as the size and colour of the respective capsules. These differences are minor and do not result in differences in dissolution profiles (or *in vivo* performance).

The clinical batches were initially manufactured by a different finished product manufacturer. The proposed commercial manufacturer uses the same manufacturing process. The impact of changes made to the active substance manufacturing process was studied during pharmaceutical development. During the procedure, a major objection was initially raised as the impact of the change in particle size on expected *in vivo* behaviour was not sufficiently addressed. Overall, it was concluded that the optimisation for the active substance is unlikely to have an impact on *in vivo* performance. Thus, the absence of an *in vivo* bioequivalence study between finished product used in clinical trials and finished product proposed for marketing is acceptable. The particle size of vimseltinib active substance is routinely controlled in the active substance specification. The major objection is resolved.

A biowaiver of strengths has been requested for the commercial strengths of 14 mg, 20 mg and 30 mg. Data supporting the justification for the biowaiver were provided in the clinical part of the dossier (section 5.3.1.2). The relevant pharmaceutical aspects were further discussed in the quality part of the dossier (under pharmaceutical development). To support the biowaiver of strengths, the 2 mg and 10 mg hard capsules used in pivotal clinical trials were compared to the 14 mg, 20 mg, and 30 mg hard capsules proposed for marketing. The biowaiver of strengths was justified by the following:

- the composition of the finished products is proportionally similar with regard to active substance and excipients
- the manufacturing process for the finished products is the same
- pharmacokinetics are linear in the relevant range
- *in vitro* dissolution profiles are similar.

During the procedure, a major objection was initially raised on the request for a biowaiver of strengths and the provided dissolution data to support the request. In response, and to demonstrate similarity of dissolution behaviour, dissolution data was provided using the medium used for QC testing (QC dissolution method: paddle apparatus, rpm 75, 900 mL, 200 mM sodium citrate buffer at pH 2.9), as well as in pH 1.2, pH 4.5 and pH 6.8 (using paddle apparatus, 75 rpm and Ph. Eur. dissolution media/buffers) for each strength. Dissolution of the 30 mg hard capsule proposed for marketing was compared to three 10 mg hard capsules used in clinical studies. Similarly, dissolution of the 20 mg hard capsule was compared to two 10 mg hard capsules. Dissolution of the 14 mg hard capsule was studied in comparison to two 2 mg hard capsules and one 10 mg hard capsule. The approach used for the comparative dissolution studies is acceptable and in line with the requirements set out in the Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98, section 4.2.2), with the exception of the applied paddle rotation speed of 75 rpm (instead of 50 rpm). The solubility of the active substance is pH dependent. Therefore, it was accepted that dissolution at 50 rpm was not studied. Overall, the dissolutions studies conducted, and the results presented adequately justify the biowaiver of strengths. The biowaiver criteria a), b) and c) indicated in the Guideline on the Investigation of Bioequivalence (section 4.1.6) are fulfilled as regards pharmaceutical quality. The major objection is resolved.

The development of the dissolution method for QC testing has been described in sufficient detail. The solubility characteristics of the active substance were taken into account for the choice of the test method. The method was developed and validated using 14 mg, 20 mg and 30 mg hard capsules as proposed for marketing. Extensive development was conducted to optimise the dissolution conditions to ensure a suitably slow dissolution profile and discriminatory power of the method. A tier 2 method was also developed. Extensive development work was conducted to find the optimal concentration of a suitable enzyme (pepsin) to mitigate gelatine cross-linking without interfering with the dissolution of the active substance. The tier 2 protocol is only foreseen to be used when there is evidence of cross-linking in the gelatine capsules (i.e. for the testing of samples from accelerated stability studies).

The discriminatory power of the dissolution method used for QC testing was evaluated. A bracketing approach was used. The discriminatory power of the tier 1 dissolution method was demonstrated. It was demonstrated that the enzyme used in the tier 2 dissolution method does not alter the dissolution profile of capsules with no cross-linking. Considering that the only difference between the tier 1 and tier 2 dissolution method is the addition of enzyme allowing release of capsule content, the discriminatory power can be concluded also for Tier 2.

The development of the manufacturing process of the finished product has been sufficiently described from early development onwards. The manufacturing process consists of blending, capsule filling and packaging. Potentially critical manufacturing steps were assessed using risk assessment tools, prior knowledge and experimental data. Target values for process parameters, or ranges, were evaluated against the critical quality attributes of the finished product. The final process parameters were selected based on process development studies. No design space is claimed.

The primary packaging is oPA/Aluminium foil/PVC-film blister with push-through aluminium foil lidding. The material complies 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.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site. Satisfactory GMP documentation of the site has been provided.

The manufacturing process consists of three main steps: blending of components, capsule filling and packaging. The process is considered to be a standard manufacturing process.

The manufacturing process has described in sufficient detail and the batch formula provided. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form. In-process controls, target values for process parameters and proven acceptable ranges (PARs) were defined based on development studies.

The proposed hold time for bulk hard capsules of all three strengths (14 mg, 20 mg, and 30 mg) is supported by stability studies and considered acceptable.

A process validation scheme has been presented and is considered acceptable. The process will be validated on 2 consecutive batches of each tablet strength before commercialisation. Based on batches manufactured so far, it has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: description (visual), identification (UPLC, UV), assay (UPLC), degradation products (UPLC), uniformity of dosage units (Ph. Eur.), dissolution (in-house), water content (Karl Fischer), microbial limits (Ph. Eur.) and absence of E. Coli (Ph. Eur.).

The specification for the finished product (14 mg, 20 mg and 30 mg strength) is acceptable and in line with the requirements set out in ICH Q3B, Q6A and the European Pharmacopoeia. It includes all parameters necessary for the dosage form. Adequate justification for the proposed specification limits has been provided. The specification limits for release and at shelf life are the same.

Based on the maximum daily dose of Romvimza (30 mg), the identification threshold for impurities is 0.2% in line with ICH Q3B. Accordingly, the limit for unspecified impurities (0.2% is acceptable). No specified impurities are included in the specification.

The same dissolution limit is proposed for all three strengths. During phase 3 clinical trials, hard capsules in a strength of 2 mg and 10 mg were used and therefore, the specification can't be based on the biobatch. These strengths are not proposed for marketing; however, they are used to justify the dissolution limit. A multi-unit dissolution testing approach was followed in the dissolution tests conducted to justify the specification of the 14 mg, 20 mg and 30 mg strength hard capsules (1x10 mg+2x2 mg used in lieu of 14 mg hard capsules, 2x10 mg used in lieu of 20 mg hard capsules and 3x10 mg used in lieu of 30 mg hard capsules). Based on the slowest dissolution results, the specification limit of NLT 75% (Q) in 30 minutes is acceptable.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities (option 2b). No elemental impurities were identified as having the potential to be present at a level of greater than 30% of the PDE limit for oral administration. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification. The information on the control of elemental impurities is satisfactory.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product was, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). The risk assessment was not considered acceptable because risks were identified, including secondary amines in the active substance, its impurities and several reagents and solvents used in the process and potential nitrite in the excipients, yet no confirmatory testing results were provided, resulting in a major objection. In response, the applicant submitted test data for several active substance-derived and small-molecule nitrosamines using a validated and sufficiently sensitive analytical method. All results were below 10% of the acceptable intake of the respective nitrosamine. In addition to the confirmatory testing, a scientific justification was provided for several active-substance-related impurities as to why there is negligible risk of formation of nitrosamines. The justification was considered acceptable. Based on the information provided, it is accepted that there is no risk presence of nitrosamines in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary. The major objection is resolved.

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 3 registration batches manufactured at commercial scale for the 14 mg and 30 mg strengths, and 1 registration batch manufactured at commercial scale for the 20 mg strength hard capsule. The bracketing approach was considered acceptable as the three strengths are manufactured from a common blend and differ only in fill weight, capsule size and capsule colour. Results confirm 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.

2.4.3.4. Stability of the product

Stability data from 3 commercial-scale batches of finished product was provided for the 14 mg and 30 mg hard capsules. Stability data from 1 commercial-scale batch of finished product was provided for the 20 mg

strength. Batches of finished product were stored for up to 24 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing. The bracketing approach is considered acceptable, as discussed above. Samples were tested according to the same specification as for release. The analytical procedures used are stability indicating. Assay results increased slightly during stability studies but remained within specification limits. The increase is attributed to a change of sample preparation (testing of the capsule content only was replaced by testing of the whole capsule). Dissolution rate decreased significantly under accelerated conditions due to cross-linking of gelatine. As further discussed above, a tier 2 analytical method was developed for samples showing evidence of cross-linking. The affected batches were re-tested at the end of the accelerated stability studies, and results were within specification. Overall, no significant changes have been observed under long-term or accelerated conditions. Results are consistent between the different batches.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. Results show that the product is not photosensitive.

Results from forced degradation studies were presented. Samples of finished product capsules were exposed to thermal, thermal/humidity, oxidative and photolytic stress conditions. The conditions tested are appropriate for the dosage form. The assay value for decreased for samples exposed to thermal/humidity stress compared to the control. However, no new degradation peaks were detected. At the time this forced degradation study was conducted, the improved whole capsule assay sample preparation had not been implemented. Therefore, all assay values were lower than expected due to adsorption of vimseltinib on the inside surface of the capsule shell. In addition, capsule samples attained a rubbery state after stressing, further exacerbating adherence of active substance to the gelatine capsule. No potential degradants were identified during forced degradation studies.

Based on available stability data, the proposed shelf-life of 3 years and storage condition "This medicinal product does not require any special temperature storage conditions. Store in the original package in order to protect from moisture" as stated in the SmPC (sections 6.3 and 6.4) are acceptable.

2.4.3.5. Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

Gelatine obtained from bovine sources is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture is provided.

2.4.4. 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. Major objections initially raised, including the evaluation of potentially genotoxic impurities, were resolved 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.

2.4.5. 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. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Vimseltinib is a selective tyrosine kinase inhibitor that targets colony stimulating factor 1 receptor (CSF1R) kinase.

Non-clinical development programme was designed according to the ICH M3(R2) guideline. Biochemical and cellular kinase activity assays were used to assess the selectivity and potency of vimseltinib for CSF1R. Off-target functional inhibition or binding was assessed using large panels of kinases, receptors, enzymes and ion channels. In vitro efficacy was assessed using monocytic cell lines, osteoclast precursors, and monocytes from freshly drawn whole blood samples. Additional in vitro studies included CYP metabolism/inhibition studies, CYP reaction phenotyping, metabolite identification, microsomal and hepatocyte stability, hepatocyte induction, plasma protein binding, and transporter substrate/inhibition.

In vivo, PK/PD studies were performed in mice to evaluate exposures required for inhibition of CSF1R signalling, and efficacy was evaluated in a tumour xenograft model in nude mice and a syngeneic mouse cancer model in immunocompetent mice. PK studies were performed in rodents (mice, rats) and non-rodents (dogs, cynomolgus monkeys).

Vimseltinib was assessed in nonclinical safety pharmacology studies including evaluation of neurobehavioral effects, respiratory function, and evaluation of impact on cardiovascular parameters using the in vitro hERG assay and telemetered dogs.

Toxicology studies have been conducted in mice, rats, rabbits, and dogs. Repeat-dose toxicity studies, in which vimseltinib was administered once daily, were conducted in mice treated for up to 6 months (carcinogenicity study in RasH2 transgenic mice), rats treated for up to 2 years, rabbits for up to 13 days (embryo foetal development DRF study), and in dogs treated for up to 9 months in accordance with the ICH M3(R2) guidance. All pivotal repeat-dose studies included toxicokinetic (TK) evaluation.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

The proliferation of tenosynovial giant cell tumour (TGCT) is driven by a small subpopulation of neoplastic cells with high CSF1 levels, which attract and induce proliferation of CSF1R-expressing monocytes. The neoplastic cells also attract a large number of bystander macrophages. In addition, TGCT contain multinucleated giant cells that feature some markers associated with osteoclast differentiation, which may in turn explain the bone destruction observed in some patients (van IJzendoorn et al, 2022).

Vimseltinib has been developed as a selective inhibitor of CSF1R kinase. Whereas unphosphorylated CSF1R is inactive, its phosphorylation in the inhibitory JM domain activates the kinase enabling it to in turn phosphorylate downstream targets. Additional phosphorylation in the activation loop stabilizes the active conformation of CSF1R. Vimseltinib demonstrated preferential inhibition of the JM domain phosphorylated CSF1R kinase activity with an IC_{50} value of 2.8 nM as compared to the fully phosphorylated CSF1R (IC_{50} = 290 nM). In line with these results, vimseltinib binds CSF1R protein with a *K*d of 3.6 nM. The affinity for the unphosphorylated CSF1R is substantially lower (*K*d = 79 nM). Vimseltinib is a reversible CSF1R inhibitor with an inhibitory residency half-life at the JM-phosphorylated kinase of 170 min. The major human metabolite of vimseltinib, DP-7005, is ca. 20-fold less potent than the parent compound in the inhibition of CSF1R activity (the IC_{50} was 65 nM for the JM domain phosphorylated CSF1R and 6.4 µM for the fully phosphorylated kinase).

Vimseltinib demonstrated inhibitory activity in cellular context. The IC_{50} for the inhibition of proliferation of M-NFS-60 cells, a CSF1R-dependent mouse myelogenous leukaemia cell line, was 10.2 nM and was marginally influenced by high CSF1 concentrations (less than 2-fold increase in IC_{50}). DP-7005 was much less active in this cell line (IC_{50} = 6.2 µM). Vimseltinib reduced CSF1-stimulated phosphorylation of CSF1R in the THP1 human acute monocytic leukaemia cell line with an IC_{50} of 18.8 nM. The inhibitory effect was retained at ca. 50% 6 hours and at ca. 30-40% at 24 h after vimseltinib withdrawal. In THP1 cells, the metabolite DP-7005 was less potent with an IC_{50} of 260 nM. In whole human blood from a healthy donor, vimseltinib inhibited CSF1-stimulated downstream signalling (assessed based on pERK levels) with an average IC_{50} of 310 nM. Taking into account plasma protein binding (free fraction of 3.4%), the IC_{50} value for the unbound drug was estimated to be around 11 nM, which is in agreement with the data from other assays.

Taken together, the data above demonstrate biochemical and cellular activity of vimseltinib towards CSF1R at clinically relevant concentrations (clinical $C_{max,u}$ was estimated to be 58.8 nM). The overall potency of the metabolite DP-7005 was markedly lower. Given that and relatively low levels of DP-7005 in human systemic circulation, the metabolite is unlikely to contribute much to the pharmacodynamic effects of vimseltinib. The cell lines used in primary PD studies do not represent models of TGCT. With respect to neoplastic cells within TGCT representing a driving force of tumour growth, vimseltinib is expected to act on CSF1R-expressing neoplastic cells but its activity on the neoplastic cells without CSF1R is uncertain.

At a concentration of 100 nM, vimseltinib inhibited macrophage-dependent tumour cell migration *in vitro*. It should be noted that the concentration chosen for this assay is higher than the clinical unbound C_{max} of 58.8 nM.

Osteoclast differentiation was inhibited with an IC_{50} value of 9.3 nM. The giant cell population in TGCT is described as "osteoclast-like", however, at present it is not known to what extent they are similar to

osteoclasts, although they appear to express specific markers of osteoclast development (van IJzendoorn et al, 2022).

During the development of vimseltinib, a PK/PD model for CSF1R-targeted agents was reported (Manthey et al. 2009) and adopted for the evaluation of vimseltinib. cFOS mRNA levels in vimseltinib-treated DBA/1 mice following CSF1 stimulation were evaluated. Sustained inhibition of cFOS mRNA expression (by 77% up to 24 h) was observed at the lowest single dose, 3.75 mg/kg vimseltinib, characterized by a C_{max} of 2,783 ng/mL (6.45 µM corresponding to $C_{max,u}$ of 174 nM in mice with f_u = 2.7%). These vimseltinib levels are higher than the clinically expected. After repeated vimseltinib administration, sustained reduction in cFOS mRNA by ca. 50% up to 48 h was seen at 3 mg/kg/day and by ca. 75% for 6 h at 1 mg/kg/day. By plotting cFOS mRNA levels vs. plasma concentrations, an EC_{50} value for the inhibition was determined as 430 ng/mL and the EC_{80} as 1,700 ng/mL, corrected for protein binding in mice as 26.9 nM and 106.4 nM, respectively, which is in the clinically expected range.

In the syngeneic, immunocompetent MC38 colorectal cancer model in mice, vimseltinib at 10 mg/kg/day (for 7 days) modestly increased plasma CSF1 levels, significantly reduced circulating CD14+/CD16+ monocytes by 11-fold, significantly decreased intratumoural tumour-associated macrophages by 3-fold within the CD45+ population of cells in the primary tumour and increased the ratio of cytotoxic CD8+ T cells to Treg cells by 4-fold, the latter finding indicating a shift of the adaptive immune system away from an immunosuppressive state. In this model, 10 mg/kg/day vimseltinib alone led to significant tumour growth inhibition by 48% on day 32. When combined with an anti-PD1 antibody, vimseltinib produced 68% tumour growth inhibition. Macrophage levels were also reduced in the liver of normal rats by 68% (significantly) and in the rat colon by 47%. The models employed in the in vivo primary PD studies are CSF1R-dependent but not TGCT models.

2.5.2.2. Secondary pharmacodynamic studies

Vimseltinib demonstrated >100-fold selectivity for inhibition of CSF1R kinase activity over a panel of 298 kinases including the closely related CSF1R family members FLT3, KIT, PDGFRα, and PDGFRβ. Only LCK was an exception with an IC_{50} of 208 nM at 10 µM ATP (CSF1R IC_{50} was 4.7 nM). At higher ATP concentrations of 1 and 4 mM, which are more relevant in cellular context (Huang et al, 2010), all kinases but CSF1R had IC_{50} values over 700 nM. Inhibition of FLT3, KIT, PDGFRα, and PDGFRβ in cellular assays was much weaker compared to vimseltinib (>25-fold).

Among the battery of 104 receptor binding and 31 enzyme and uptake assays, vimseltinib at 10 µM inhibited MT3 (ML2) (agonist radioligand) by 68.2%, ABL kinase by 86.2%, FYN kinase by 42.8% and LYN kinase by 90.6%. The IC_{50} values for the latter three targets were all higher than 2 µM. No IC_{50} value was determined for MT3 but this is acceptable as this interaction is unlikely clinically relevant.

Thus, vimseltinib was shown to be a selective inhibitor of CSF1R. The metabolite DP-7005 was evaluated against only three kinases. It was found to inhibit KIT with an IC_{50} of 780 nM but not KDR or PDGFRβ.

2.5.2.3. Safety pharmacology programme

Vimseltinib significantly inhibited hERG current by 8.3% at 10 µM and by 17.2% at 30 µM. DP-7005 significantly inhibited hERG at 30 µM by 9.2%. This extent of inhibition is, however, not clinically relevant. Following single oral dosing of 15 mg/kg vimseltinib to conscious telemetered male Beagle dogs minimal significant shortening of PR interval and minimal significant increase in heart rate were documented. As these, likely related, effects were small in magnitude, not dose-dependent and largely contributed by one

animal, they were not considered test-article related. No other cardiovascular findings were noted up to 15 mg/kg.

In the CNS safety pharmacology study in male Sprague Dawley rats administered vimseltinib orally up to 30 mg/kg, incidental decrease in locomotor activity was observed. It was not dose-dependent and occurred also in the vehicle group; the finding was therefore considered not test-item related.

The respiratory safety pharmacology study in male Sprague Dawley rats revealed mild transient increase in tidal volume after an oral dose of 30 mg/kg vimseltinib. Due to the reversibility, small magnitude and unaffected minute volume, this effect was not considered physiologically relevant, although test-article related. A trend to a not significantly lower respiration rate was seen at 30 mg/kg but the effect was small in magnitude and probably a compensatory response to a higher tidal volume. It is thus unlikely to be of physiological relevance.

2.5.2.4. Pharmacodynamic drug interactions

No studies have been conducted, which is acceptable as vimseltinib is supposed to be used as monotherapy.

2.5.3. Pharmacokinetics

2.5.3.1. Analytical methods

The applicant has developed and validated the following bioanalytical methods (Table 2).

Table 2. Overview of the validated bioanalytical methods

Study nr. DCC-3014-	**Analyte**	**Matrix**	**Range**	**Method**	**GLP status**
03-0016	vimseltinib	dog plasma	20 – 20,000 ng/mL	HPLC-MS/MS	no formal GLP
03-0018	vimseltinib	rat plasma	20 – 20,000 ng/mL	HPLC-MS/MS	no formal GLP
03-0019	DP-7005	dog plasma	20 – 20,000 ng/mL	HPLC-MS/MS	no formal GLP
03-0020	DP-7005	rat plasma	20 – 20,000 ng/mL	HPLC-MS/MS	no formal GLP
04-0028	vimseltinib DP-7005	rat plasma	20 – 20,000 ng/mL 2.0 – 2,000 ng/mL	UHPLC-MS/MS	GLP
04-0030	vimseltinib DP-7005	mouse plasma	10 – 10,000 ng/mL 5.0 – 5,000 ng/mL	LC-MS/MS	no formal GLP

2.5.3.2. Absorption

The absorption of vimseltinib was investigated after single intravenous and oral administration to healthy mice, rats, dogs and monkeys. Oral bioavailability was also estimated.

An overview of the pharmacokinetic parameters of vimseltinib is presented in Table 3.

Table 3. Pharmacokinetic data for vimseltinib and DP-7005 in animal models

Species	Study nr. DCC-3014-03	Dose (mg/kg) /route	Analyte	N/Sex	$T_{1/2}$ (hr)	T_{max} (hr)	C_{max} (ng/mL)	AUC_{0-t} (hr•ng/mL)	CL (L/h/kg)	F (%)
Cynomolgus monkeys	-0004	1 / IV	vimseltinib	3/M	3.57	0.08	920	1544	0.773	n.a.
			DP-7005	3/M	14.4 [n=1]	0.08	1523	4018	0.16 [n=1]	n.a.
Swiss mice	-0005	1 / IV	vimseltinib	3/M	6.89	0.08	2664	15418	0.06	n.a.
Sprague Dawley rats	-0012	1 / IV	vimseltinib	3/M	14.19 ± 3.07	0.08 ± 0.00	2906 ± 353	21473 ± 2350	0.03 ±0.00	n.a.
		10 / PO	vimseltinib		19.83 ± 5.93	2.67 ± 1.16	16115 ± 2868	164004 ± 13970	0.04 ±0.01	76.38
			DP-7005	3/M	3.30 ± 0.32	0.08 ± 0.00	2363 ± 498	2927 ± 435	0.34 ±0.05	n.a.
	-0011	10 / PO	vimseltinib	3/M	n.a.	8.00 ± 4.00	5360 ± 1580	103000 ± 30500	n.a.	n.a.
		30 / PO		3/M	n.a.	6.67 ± 4.62	18500 ± 1900	344000 ± 30500	n.a.	n.a.
		100 / PO		3/M	n.a.	24.00 ± 1.16	48000 ± 9930	942000 ± 205000	n.a.	n.a.
		300 / PO		3/M	n.a.	24.00 ± 0.00	64500 ± 11600	1150000 ± 315000	n.a.	n.a.
		500 / PO		3/M	n.a.	17.3 ± 11.5	5850 ± 9040	1060000 ± 180000	n.a.	n.a.
	-0022	10 / PO	[^{14}C]vimseltinib	4/M	19.1	2.00	18700 ng eq/g	263000 ng eq•hr/g	n.a	n.a.
				4/F	19.1	1.00	16600 ng eq/g	326000 ng eq•hr/g	n.a.	n.a.
Beagle dogs	-0013	1 / IV	vimseltinib	3/M	6.82 ± 3.17	0.14 ± 0.10	2512 ± 773	7039 ± 3122	0.15 ± 0.06	n.a.
		3 / PO			10.62 ± 3.20	1.67 ± 0.58	1304 ± 590	7032 ± 3506	0.45 ± 0.24	33.30
		10 / PO			9.23 ± 1.55	0.83 ± 0.29	3307 ± 2887	19534 ± 19530	0.83 ± 0.60	27.75
		30 / PO			10.51 ± 5.41	1.33 ± 0.58	7290 ± 7540	50797 ± 57810	1.16 ± 0.87	24.05
	-0014	1 / IV	vimseltinib	3/M	7.84 ± 0.5	0.08 ± 0.00	1503 ± 268	4233 ± 543	0.22 ± 0.01	n.a.
		-	DP-7005		19.75 ± 0.06	4.00 ± 0.00	367 ± 50	4590 ± 883	n.a.	n.a.
		1 / IV	DP-7005		11.04 ± 0.71	0.08 ± 0.00	2017 ± 214	7532 ± 287	0.13 ± 0.00	n.a.
		10 / PO	vimseltinib		6.91 ± 0.70	1.67 ± 0.58	1676 ± 1346	11263 ± 10217	1.39 ± 0.84	61
		-	DP-7005		15.15 ± 2.78	4.00 ± 0.00	904 ± 690	14724 ± 13435	n.a.	
	-0010	30 / PO	vimseltinib	3/M	n.a.	1.67 ± 0.58	6500 ± 7140	42200 ± 32300	n.a.	n.a.
		100 / PO		3/M	n.a.	1.67 ± 0.58	21400 ± 8940	132000 ± 64400	n.a.	n.a.
		300 / PO		3/M	n.a.	2.67 ± 1.15	14600 ± 586	13000 ± 29000	n.a.	n.a.
	-0017 (capsule formulations)	~4.2 / PO	vimseltinib	3/M	n.a.	16.33 ± 13.28	395 ± 108	5377 ± 1135	n.a.	n.a.
		-	DP-7005		n.a.	24.00 ± 0.00	265 ± 57	5365 ± 1225	n.a.	n.a.
		~4 / PO	vimseltinib		10.93 [n=1]	9.00 ± 13.00	341 ± 269	3355 ± 3649	7.98 [n=1]	n.a.
		-	DP-7005		13.50 [n=1]	11.33 ± 11.02	144 ± 102	2697 ± 2098	n.a.	n.a.
	-0021	1 / IV	[^{14}C]vimseltinib	3/M	13.7 ± 1.69	0.083 ± 0.00	1210 ± 81.4 ng eq/g	11600 ± 1360 ng eq•hr/g	n.a.	n.a.
				3/F	13.0 ± 2.36	0.083 ± 0.00	1170 ± 67.2 ng eq/g	10000 ± 1390 ng eq•hr/g	n.a.	n.a.
		10 / PO	[^{14}C]vimseltinib	3/M	13.0 ± 1.55	3.00 ± 1.00	5770 ± 4550 ng eq/g	97700 ± 74400 ng eq•hr/g	n.a.	61.7
				3/F	14.8 ± 6.65	2.00 ± 1.00	5710 ± 4110 ng eq/g	91200 ± 66000 ng eq•hr/g	n.a.	101

2.5.3.3. Distribution

The plasma protein binding of vimseltinib and the metabolite DP-7005 at 1 and 10 µM were investigated in mouse, rat, dog, cynomolgus monkey, and human plasma (table below).

Table 4. Protein binding in animal and human plasma

Species	Vimseltinib % Bound		DP-7005 % Bound	
	1 µM	10 µM	1 µM	10 µM
Mouse	97.4	97.2	91.4	89.2
Rat	99.4	99.3	98.5	98.3
Dog	96.7	96.4	90.9	89.0
Monkey	96.1	95.4	86.4	84.7
Human	96.7	96.5	94.3	92.4

The PK of CNS exposure and peripheral plasma exposure to vimseltinib was evaluated in male Sprague Dawley rats administered 1 mg/kg IV doses of vimseltinib (DCC-3014-03-0015). Blood and brain tissue were collected from each rat at 0.083, 0.25, 0.5, 1, 2, 4, 6, 10, and 24 hours post dose. Plasma and brain homogenate were prepared and then analysed for vimseltinib. The quantitation of vimseltinib in rat plasma and brain was performed using an LC-MS/MS working method (LLOQ of 32 ng/mL). The results are presented in Table 5.

Table 5. PK parameters in rat plasma and brain tissue following administration of a 1.0 mg/kg IV dose of vimseltinib

Parameter (units)	Plasma	Brains
C_{max} (ng/mL)	1997	1076
t_{max} (h)	0.25	0.08
AUC_{0-t} (ng*h/mL)	15144	11100
AUC_{inf} (ng*h/mL)	18236	N/A
$t_{1/2}$ (h)	9.74	N/A
Vz_obs (L/kg)	0.77	N/A
Cl_obs (L/h/kg)	0.05	N/A

The distribution of [^{14}C]-vimseltinib in tissues was assessed after a single oral administration to Sprague Dawley and Long Evans rats. A single oral dose of 10 mg/kg (100 acid/kg) [^{14}C]-vimseltinib was administered to fasted male Sprague Dawley rats (n=5) and Long Evans rats (n=9). In male rats, the maximum mean blood and plasma concentration (C_{max}) of radioactivity were 10800 and 18700 ng eq/g, respectively, observed at 2 hours post dose. In females, the C_{max} values of radioactivity were 10300 and 16600 ng eq/g, observed at 4 and 1 hours post dose, respectively. Blood to plasma concentration ratios of radioactivity after oral dosing to Sprague Dawley and Long Evans rats were generally <1 (>1 at 120 hours in Sprague Dawley rats), suggesting a limited distribution of radioactivity into the cellular fraction of a whole blood. Blood to plasma concentration ratios of radioactivity were increasing overtime. The radioactivity in tissues collected from Sprague Dawley and Long Evans rats from 0.5-72 hours and 0.5-672 hours post dose, respectively, was determined by QWBA. [^{14}C]-vimseltinib-derived radioactivity was widely distributed to almost all tissues by the first collection time point (0.5 hours post dose). Almost all tissues reached C_{max} by 4 hours. The tissues showing the highest maximum concentrations of radioactivity in Sprague Dawley rats included liver, adrenal gland, harderian gland, urinary bladder, fat (brown), kidney cortex, kidneys, myocardium, kidney medulla, and intervertebral ligaments. Radioactivity was still quantifiable in almost all tissues at 72 hours. The tissues showing the highest maximum concentrations of radioactivity in Long Evans rats included eye uveal tract,

eye(s), hair (follicle), liver, meninges, adrenal gland, harderian gland, stomach, kidney cortex, and kidney(s). Radioactivity was cleared from most tissues by 168 hours post dose, but was still quantifiable in the meninges, eye uveal tract, eye(s), and eye vitreous humour at 672 hours, suggesting melanin binding.

The blood-plasma partitioning was also assessed in male and female dogs (n=3/sex/group) (DCC-3014-03-0021). Following oral administration of 10 mg/kg (~ 20 µCi/kg) ^{14}C-vimseltinib to dogs, the mean blood and plasma maximum observed concentrations (C_{max}) of radioactivity were 4690 and 5770 ng eq/g at 3.33 and 3 hours post dose, respectively, for males, and were 4300 and 5710 ng eq/g, respectively at 2 hours post dose for females. Following an IV administration of ^{14}C-vimseltinib at 1 mg/kg (~ 20 µCi/kg) to dogs, the mean maximum blood and plasma concentrations (C_{max}) of radioactivity at the first collection time point (0.083 hours post dose) were 911 and 1210 ng eq/g, respectively, for males, and were 876 and 1170 ng eq/g, for females. Mean blood-to-plasma radioactivity concentration ratios after oral and IV dosing were generally <1 in early time points and were >1 in later time points, where calculated, suggesting distribution of radioactivity into the cellular fraction of a whole blood was increasing overtime.

2.5.3.4. Metabolism

Metabolism of vimseltinib was species dependent. Little metabolism was observed in liver microsomes of human and animal species beside monkey. In hepatocytes, some metabolism was seen in dog (42.6% compound loss). In monkey hepatocytes, vimseltinib was almost completely metabolized. *N*-dealkylated metabolite DP-7005 present in hepatocytes and liver microsomes across species was the major component in monkey hepatocytes (34% of the sample radioactivity) and accounted for ca. 13% of the radioactivity in dog hepatocytes. Limited metabolism in human was attributed to CYP3A4 and CYP2D6. There were no human-specific metabolites.

In Sprague Dawley rats, N-dealkylation and oxidation were the major metabolic pathways of vimseltinib. Minor contributions to biotransformation included dehydrogenation, O-dealkylation, and glucuronidation. A large abundance of metabolites in faeces but not in bile indicated possible gastrointestinal metabolism. In Beagle dogs, vimseltinib was mainly metabolized by N-dealkylation to form DP-7005 with oxidation, dehydrogenation, and glucuronidation playing a minor role. Male dogs demonstrated markedly higher metabolism, which may explain gender differences in toxicokinetics.

2.5.3.5. Excretion

The excretion of [^{14}C]-vimseltinib was evaluated after single oral dosing of 10 mg/kg (11.3 µCi/mg) to intact fasted male and female Sprague Dawley rats and bile duct cannulated (BDC) male Sprague Dawley rats (DCC-3014-03-0022) as well as after a single dose of 1 mg/kg (20 µCi/kg) [^{14}C]-vimseltinib administered via IV bolus or a single-dose of 10 mg/kg (20 µCi/kg) [^{14}C]-vimseltinib given orally to fasted male and female Beagle dogs.

Table 6. Excretion routes of vimseltinib

Species	N /sex	Dose(mg/kg) /route	Urine (% dose)	Faeces (% dose)	Bile (% dose)	Carcass (% dose)	Cage wash (% dose)	Recovery (% dose)	Time (h)
	3/M	10/PO	4.24 ± 0.37	77.4 ± 10.5	n.a.	1.54 ± 0.10	0.03 ± 0.01	83.6 ± 10.1	0-168

Sprague Dawley rat	3/F		2.20 ± 0.16	79.1 ± 7.69	n.a.	0.90 ± 0.18	0.03 ± 0.02	82.4 ± 7.68	0-168
Sprague Dawley rat BDC	3/M	10/PO	9.75 ± 2.81	62.4 ± 5.61	14.5 ± 2.95	2.06 ± 0.50	0.18 ± 0.09	89.6 ± 3.72	0-120
Beagle dogs	3/M	10/PO	6.81 ± 5.33	84.1 ± 6.65	n.a.	n.a.	0.03 ± 0.02	92.2 ± 1.21	0-168
	3/F		6.37 ± 3.89	82.5 ± 2.38	n.a.	n.a.	0.03 ± 0.01	89.8 ± 3.92	0-168
	3/M	1/IV	7.51 ± 1.02	73.7 ± 1.66	n.a.	n.a.	0.02 ± 0.01	82.3 ± 0.57	0-168
	3/F		6.91 ± 1.11	76.4 ± 3.55	n.a.	n.a.	0.03 ± 0.03	84.9 ± 3.86	0-168

2.5.3.6. Pharmacokinetic drug interactions

In vitro studies assessing possible relevance of CYP enzymes for drug interactions of vimseltinib are summarised in Table 7. In vitro studies for the potential of DP-7005 to influence CYP enzymes are summarised in Table 8.

Table 7. Overview of in vitro studies assessing relevance of metabolic enzymes for drug interactions of vimseltinib

Study nr. DCC-3014-	Vimseltinib:	Study system	Enzymes	Results / unbound IC_{50} or K_i	Implications
03-0001	inhibitor	human liver microsomes	CYP1A2	<10% inhibition at 100 μM no time / NADPH shift	no in vivo study needed*
			CYP2B6	21% inhibition at 100 μM no time / NADPH shift	
			CYP2C8	IC_{50} = 75 μM no time / NADPH shift	
			CYP2C9	IC_{50} = 78 μM no time / NADPH shift	
			CYP2C19	44% inhibition at 100 μM no time / NADPH shift	
			CYP2D6	<10% inhibition at 100 μM no time / NADPH shift	
			CYP3A4 (testosterone)	<10% inhibition at 100 μM no time / NADPH shift	
			CYP3A4/5 (midazolam)	<10% inhibition at 100 μM no time / NADPH shift	
03-0009	inducer	human hepatocytes 0.1–100 μM	CYP1A2	↓mRNA, ↓activity in 3/3 donors	no in vivo study needed#
			CYP2B6	↑mRNA in 2/3 donors, conc.-dep., FC>2 at ≥30 μM ↑activity in 1/3 donors	

		≥30 μM cytotoxicity	CYP3A4	↑mRNA in 2/3 donors, not conc.-dep. no change in activity	

need for in vivo study as estimated by the CHMP according to the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**) and draft ICH M12 guideline on drug interactions: in vivo evaluation is warranted if

at least in one donor a drug increases mRNA expression of a CYP enzyme in a concentration-dependent manner and the fold-change (FC) of CYP mRNA expression is ≥ 2 at ≤50×$C_{max,u}$ (2.94 μM)

*[I]/K_i ≥ 0.02 where [I] is the unbound mean C_{max} obtained during treatment with the highest recommended dose ([I] = 58.8 nM), for CYP3A [I]/K_i ≥ 10 where [I] is max. dose taken one occasion (30 mg)/ 250 mL

Table 8. Overview of in vitro studies assessing relevance of metabolic enzymes for drug interactions of DP-7005

Study nr. DCC-3014-	DP-7005:	Study system	Enzymes	Results / unbound IC_{50} or K_i	Implications
03-0001	inhibitor	human liver microsomes	CYP1A2	<20% inhibition at 40 μM no time / NADPH shift	no in vivo study needed*
			CYP2B6		
			CYP2C8		
			CYP2C9		
			CYP2C19		
			CYP2D6		
			CYP3A4 (testosterone)		
			CYP3A4/5 (midazolam)		

need for in vivo study as estimated by the CHMP according to the EMA guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2**) and draft ICH M12 guideline on drug on drug interactions: in vivo evaluation is warranted if

*[I]/K_i ≥ 0.02 where [I] is the unbound mean C_{max} obtained during treatment with the highest recommended dose ([I] = 1.53 nM)

In vitro studies assessing possible relevance of transport proteins for drug interactions of vimseltinib are summarised in Table 9. In vitro studies for the potential of DP-7005 to interact with transporters are summarized in Table 10.

Table 9. Overview of in vitro studies assessing relevance of transporters for drug interactions of vimseltinib

Study nr. DCC-3014-	Vimseltinib:	Study system	Transporters	Results / unbound IC_{50} or K_i	Implications
-03-0006	inhibitor	Caco-2	P-gp	IC_{50} = 4.35 μM	in vivo study warranted**
		MDCKII/BCRP cells	BCRP	IC_{50} = 0.556 μM	
		inside-out vesicles expressing BSEP	BSEP	IC_{50} = 10.6 μM	no in vivo study needed**
			OATP1B1	IC_{50} = 10.4 μM	
			OATP1B3	IC_{50} = 28.8 μM	
			OAT1	IC_{50} = 51.5 μM	

		HEK293 cells overexpressing transporters	OAT3	IC_{50} = 23.7 μM	
			OCT2	IC_{50} = 0.456 μM	
	substrate	inside-out vesicles expressing BSEP	BSEP	uptake ratio to mock cells <2	no in vivo study needed, not a transporter substrate
		HEK293 cells overexpressing transporters	OATP1B1		
			OATP1B3		
			OAT1		
			OAT3		
			OCT2		
		MDCKII cells overexpressing transporters	BCRP	efflux ratio to mock cells <2	
			P-gp	efflux ratio to mock cells 2.62 ↓with P-gp inhibitor	in vivo study warranted, transporter substrate
03-0024	substrate	HEK293 cells overexpressing transporters	MATE1	uptake ratio to mock cells <2	no in vivo study needed, not a transporter substrate
			MATE2-K		
	inhibitor	HEK293 cells overexpressing transporters	OATP1B1	IC_{50} = 9.21 μM	no in vivo study needed**
			OATP1B3	IC_{50} = 10.1 μM	
			MATE1	IC_{50} = 7.58 μM	
			MATE2-K	IC_{50} = 23.3 μM	

**need for in vivo study as estimated by the assessor according to the ICH M12 draft guideline on drug interactions: in vivo evaluation is warranted if IC_{50} ≤
- for BCRP and P-gp: 0.1-fold the maximum dose on one occasion (30 mg)/250 mL
- for OATP1B1 and OATP1B3: 10-fold the unbound hepatic inlet concentration (128.8 nM)
- for OCT2, OAT1 and OAT3: 10-fold unbound C_{max} (58.8 nM)
- for MATE1 and MATE2-K: 50-fold unbound C_{max} (58.8 nM)

Table 10. Overview of in vitro studies assessing relevance of transporters for drug interactions of DP-7005

Study nr. DCC-3014-	DP-7005:	Study system	Transporters	Results / unbound IC_{50} or K_i	Implications
-03-0006	inhibitor	Caco-2	P-gp	≤35% inhibition at 10 μM	no in vivo study needed**
		MDCKII/BCRP cells	BCRP		
		inside-out vesicles expressing BSEP	BSEP		
			OATP1B1		
			OATP1B3		

		HEK293 cells overexpressing transporters	OAT1		
			OAT3		
			OCT2		
-03-0024	substrate	HEK293 cells overexpressing transporters	MATE1	uptake ratio to mock cells <2	no in vivo study needed, not a transporter substrate
			MATE2-K		
	inhibitor	HEK293 cells overexpressing transporters	OATP1B1	37% inhibition at 27 μM	no in vivo study needed[§]
			OATP1B3	IC_{50} = 19.4 μM	
			MATE1	46% inhibition at 22 μM	
			MATE2-K	33% inhibition at 22 μM	

2.5.4. Toxicology

The nonclinical safety profile of vimseltinib (including its major metabolite, DP-7005) has been characterised in *in vitro* and *in vivo* toxicological studies in mice, rats, and dogs. The toxicological profile of vimseltinib has been evaluated in single and repeat-dose toxicity studies in rats and dogs, genotoxicity studies, carcinogenicity in rats (ongoing) and mice, reproductive and developmental toxicity studies in rats and rabbits, repeat-dose toxicity studies and a phototoxicity study. Vimseltinib was given by oral gavage once a day, as this is the intended clinical administration route.

Rats, rabbits, dogs, and mice were selected as relevant species in the toxicology studies based on high protein homology (up to 96%) of the pharmacologic target of vimseltinib.

2.5.4.1. Single dose toxicity

Single-dose toxicity studies were not conducted with vimseltinib.

2.5.4.2. Repeat dose toxicity

Non-GLP pilot repeat-dose toxicity studies were conducted in rats and dogs up to 14 days following oral gavage administration.

In rats, administration of vimseltinib resulted in the early euthanasia/death of all animals at the highest dose tested (60 mg/kg/day) due to adverse clinical observations (bone marrow toxicity, liver injury and/or dysfunction, and and/or degeneration/necrosis of individual cells in multiple organs) and/or decreased body weight. After multiple dosing, significant accumulation was observed at the highest dose tested. The NOAEL was set 15 mg/kg/day, corresponding to a C_{max} of 18,3/19,8 ng/mL in males/females and an AUC_{0-24} of 317,000/348,000 ng*h/mL in males/females.

Degeneration of blood vessels in multiple tissues and increased physis thickness was observed in rats receiving 5 mg/kg/day (approximately 4 times the unbound vimseltinib exposure at the recommended human dose based on AUC).

In dogs, all animals given ≥50 mg/kg/day were euthanized on Days 4 (150 mg/kg/day) and Days 12 or 13 (50 mg/kg/day) due to vimseltinib-related adverse clinical observations. Clinical observations included emesis/vomitus, hypoactivity, excessive salivation, abnormal faeces (few, liquid, non-formed, or mucoid), clear eye discharge, squinted eyes, and/or red skin inside of ears. Body weight loss and a decrease in food consumption also were noted at these doses. Elevated liver enzymes (ALT, AST, LDH and/or GLDH activities) in animals given ≥15 mg/kg/day were evident of hepatocellular and possible other nonspecific tissue injury, which correlated with hepatocellular degeneration/necrosis observed microscopically in animals given 50 mg/kg/day. The HNSTD after two weeks of dosing was considered to be 15 mg/kg/day, corresponding to mean values of C_{max} and AUC_{0-24} of 6,970 ng/mL and 60,400 ng*h/mL in males and 5,110 ng/mL and 51, 000 ng*h/mL in females.

GLP repeat-dose toxicity studies were conducted with vimseltinib in rats and dogs up to 26 and 39 weeks of duration, respectively. All of these studies included a 4-week recovery period.

Findings related direct to vimseltinib were observed in liver, kidney, and vascular system. Other findings were driven by the pharmacological effects of CSF1R inhibition since the natural ligands of CSF1R and KIT regulate many pathways, such as growth and proliferation of macrophages and osteoclasts, haematopoiesis, spermatogenesis, oogenesis and folliculogenesis.

Effects on liver

Elevated liver enzymes were noticed in all rat studies (non-GLP and GLP). However, hepatocellular and hepatobiliary injury and/or dysfunction leading to deaths of the animals occurred only in the 14-day DRF study at the dose of 60 mg/kg/day. In the 28-day study microscopic liver changes were not evident; in the 13-week study reversible hepatocyte hypertrophy occurred at the dose of 7.5 mg/kg/day, and in the 26-week study a reversible increase in pigmented Kupffer cells was observed in females administered 2.5 mg/kg/day and in males administered 5.0 mg/kg/day (approximately 7.5 and 14-times the exposure at the recommended human dose, respectively).

In dogs, elevated liver enzymes accompanied by microscopic liver changes (multifocal degeneration/necrosis of hepatocytes, moderate multifocal infiltrates of macrophages, and slight multifocal periportal infiltrates of mixed cells) were only noticed in animals given 50 mg/kg/day in the DRF study. In the 4-, 13-, and 26-week studies, elevated liver enzymes did not correlate with microscopic changes.

Effects on kidney / urinalysis

In the 13-week rat study, urinalysis effects were limited to a higher incidence and/or severity of urine protein in animals administered ≥1.876 mg/kg/day. It is hypothesized that this may have been related to proteinaceous casts and/or tubule degeneration noted microscopically in the kidney. A similar effect was noted in the 26-week rat study, where protein loss in the kidneys and correlated microscopic findings of increased incidence and/or severity of CPN with proteinaceous casts, inflammation and/or tubule degeneration was found in females resulting in chronic progressive nephropathy at doses of ≥2.5 mg/kg/day (about 7.5x the exposure at the recommended clinical dose).

No vimseltinib-related changes in urinalysis were found within the dog studies.

Effects on brain

Vimseltinib was highly brain penetrant in rats and radioactivity was still quantifiable after 72 h (see PK section). It is mentioned that no macroscopically nor microscopically changes were observed in brain. However, a discussion about the underlying toxic effects about CSF1R inhibition is missing, especially the influence of a negative effect on microglia structure in brain.

In dogs, no macroscopic or microscopic changes in brain were observed.

Inflammation

In the rat inflammation of several organs was determined, e.g. in ear and kidney, (4-week study), in the skin (13-week study), foot/footpad and kidney (26-week study),

Vimseltinib administration in dogs for was associated with inflammation in multiple organs and correlating clinical pathology changes of inflammatory markers of inflammation. Microscopic inflammation was evident in pancreas (14-day DRF study), gall bladder (28-day study).

Effects on bone

It is known that the natural ligands of CSF1R and KIT regulate many pathways, such as growth and proliferation of macrophages and osteoclasts. Degeneration/necrosis and dental hyperplasia were observed in the left and right upper molar teeth of rats in the 26-week repeat-dose toxicity study administered ≥1 mg/kg/day. The dental effects at doses of 5 mg/kg/day in male rats were associated with lower food consumption and reduced body weight.

Hematopoietic effects

Effects on haematopoiesis were observed in rats and included decreased absolute reticulocyte count, lower red cell mass (red blood cell count, haemoglobin concentration, and haematocrit), and pan leukopenia at all dose levels in the DRF study. In the 4-week repeat-dose toxicity study lower platelet counts reflected bone marrow suppression/toxicity and microscopically with necrosis/apoptosis in lymphoid tissues. In the 13-week study, haematology changes included lower red cell mass (i.e. red blood cell count, haemoglobin, and haematocrit ranging from -3 to -20%) in animals administered ≥3.75 mg/kg/day, lower reticulocyte (-14 to -37%) and lymphocyte (-18 to 44%; except females administered 1.876 or 3.75 mg/kg/day) counts, and higher neutrophil (+29 to +443%) counts in animals administered ≥1.876 mg/kg/day. Additional findings limited to animals administered 7.5 mg/kg/day included higher red cell distribution width (+4 to +14%; also in females administered ≥3.75 mg/kg/day), and increased mean corpuscular volume (+3 to +9%) and mean corpuscular haemoglobin (+3 to +8%).

In the 13-week dog study, haematology effects included mildly decreased red blood cell mass (red blood cell count [-16.2%], haemoglobin concentration [-17.2%], and haematocrit [-17.9%]) on Day 92 of the dosing phase in females and mildly increased platelet count (+60.5% for males; +51.3% for females) on Days 24 and 92 of the dosing phase in both sexes without histopathologic correlates.

In the 39-week dog study, vimseltinib-related haematology findings included a mild increase in platelets and were observed in animals administered 8 mg/kg/day and lacked microscopic correlates.

2.5.4.3. Genotoxicity

Genotoxicity testing of vimseltinib was carried out *in vitro* (gene mutation test in bacteria, chromosome aberration test) and *in vivo* (rat combined micronucleus test/COMET assay) in accordance with ICH S2(R1) guidance and GLP requirements.

Dose selection was based on the results of a repeat dose and DRF study resulting in similar toxicity and TK parameters for both sexes and a MTD of 200 mg/d. Vimseltinib was tested negative for an increase in reverse mutations in an AMES test with and without metabolic activation up to the recommended top concentration of 5000 µg/plate for this assay. An increase in revertant numbers at 50 µg/plate with metabolic activation in E.coli strain WP2 uvrA was small (2.1 x) and not dose dependent. Vimseltinib was tested positive for an increase in the number of micronuclei at (16 - 30) µg/ml without metabolic activation (24 h) in human lymphocytes. No precipitation was observed at these dose levels with cytotoxicity of ~ 50 % determined at 30 µg/ml. Short-time incubation (3 h) experiments were negative for an increase of chromosomal aberrations, polyploidy, and endoreduplication up to the highest doses tested with and without metabolic activation. Therefore, vimseltinib was positive for inducing chromosomal aberrations and increasing the mutant frequency under the conditions of the study.

Vimseltinib was tested negative in a combined micronucleus/COMET assay in rats for an increase in micronucleated PCEs and in tail intensity/induction of DNA strand breaks up to the MTD (200 mg/kg). Cytotoxicity to the bone marrow was not observed after 3 days of administration and clinical signs were comparable to those observed in other toxicology studies conducted in rats at related doses. Vimseltinib was detected in the plasma but bone marrow exposure was not confirmed in this study. In a biodistribution study in rats vimseltinib was distributed in bone marrow. TK data (200 mg/kg) resulted in MoE ≥ 318 x or 238 x to the clinical exposure (C_{max} total 0.433 µg/ml or C_{max} 0.747 µg/ml) based on C_{max}. AUC was not determined. The positive in vitro micronucleus test could not be confirmed in an in vivo micronucleus test in the rat. In conclusion, the genotoxicity of vimseltinib was sufficiently addressed.

2.5.4.4. Carcinogenicity

Carcinogenicity testing of vimseltinib was carried out in a short-term 6-month oral carcinogenicity study in hemizygous RasH2 mice in compliance with GLP. Dose selection based on data collected from the 5 days MTD (MTD 50 mg/kg) and the 28 days DRF (NOAEL 50 mg/kg) repeat dose toxicity studies in wild type RasH2 mice and the decision of the FDA Carcinogenicity Assessment Committee. Due to the possible progress of dose limiting findings that could be influencing the results with dosing extension up to 6 month the high dose selected was 12.5 mg/kg which corresponds to 7.1 x the clinical dose (30 mg/2 x w → ~ 8.6 mg/d, SM ~ 2 x for 30 mg single dose) with scaling for species differences based on body surface area. In the MTD/DRF studies dose limiting findings were mixed cell inflammation in the meninges, hepatocellular/muscle alterations, changes in haematology parameters, inflammation, dehydration, and stress. Moderate to marked decreases in haematology parameters (bone marrow suppression, disturbance of erythropoiesis) and minimal to mild increases in clinical chemistry parameters (inflammation) were previously reported by Radi (2011) and Wang (2011) and most likely caused by mechanistic consequence of CSF1R inhibition of macrophage function that promotes elevations in AST, ALT and GLDH without liver injury. Equal disturbance of the haematology and clinical chemistry parameters were observed in the repeat dose toxicity studies in rat at all dosages. Target organs were the prostate (increased weight) without histologic correlate and the thymus in males (decreased weight, increased apoptosis). According to Elmore (2006) and Pearse (2006) these findings were probably caused secondary to stress (Elmore, 2006; Pearse, 2006).

Main target organ was the meninges observed in both genders with a dose dependent increasing mixed cell inflammation with respect to incidence and severity with females more sensitive than males. This finding was not observed in chronic rat studies up to 6 months. The daily administration of vimseltinib for six month had no effect on mortality and survival for both genders. Animal fade was caused by incidental fatal neoplasms without a dose response.

Minimal to slight non-neoplastic alterations respectively target organs which might be related to vimseltinib were observed in the spleen (all dose groups) and the femur/stifle joint (mid/high dose group) of both genders. All other findings were randomly distributed across study groups and considered spontaneous or incidental and expected in mice of this age and strain (Nambiar et al., 2012; Takaoka et al., 2003; Kanno et al., 2003; Morton et al., 2002; Paranjpe et al., 2013a; Paranjpe et al., 2013b; Paranjpe et al., 2019).

Vimseltinib had no statistically significant effects on the incidence or types of neoplastic alterations. All neoplasms observed in control and treatment groups had either no clear dose relationship, no statistical significance in tumour type or incidence, were of low incidence consistent with normal variation, or represented the types commonly reported and representative of the spontaneous, background findings observed for the RasH2 mouse model in 6 month studies (Nambiar et al., 2012). The NOAEL for carcinogenicity was determined at 12.5 mg/kg/d the highest dose tested.

TK data for vimseltinib and the PD active main metabolite DP-7005 was obtained from a subset of each study group and determined only on day 182 for plasma. No sex differences in exposures were observed (< 2 x). In plasma, for both gender the exposures were approximately dose proportional with increasing doses from the low to the high dose group without accumulation.

Dependent on the human exposure data (SPC C_{max} total 433 ng/ml and $AUC_{0-\infty}$ total 59100 ng h/ml and Nonclinical Overview $C_{max\ total}$ 747 ng/ml and $AUC_{0-24h\ total}$ 13400 ng/kg respectively) at the NOAEL (12.5 mg/kg), multiples of exposures were approximately 17 x / 9.8 x ($C_{max\ total}$) and 1.7 x / 7.6 x (AUC_{total}) for both genders combined.

A long–term rat 2-year carcinogenicity study in rats is ongoing and will be submitted post-marketing. During a Pre-submission meeting held on 17 April 2024, the rapporteur agreed that it is acceptable to submit the report of the 2-year rat carcinogenicity study as a post-marketing commitment. The study design and the dose selection have already been submitted. Dose selection was based on the findings (mortality, swelling of limbs, skin changes, inflammation, erythroid mass reductions, effects on lymphoid organs, vascular changes, bone/teeth alterations) and TK of the repeat dose toxicity studies of 4, 13, and 26 w repeat dose toxicity studies in rats, the ICH S1C(R2) guideline and the decision of the FDA Carcinogenicity Assessment Committee. The high doses selected (STD_{10}: ~ ♂ 1 mg/kg/d and ♀ 1.5 mg/kg/d) corresponds to approximately 1 (♂) – 1.7 (♀) x the clinical dose (30 mg/2 x w → ~ 8.6 mg/d) respectively as single dose 0.3 (♂) – 0.5 (♀) x with scaling for species differences based on body surface area.

2.5.4.5. Reproductive and developmental toxicity

Developmental and reproductive toxicology studies comprised studies on male and female fertility and early embryonic development, in rats, embryo-foetal development, in rats and rabbits (only dose range study in the rabbit), and pre- and post-natal development, in rats. In all studies, vimseltinib was administered once daily by oral gavage. Except for dose range finding embryo-foetal development studies, all the others were GLP compliant.

Fertility and early embryonic development:

In the male and female fertility and early embryonic development study, vimseltinib was administered at dose levels of 1, 5 or 10 mg/kg/day.

The study revealed general toxicity in both males and females. Periorbital red staining and discharge of the eye also occurred at ≥1 mg/kg/day, primarily in males. Other vimseltinib-related effects included reduced mean body weight gain and food consumption in females at ≥ 5 mg/kg/day during the first week of dose

administration; increased macroscopic observations in the lymph nodes of males at ≥1 mg/kg/day; reduced reproductive organ weights in males at 5 mg/kg/day; increased post-implantation loss in treated females at 10 mg/kg/day; and increased uterine weights at 10 mg/kg/day.

No vimseltinib -related effects were observed on sperm parameters in treated males, oestrous cycling in treated females, or mating and fertility in treated males and females at any dose level.

The mean percent of post-implantation loss was increased at the paternal doses of 1 and 5 mg/kg/day

Based on these findings, a no-observed-adverse-effect-level (NOAEL) of vimseltinib for general toxicity was not achieved. The NOAEL for mating and fertility was 5 and 10 mg/kg/day in males and females, respectively, and for early embryonic development was 5 mg/kg/day in treated males and females.

The C_{max} and AUC_{0-24} in females at the mating and fertility NOAEL were 15,600 ng/mL and 269,000 ng*h/mL, respectively. Based on these data a safety margin of 20 can be calculated.

Embryo-foetal development:

Embryo-foetal development studies comprised dose range finding studies in rats and rabbits (Studies DCC-3014-04-009 and DCC-3014-04-010) and a pivotal study in rats (Study DCC-3014-04-0011).

Oral administration of vimseltinib in the nonpivotal study in rabbits resulted in abortions in the 5, 10, and 20 mg/kg/day dose groups and clinical signs were observed in all dose groups throughout the dose and post dose periods. The number of post implantation losses were increased which resulted in reductions in the mean number of live and total foetuses per litter at 20 mg/kg/day

Based on maternal toxicity and abortions observed at ≥2.5 mg/kg and ≥5 mg/kg, respectively, following administration of vimseltinib in New Zealand White rabbits, and in conjunction with teratogenicity observed in rats at 15 mg/kg/day, a definitive EFD assessment was not conducted in rabbits, consistent with ICH S5(R3) guidance.

In the rat at a maternal dose of 15 mg/kg/day malformations of the cardiovascular and skeletal systems occurred. Additional indications of developmental toxicity, including structural anatomic variations and indications of developmental delay, also occurred at this dose.

In conclusion, vimseltinib at a dose of 15 mg/kg/day was a selective developmental toxicant (teratogenic) in rats. Under the conditions of this study at a maternal dose of 15 mg/kg/day malformations of the cardiovascular and skeletal systems occurred. Additional indications of developmental toxicity, including structural anatomic variations and indications of developmental delay, also occurred at this dose.

No adverse maternal effects were attributed to DCC-3014 administration, and therefore, the maternal no-observed-adverse-effect level (NOAEL) for DCC-3014 was 15 mg/kg/day DCC-3014: C_{max}: 19000 ng/mL and $AUC_{(0-t):}$313000 hr*ng/mL, the highest dose tested.

Although a limited number of skeletal variations were induced at 2.5 and 5 mg/kg/day, they were attributed to developmental delay that would be anticipated to resolve with continued development and were therefore considered non-adverse. Based on these data, the developmental NOAEL for vimseltinib was 5 mg/kg/day (vimseltinib: maternal C_{max} 6800 ng/mL and $AUC_{(0-t)}$; 106.000 hr*ng/mL). Following administration of vimseltinib, maternal systemic exposure to vimseltinib and DP-7005 was observed on GD 11, increased with increasing dose for the dose levels evaluated, and was approximately dose-proportional.

Prenatal and postnatal development:

Pre- and post-natal development studies comprised a study in rats. In this study, vimseltinib was administered from GD 6 through LD 20 at the tested dose levels of 0.1, 1 and 3 mg/kg/day.

Based on the maternal moribundity, mortality and total litter losses noted in the 3 mg/kg/day group, a dose level of 1 mg/kg/day was considered the no-observed-adverse-effect level (NOAEL) for maternal systemic toxicity of vimseltinib administered orally by gavage to maternal Crl:CD(SD) rats. Based on the lower mean pup survival and adverse lower mean body weights noted for F1 pups in the 3 mg/kg/day group during the preweaning and postweaning periods, the NOAEL for F1 neonatal and systemic toxicity was considered to be 1 mg/kg/day. There were no adverse effects on developmental landmarks noted at any dose level. The higher mean ages of attainment of balanopreputial separation for F1 males in the 1 and 3 mg/kg/day groups were attributed to vimseltinib- related developmental delay. The NOAEL for F1 neurobehaviour, F1 reproductive and developmental, and F2 early embryonic toxicity is considered to be 3 mg/kg/day.

Systemic exposure (C_{max} and AUC_{0-24hr} values) to vimseltinib decreased for female rats following repeated administration of vimseltinib.

Systemic exposure (C_{max} and AUC_{0-24hr} values) to the metabolite DP-7005 decreased (C_{max}) or did not appear to change (AUC_{0-24hr}) for female rats following repeated administration of vimseltinib. Systemic exposure (AUC_{0-24hr} values) to DP-7005 was < 1% the systemic exposure of DCC-3014 in female rats on Gestation Day 20 and Lactation Day 20.

Juvenile animal studies:

Juvenile animal studies have not been conducted.

2.5.4.6. Toxicokinetic data

Toxicokinetic data was obtained in the repeat-dose studies performed in rats and dogs and in the reproduction toxicity study in rats.

In rats and dogs, exposures (C_{max} and AUC_{0-24}) of vimseltinib and the metabolite DP-7005 increased dose proportionally. In rats, no apparent differences were observed in vimseltinib mean C_{max} and AUC_{0-24} values by sex. In dogs, exposure was highly variable and sex differences thus, inconsistent, mainly in the 13- and 39-week studies.

Mean exposures for the metabolite in the dog studies were in general higher (up to approximately 5-fold) than the parent drug probably due to the fact that DP-7005 is known to be formed at higher levels in dogs compared to rats. However, if the high level of metabolite is responsible for minor adverse events in dogs and the possible mechanism behind remains unclear and should be discussed.

Accumulation of vimseltinib and DP-7005 was observed after multiple doses in rats, but not in dogs.

2.5.4.7. Local tolerance

No specific tolerance studies were conducted.

2.5.4.8. Other toxicity studies

Phototoxicity

Vimseltinib revealed distribution of to the eyes and skin with affinity to melanin containing tissues. It absorbed light with three absorption maxima in the UV-vis spectrum with corresponding molar extinction coefficients (MEC) ≥ 21000 l mol^{-1} cm^{-1}. Therefore, the phototoxic potential of vimseltinib was determined in four GLP compliant in vitro 3T3 NRU phototoxicity tests using Balb/c 3T3 mouse fibroblasts. Due to the absence of cytotoxicity up to the max. soluble concentration of 31.7 µg/ml the IC_{50} (± UVA/B) were not achieved and a photo-irritancy factor (PIF) could not be calculated. The mean photo effect (MPE) was ≤ 0.069 for all experiments. Based on the PIF (≥ 5) and MPE (≥ 0.15) criterion vimseltinib demonstrate no phototoxic potential under the conditions of the study. Compared to the average clinical exposure (SPC: single dose, 30 mg, oral, C_{max} 0.433 µg/ml) a safety margin of 73.2 x to the max concentration (31.7 µg/ml) used in the in vitro study could be achieved. Furthermore, vimseltinib was photostable in a photostability test in accordance with ICH Q1B. Under photolytic conditions, no degradation products could be detected. In conclusion, based on the data submitted the phototoxic potential of vimseltinib is considered to be low.

Potential genotoxic impurities

For all potential genotoxic impurities that appeared in drug starting materials, in synthesis, as intermediates, or as synthetic precursors that exceeded the ICH Q3A reporting threshold the genotoxic potential was assessed in an in-silico assessment with the complementary Quantitative Structure-Activity Relationship ((Q)SAR) methodologies and categorised respectively controlled according to ICH M7. If appropriate subsequently AMES tests were conducted. All study reports (in-silico, AMES) were provided and the classification according M7 was acceptable.

2.5.5. Ecotoxicity/environmental risk assessment

Table 11. Summary of main study results

Substance (INN/Invented Name): Vimseltinib			
CAS-number (if available): 1628606-05-2			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log Dow (pH 5) = 2.84 log Dow (pH 7) = 3.28 log Dow (pH 9) = 3.27	Potential PBT: N
PBT-statement :	The compound is not considered as PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{sw}, refined	0.00214	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			N

$PEC_{surfacewater}$ for vimseltinib is below the action limit of 0.01 µg/L. Consequently, a Phase II risk assessment is not required.

2.5.6. Discussion on non-clinical aspects

Pharmacology

The driving force of TGCT proliferation is a small fraction of neoplastic cells producing high CSF1 levels. These cells attract and stimulate CSF1R-expressing monocytes and bystander macrophages. TGCT also include multinucleated giant cells that are often referred to as "osteoclast-like", however, their involvement in bone degradation has not been well documented (van IJzendoorn et al, 2022).

Vimseltinib is a potent inhibitor of CSF1R kinase with a higher affinity for the JM domain phosphorylated kinase (*K*d= 3.6 nM) than for the unphosphorylated CSF1R (*K*d = 79 nM). It demonstrates preferential inhibition of the JM domain phosphorylated CSF1R activity (IC_{50} = 2.8 nM) over the fully phosphorylated kinase (IC_{50} = 290 nM). Vimseltinib retained its potency in the presence of high ATP concentrations, simulating physiological conditions. The major human metabolite of vimseltinib, DP-7005, is also pharmacologically active but ca. 20-fold less potent than the parent compound.

Biochemical and cellular activity of vimseltinib towards CSF1R at clinically relevant concentrations was demonstrated. The major metabolite (DP-7005) was found to be pharmacologically active but less potent. The cell lines used in primary PD studies do not represent models of TGCT. However, it is acknowledged that cell line models of TGCT are scarce and may have not been available at the time of development. Vimseltinib is expected to act on CSF1R-expressing neoplastic cells within TGCT that represent a driving force of tumour growth but its activity on neoplastic cells without TGCT is uncertain.

In a PK/PD study, sustained inhibition of cFOS mRNA expression was observed in vimseltinib-treated DBA/1 mice following CSF1 stimulation at a single dose of 3.75 mg/kg and after repeated administration of 3 mg/kg/day or 1 mg/kg/day vimseltinib. Graphing cFOS mRNA levels vs. plasma concentrations revealed an EC_{50} value for the inhibition of 430 ng/mL and the EC_{80} of 1,700 ng/mL. Corrected for protein binding in mice (f_u = 2.7%), the corresponding values are 26.9 nM and 106.4 nM, respectively, which is in the range of clinically expected concentrations.

The pharmacological activity of vimseltinib as a potent CSF1R inhibitor has been demonstrated in animal models, but the proof of vimseltinib efficacy in the proposed indication can only be derived from clinical data.

Vimseltinib was demonstrated to be a selective CSF1R inhibitor. At ATP concentrations of 1 and 4 mM relevant in cellular context, it was more than 100-fold selective for CSF1R inhibition over other 298 kinases. Vimseltinib showed no clinically relevant interactions in a panel of 104 receptor binding and 31 enzyme and uptake assays. The major metabolite DP-7005 was evaluated only on three kinases. It inhibited KIT >10-fold weaker than CSF1R and revealed no inhibition of KDR or PDGFRβ. No data on binding of DP-7005 to receptors, enzymes and ion channels were submitted. Such an assay had not been performed due to the structural similarity to vimseltinib and low plasma levels of the unbound metabolite.

Vimseltinib did not demonstrate a clinically relevant hERG inhibition. The only cardiovascular effects observed after dosing of Beagle dogs with 15 mg/kg vimseltinib were not considered test-item related. No effects on CNS were observed in Sprague Dawley rats up to 30 mg/kg vimseltinib. The drug induced a mild transient increase in tidal volume in Sprague Dawley rats following oral dosing of 30 mg/kg, which was not seen as physiologically relevant.

Pharmacokinetics

The bioanalytical methods for determination of vimseltinib and DP-7005 in rat, dog and mouse plasma were developed and successfully validated.

Following oral dosing, vimseltinib exposure increased dose-proportionally up to 300 mg/kg in rats and up to 100 mg/kg in dogs, at higher doses a saturation of absorption was seen. Bioavailability was lower in male dogs, which was attributed to a higher first-pass metabolism.

After intravenous dosing to rats, brain penetration was estimated based on the AUC values to be 73%. Following oral administration of [^{14}C]-vimseltinib to Sprague Dawley rats, highest concentrations of radioactivity were seen in liver, adrenal gland, harderian gland, urinary bladder, fat (brown), kidney cortex, kidneys, myocardium, kidney medulla, and intervertebral ligaments. Importantly, radioactivity was still quantifiable in almost all tissues after 72 h, in line with low clearance of vimseltinib and relatively low recovery observed in excretion studies. Organs with the highest levels of radioactivity in Long Evans rats were eye uveal tract, eye(s), hair (follicle), liver, meninges, adrenal gland, harderian gland, stomach, kidney cortex, and kidney(s). Radioactivity was still quantifiable in the meninges, eye uveal tract, eye(s), and eye vitreous humour at 672 hours implying melanin binding. Prolonged retention of radioactivity in tissues may represent a safety concern and is therefore addressed in the SmPC section 5.3.

Metabolism of vimseltinib was species dependent. Little metabolism was observed in liver microsomes of human and animal species beside monkey. In hepatocytes, some metabolism was seen in the dog (42.6% compound loss). Limited metabolism in human was attributed to CYP3A4 and CYP2D6.

In Sprague Dawley rats, N-dealkylation and oxidation were the major metabolic pathways of vimseltinib. A large abundance of metabolites in faeces but not in bile indicated possible gastrointestinal metabolism. In Beagle dogs, vimseltinib was mainly metabolized by N-dealkylation to form DP-7005. Male dogs showed markedly higher metabolism, which may explain gender differences in toxicokinetics.

Vimseltinib was mainly excreted via faeces, with renal excretion representing a minor elimination pathway. The total recovery was relatively low in both rat and dog consistent with tissue accumulation.

Vimseltinib and DP-7005 were not inhibitors of CYP enzymes. Vimseltinib was not considered an inducer of CYP1A2 and CYP3A4 but it appeared to induce CYP2B6 at concentrations of 30 μM and higher, which are higher than clinically relevant (>50×$C_{max,u}$ of 2.94 μM). However, this finding may be a result of vimseltinib cytotoxicity to hepatocytes at >30 μM. Given a more than 2.0-fold increase in CYP3A4 mRNA levels in cultured human hepatocytes following treatment with up to 10 μM of vimseltinib, the potential drug-drug interaction risk with CYP3A4 substrates, particularly at the intestinal level, cannot be completely ruled out. For CYP1A2, concentration-dependent down-regulation was noted. In vitro, vimseltinib inhibited P-gp, BCRP and OCT2 to a clinically relevant extent warranting in vivo investigation. Given the widespread use of P-gp and BCRP substrates, close attention should be paid to concomitant drug use in clinical practice. Vimseltinib was a substrate of P-gp and not a substrate of other transporters. Thorough evaluation of the DDI potential of DP-7005 is not warranted as it accounts for less than 10% of drug-related material in circulation.

Repeat-dose toxicology

The toxicology program of vimseltinib (including its active metabolite DP-7005) was performed in agreement with ICH M3(R2).

The choice of mice, rats, rabbits and dogs as relevant toxicology species is, in principle, agreed since the pharmacologic target, CSF1R, is expressed in all these species and there is a high homology of the pharmacological target of vimseltinib between the used species.

Vimseltinib was orally administered to rats and dogs in repeat-dose toxicology studies up to 26- and 39-weeks, respectively, since oral administration is the intended clinical administration route. All of the pivotal studies included a 4-week recovery period.

In general, toxicity observed in rats is more pronounced than the one observed in dogs. This difference might be due to differences in specificity of the CSF1R inhibition (rodent/non-rodent). Multiple vimseltinib-treatment related toxicity findings in both species were suggestive of liver, cardiovascular and pancreatic toxicity.

Findings related direct to vimseltinib were observed in liver, kidney, and vascular system. Other findings were driven by the pharmacological effects of CSF1R inhibition since the natural ligands of CSF1R and KIT regulate many pathways, such as growth and proliferation of macrophages and osteoclasts, haematopoiesis, spermatogenesis, oogenesis and folliculogenesis.

Hepatotoxicity and nephrotoxicity are causes of concern in the clinical setting. With respect to hepatotoxicity it should be noted that changes in the liver leading to deaths only occurred in the DRF study in rats and only at the highest dose tested. Reversible microscopic changes were noticed in the long–term studies. Elevated liver enzymes in dogs accompanied by microscopic liver changes occurred only in the DRF study equivalent to the rat study. Based on these results, the potential risk of hepatic toxicity might not be evident. However, due to accumulation of vimseltinib and the metabolite DP-7005 and the small margins of exposure, hepatic toxicity cannot be ruled out. It is, however, acknowledged that vimseltinib does not have structural features for metabolic activation via the formation of reactive intermediates as seen by pexidartinib. Chronic progressive nephropathy occurred in rats receiving ≥2.5 mg/kg/day (approximately 7.5-times the exposure at the recommended human dose).

In rats, dose-limiting toxicity included bone marrow suppression, lymphoid tissue hypocellularity and/or necrosis at the highest dose tested in the 28-day study leading to termination of all animals for welfare reasons. In the 13-week study, the high-dose level resulted in adverse events including mixed cell inflammation, oedema, ulcer, and/or serocellular crust of the skin/subcutis of the limb or feet, leading also to deaths/early termination of animals (1 male, 1 female, 2 females of the toxicokinetic group, 1 female during recovery) at the highest dose tested. These effects were attributed to the pharmacological effect of CSF1R inhibition. In the 26-week study a NOAEL could not be determined due to adverse events at all dose levels. Animals at the highest dose tested exhibited e.g. degeneration/necrosis and mixed cell inflammation/serocellular crust.

In dogs, administration of vimseltinib was, in general, well tolerated. Treatment-related effects included changes in the eyes (swelling, lacrimation) and skin (depigmentation and swelling). Mildly increased AST and CK activities observed in the 39-week study were considered as a direct effect of CSF1R inhibition. The persistent mineralisation of the epididymis epithelium might also be a direct effect of vimseltinib. The evaluation of cardiovascular parameters did not demonstrate any effect of vimseltinib on PR interval, QRS duration, QT interval, corrected QT (QTc) interval, or heart rate during the 39-week study. An involvement of the metabolite DP-7005 in cardiovascular changes is low since the kinetic values of the metabolite (Cmax and AUC) in human plasma of the metabolite are appreciably lower than the parent drug.

Vimseltinib was highly brain penetrant in mice (minimal or slight mixed cell inflammation in the meninges of animals administered ≥12.5 mg/kg/day; see also carcinogenicity section) and rats. No information about brain penetration in dogs was submitted except the information that no macroscopically or microscopically changes in the brain were examined in either rats or dogs and no adverse effects on neurobehaviour or CNS toxicity were observed in these species. Since microglia are the primary target of vimseltinib in brain, literature data were presented demonstrating that depletion of microglia with CNS-permeable CSFR1 inhibitors is reversible and does not result in adverse pharmacological effects on behaviour or cognition. Further, there is no evidence from repeat-dose studies in rats and dogs that vimseltinib depletes microglia and induces adverse effects on these structures in brain. However, radioactivity was still quantifiable after 72 h in brain (see PK section), and thus, negative effects of vimseltinib cannot completely ruled out. A statement

was included in section 5.3 of the SmPC indicating that no CNS effects were noted in dogs up to the highest tested dose of 8 mg/kg corresponding to exposure below the anticipated clinical exposure at the recommended human dose. Therefore, clinical relevance of potential accumulation of vimseltinib in meninges remains unknown. Periocular swelling and epiphora observed in dogs at 8 mg/kg at exposures below the expected exposure in humans may be related to prolonged retention of vimseltinib in ocular tissues.

In rats and dogs, exposures (C_{max} and AUC_{0-24}) of vimseltinib and the metabolite DP-7005 increased dose proportionally. Mean exposures for the metabolite in the dog studies were in general higher (up to approximately 5-fold) than the parent drug probably due to the fact that DP-7005 is known to be formed at higher levels in dogs compared to rats. There is no discussion about a possible influence of the metabolite to on-target effects as a result of this higher level; however, it is argued that the potency of DP-7005 is 23-times lower than that of the parent drug vimseltinib and thus, the presence of DP7005 is not expected to contribute significantly to on-target mediated effects.

It is important to notice that no margins of exposure were observed in the 13-week dog study at NOAEL (for free and total vimseltinib) whereas in rats, margins of exposure were around 4 at NOAEL.

Genotoxicity

Vimseltinib was positive tested for an increase in the number of micronuclei in human lymphocytes but was negative tested in a combined micronucleus/COMET assay in rats for an increase in micronucleated PCEs and in tail intensity/induction of DNA strand breaks up to the MTD. TK data resulted in MoE ≥ 238 x (worst case) to the clinical exposure (C_{max}). The positive in vitro micronucleus test could not be confirmed in an in vivo micronucleus test in the rat.

In conclusion, the genotoxicity of vimseltinib was sufficiently addressed. The risk of genotoxicity from vimseltinib administration is considered to be low.

Carcinogenicity

Carcinogenicity testing of vimseltinib was carried out in a short-term 6-month oral carcinogenicity study in hemizygous RasH2 mice. The results were negative for a carcinogenic activity.

A long–term rat 2-year carcinogenicity study in rats is ongoing and will be submitted post-marketing. During the marketing authorisation assessment, a brief notification of a neoplastic finding in the 2-year rat oral carcinogenicity study was provided.

According to the human pathologists the tumour in one animal was a putative benign/low grade myoepithelial tumour with a myoepithelial/myxoid sarcoma appearance without necrosis and negative results for myoepithelial tumours in immunohistochemistry (S-100 and pan-cytokeratin). The synovial hyperplasia /hypertrophy observed in the other joint of the animal was fibroblastic /myofibroblastic and did not appear to be related to the myxoid neoplasm.

The tumour in the second animal had epithelioid and histiocytoid tumour cells and negative results in immunohistochemistry for lymphoma (CD3 and CD20) and for histiocytic sarcoma (CD68), respectively. The cells of origin of the neoplastic lesions were uncertain. Both tumours had dissimilar histomorphological characteristics, did not meet the diagnostic criteria for rat synovial sarcoma and did not resemble human synovial sarcoma.

The diagnosis and classification were changed from initially synovial sarcoma to (rare) sarcoma, not otherwise specified (NOS), synovium, due to the location (synovial membrane and associated tissues of the

joint) of the tumours, the locally invasive/destructive behaviour and the morphologic features, in conjunction with the immunohistochemistry results.

Given the uncertain cell of origin of neoplastic lesions, and the strong association of synovial hyperplasia/hypertrophy with mixed cell inflammation, this may represent a secondary occurrence of neoplasia associated with chronic tissue injury, rather than a direct, primary effect of the test article (Boorman et al., 2004).

Vimseltinib was tested negative for genotoxicity. No evidence of carcinogenicity was observed in chronic toxicity studies in rodents (mouse/rat 6-month) and dogs (9-month). The 6-month carcinogenicity study in hemizygous RasH2 mice was negative for both genders at 7.6 times the clinical exposures based on AUC. Female rats were negative for carcinogenicity in the 2-year carcinogenicity study.

In a 2-year oral rat carcinogenicity study, 2 out of 60 high dose males were identified as having histomorphologically different sarcomas in the synovium of the femorotibial joint at exposures approximately < 1/1.4 times (unbound/total) the recommended human dose based on AUC. Both were classified as sarcoma, not otherwise specified. The relevance of this finding to humans is unknown but considering all available clinical and non-clinical data the carcinogenic risk after Vimseltinib administration is considered low.

Although no vimseltinib related promotion of tumorigenesis or proliferative disease in humans at therapeutic doses were observed with a duration of treatment for up to 4 years a number of 250 patients treated in clinical trials is "relatively small". Ongoing pharmacovigilance is therefore essential. To date, no carcinogenic risk was identified with other CSF1R inhibitors used in clinical studies or holding marketing authorisation.

Taking into account all available data, it was concluded that there is no specific risk of synovial sarcoma, but that the carcinogenic risk for humans cannot be excluded, even if low.

The RMP and SmPC section 5.3. Preclinical safety data was updated accordingly, and routine pharmacovigilance monitoring will be continued.

Genotoxic impurities

For all potential genotoxic impurities that appeared in drug starting materials, in synthesis, as intermediates, or as synthetic precursors that exceeded the ICH Q3A reporting threshold the genotoxic potential was assessed in an in-silico assessment with the complementary Quantitative Structure-Activity Relationship ((Q)SAR) methodologies and categorised respectively controlled according to ICH M7. If appropriate subsequently AMES tests were conducted. All study reports (in-silico, AMES) were provided and the classification according M7 was acceptable.

Reproductive and developmental toxicity

The package of developmental and reproductive toxicology studies is considered adequate. The lack of juvenile animal studies is acceptable. The medicinal product has been granted a product-specific waiver for all subsets of the paediatric population.

Results from the conducted studies on male and female fertility and early embryonic development do not indicate a risk of adverse effects. Male reproductive findings observed in the 26-week rat and 39-week dog studies are addressed in the SmPC. Total litter loss was observed in the pre and postnatal development study at doses corresponding to unbound vimseltinib exposures lower than those at the recommended human dose. This has been addressed in the SmPC.

Embryo-foetal development studies and the pre- and post-natal development study showed reproductive toxicity. As vimseltinib is a selective developmental toxicant (teratogenic) in rats, additional indications of developmental toxicity, including structural anatomic variations and indications of developmental delay, occurred.

Several publications can be found concerning the role of CSF1R in embryo-foetal development (Chitu and Stanley 2017, Nagra et al. 2023). Given the mentioned literature data and the cardiovascular and skeletal malformations, identified in the rat EFD study, a contraindication for pregnant women is issued. There are no available data from the use of vimseltinib in pregnant women. Based on findings from animal studies, vimseltinib may cause foetal harm when administered to pregnant women. Studies in animals have shown reproductive toxicity (foetal structural abnormalities and cardiac malformations). The pregnancy status of women of childbearing potential must be verified prior to initiating vimseltinib and during treatment.

Women should be advised to avoid pregnancy while taking vimseltinib. Pregnant women should be informed of the potential risk to the foetus. Women of childbearing potential must use effective contraception during treatment with vimseltinib and for 30 days after the final dose. Effects of vimseltinib on hormonal contraceptives have not been studied. Therefore, a barrier method should be added if hormonal contraceptives are used. A contraindication for the use in pregnancy is issued given the cardiovascular and skeletal malformations identified in the rat EFD study and the literature data (see sections, 4.3, 4.4, 4.6 and 5.3 of the SmPC).

In view of the important potential risk of embryo-foetal toxicity, the applicant will ensure that a patient card is included in each Romvimza package as an additional risk minimisation measure in the risk management plan (RMP).

It is unknown whether vimseltinib is excreted in human milk. A risk to the breast-fed child cannot be excluded. Women should not breast-feed during treatment with vimseltinib. Based on findings from animal studies, vimseltinib may impair fertility in males.

Conclusions on ERA:

$PEC_{surfacewater}$ for vimseltinib is below the action limit of 0.01 µg/L and thus, no Phase II ERA is required.

A PBT/vPvB assessment was not required as the log Dow value < 4.5.

As a result of the above considerations, vimseltinib does not pose a risk to the environment when used as indicated in the SmPC.

2.5.7. Conclusion on the non-clinical aspects

Vimseltinib has been demonstrated to be a potent and selective CSF1R inhibitor *in vitro* and *in vivo*. However, information on its efficacy in the proposed indication can only be taken from clinical data as no animal models of TGCT were employed in the non-clinical development of vimseltinib. Prolonged accumulation of vimseltinib in tissues may represent a safety concern in the proposed non-malignant indication and has therefore been addressed in the SmPC.

In toxicology studies, vimseltinib exhibited dose-dependent toxicities primarily impacting the liver, skin, and hematopoietic system, with effects linked to its pharmacological mechanism. Notably, toxicities in rats were dose-limiting and presented at relatively narrow margins, while dogs showed milder responses, suggesting species-specific variability. The package highlights the need for careful monitoring of hepatic function and

haematological parameters in clinical settings, especially at higher exposures. Given the cardiovascular and skeletal malformations, identified in the rat EFD study and the above-mentioned literature data, a contraindication for pregnant women is issued. Long-term safety was further evaluated in genotoxicity and carcinogenicity assays. A brief notification of a neoplastic finding in the 2-year rat oral carcinogenicity study has been recently provided. The relevance for humans is unknown. Considering all available clinical and non-clinical data the carcinogenic risk after vimseltinib administration is considered low. This is addressed in the SmPC accordingly.

Vimseltinib does not pose a risk to the environment when used as indicated in the SmPC.

2.6. Clinical aspects

2.6.1. Introduction

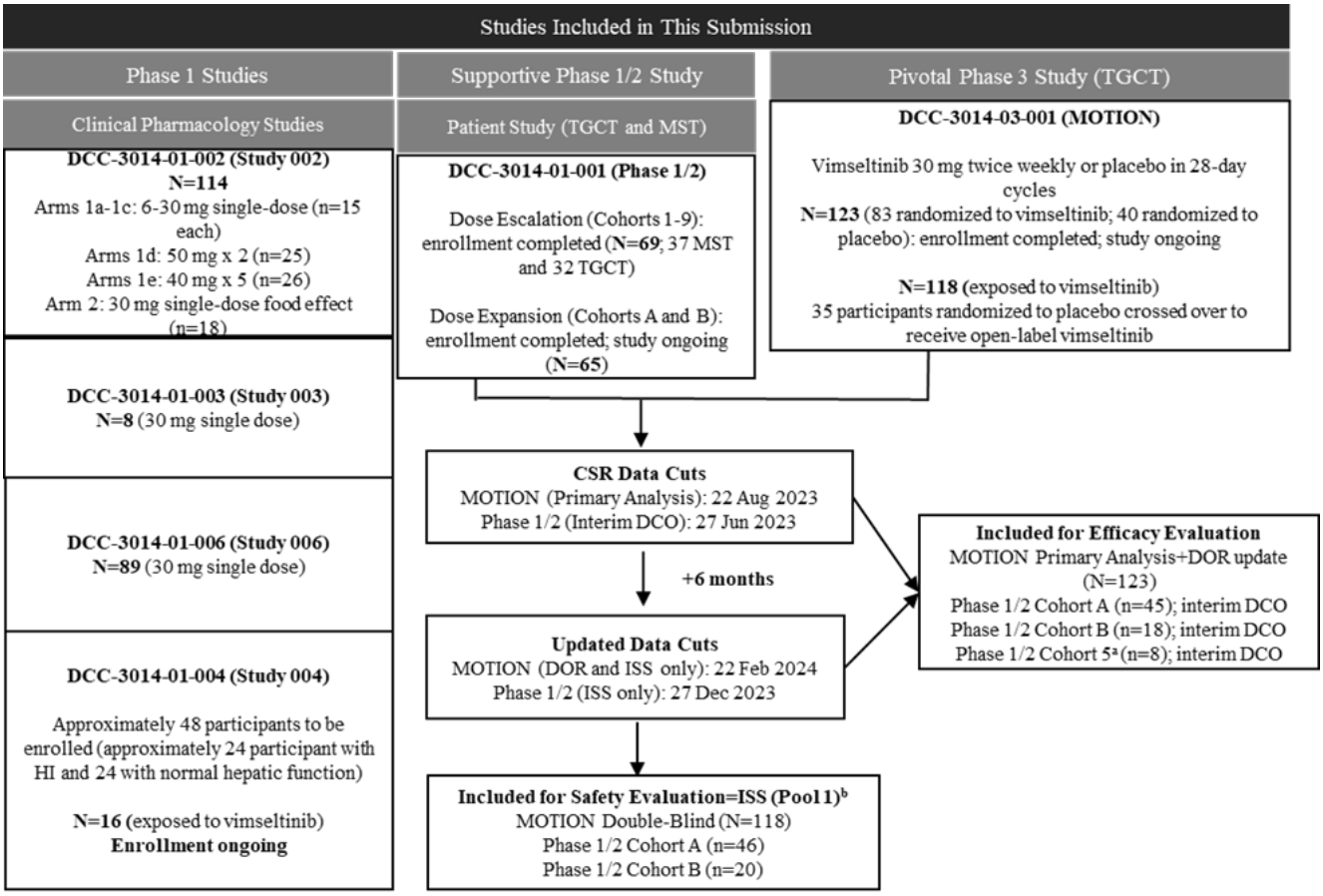
GCP aspects

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.

- **Overview of clinical studies**

Figure 2. Vimseltinib's clinical development programme



2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The clinical pharmacokinetic (PK) profile of vimseltinib was investigated in six clinical studies, population (pop)PK analysis, Physiology-Based (PB)PK modelling and simulation, exposure-response (ER) analyses and concentration QTc modelling.

Methods

The concentrations of vimseltinib and its active metabolite DP-7005 in plasma and urine were measured in clinical studies using validated liquid chromatography with tandem mass spectrometry/mass spectrometry methods. The four bioanalytical (BA) methods were qualified by determining the selectivity, specificity, matrix effect, calibration curve and range, accuracy and precision, carryover, dilution integrity, stability, method reproducibility, linearity, recovery, and limit of quantification. Common medications were tested for possible interference with DCC-3014, DP-7005, or the internal standards and met the acceptance criteria.

Method validation was performed for the commercially available ELISA kits for use in quantification of biomarker levels of human IL-34 in human plasma and for the commercially available ELISA kits for quantification of biomarker levels of human CSF1 in human plasma. Assay validation was also performed for

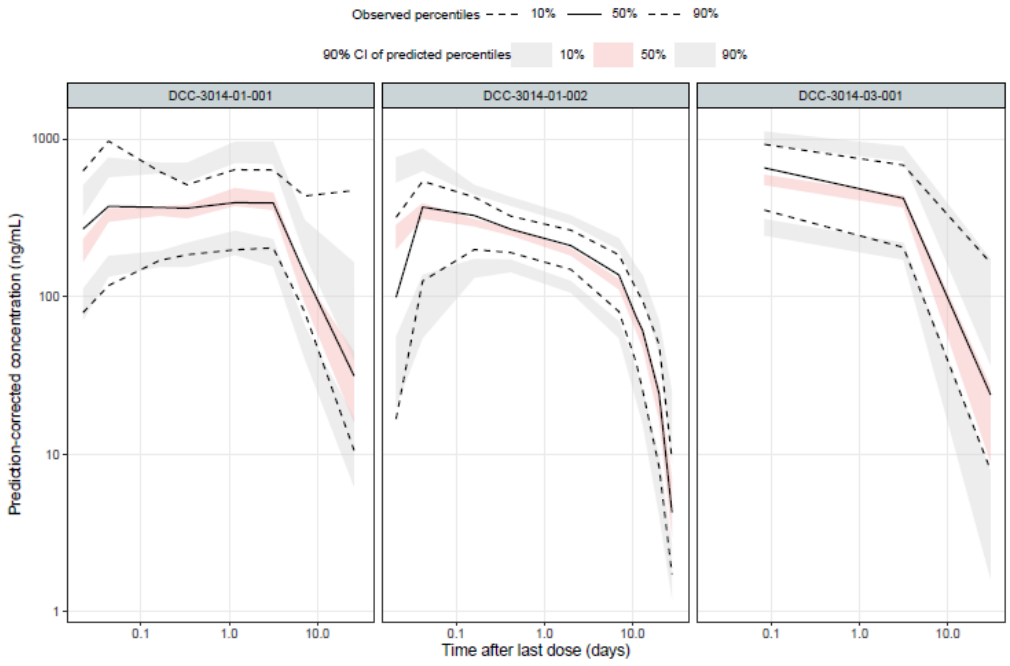
determination of circulating levels of CD14, CD16, and CSF1R positive monocytes were investigated in human whole blood.

Common PK parameters for vimseltinib and DP-7005 were derived from plasma sampling. PK parameters were summarised using common descriptive statistics. Concentration-time data were analysed using NCA methods in Phoenix™ WinNonlin® (Version 8.3. or higher) in study 01-001 with WinNonlin® NCA models 200-202, in studies 01-002 and 01-003 in conjunction with Certara IntegralTM (Version 22.10.1).

Population PK Modelling

A popPK model for vimseltinib was developed based on data from 349 subjects (healthy volunteers, malignant solid tumour (MST) patients, and TGCT patients). A two-compartment disposition model was selected to best describe the data. Body weight was included from the start as a mechanistic covariate with fixed exponents (shared exponents between CL/F and Q/F and between Vc/F and Vp/F). A first-order absorption model was not sufficient to describe the data, instead a sequential zero and first-order absorption model was selected. The exploratory covariate effects suggest a lower Vc/F for healthy volunteers. In addition, healthy volunteers had a markedly higher Vp/F. The most influential covariates in the final model on primary parameters were the food effect and body weight. Low body weight was associated with higher exposure, while high body weight was associated with lower exposure, as expected when using a flat dose. The food effect had substantial influence on the duration of absorption with ca. 6 times longer MAT for fed compared to fasted subjects but was discussed to be not of clinical relevance.

Figure 3. Prediction-corrected visual predictive check of vimseltinib PK plasma concentrations versus time after dose, for the vimseltinib PK analysis data set using the final vimseltinib PK model, stratified by study, presented on a double logarithmic scale



PBPK Modelling

A full PBPK model with ADAM absorption model was developed to simulate plasma concentration-time profiles of vimseltinib following single or multiple doses of 30 mg vimseltinib in healthy participants and to evaluate the potential for CYP-mediated and transporter-mediated DDIs with vimseltinib as a perpetrator. The

platform is not regarded as qualified to predict interactions based on P-gp, BCRP and OCT2. Based on PBPK modelling, the interaction potential of vimseltinib as a perpetrator for P-gp, BCRP and OCT2 transporters was predicted to be low.

Exposure-response Modelling

For the objective response rate dataset, data from the 30 mg treatment group were used (n=83) together with placebo data (n=34) in an enriched dataset. ORR per RECIST v1.1 and ORR per TVS at Week 25 were predicted to be 41.4% and 68.5%, respectively.

In the time to first event analysis data set, different doses were included (6, 10, 20, 30, 40 mg) and more data was available. Data from the targeted TGTC population (n=214) was pooled with data with malignant solid tumours (n=37) and tumour type was investigated as covariate. Patients with TGCT had higher risk of periorbital oedema, and lower risk of AST elevation, compared to patients with MST. A very high proportion of all patients was predicted to show AST elevation, 93.8% for 30 mg and 86.5% for 20 mg BIW. Due to limited data, the predictions based on E-R modelling are associated with large statistical uncertainty (high RSE) and should be interpreted with caution.

The PKPD relationship was further investigated using tumour size (per RECIST v1.1 and per TVS) as efficacy endpoints. As Emax was fixed to 1 to stabilize the model, both tumour models should not be used for extrapolation of tumour dynamics at Cav beyond the observed concentrations. Also, the relationship between exposure and biomarker changes was characterised for CSF1 and NCM. Covariate analysis for the CSF model showed that Subjects with MST had an 87% higher Baseline CSF1 compared to subjects with TGCT. Simulations with the final NCM model predicted a rapid decline in NCM until plateauing around five weeks after the first dose administration. The maximal relative change from baseline NCM increased at higher doses.

Absorption

Vimseltinib solubility is classified as low according to Biopharmaceutics Classification System (BCS) criteria. The *in vitro* permeability of vimseltinib was evaluated in a validated Caco-2 cell monolayer model. Permeability was higher than that of positive control minoxidil 10 µM, thus vimseltinib was classified as highly permeable. According to ICH M9, the overall BCS classification was BCS Class 2 with low solubility and high permeability.

Absolute bioavailability was not discussed by the applicant.

The bioequivalence study arm 3 of study 01-002 for the 30 mg commercial dose strength (vs. 3x10 mg clinical capsule) was not performed.

Study 01-002 was a phase 1 study to evaluate the plasma PK of vimseltinib (DCC-3014) and its metabolite DP-7005 after oral dosing of vimseltinib in adult healthy volunteers (HV). One of the secondary objectives was the assessment of the effect of a high-fat meal on the PK of DCC-3014 and its metabolite after a single oral dose. The study was conducted in four study sites across the US and each enrolled 30, 15, 38 and 31 healthy volunteers, respectively.

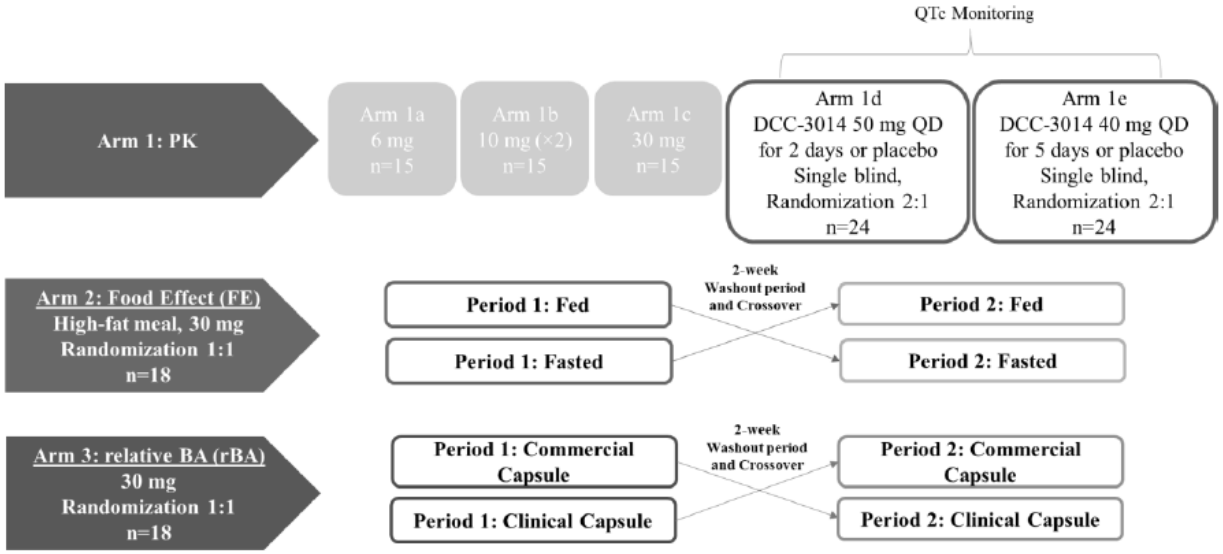
Schematic overview is given in Figure 4. The study consisted of up to 7 arms (6 arms were enrolled, arm 3 was not conducted):

- Arms 1a and 1c (both single dose on day 1), and 1b (single dose on Day 1 of Period 1 and Day 1 of Period 2 to characterise intrasubject PK variability) of this study were conducted first and were designed

to characterise the PK of vimseltinib and its metabolite DP-7005. Arm c evaluated the elimination of vimseltinib and its metabolite.

- Arms 1d and 1e were single-blinded, placebo-controlled designs to gather additional information at higher exposure (50 mg once daily [QD] for 2 days and 40 mg QD for 5 days, respectively), and to evaluate cardiac safety. Participants were randomised 2:1 to receive vimseltinib or placebo (see PD section).
- Arm 2 was a randomised, crossover design to investigate the effects of a high-fat meal on the PK of vimseltinib and the metabolite DP-7005 in clinical capsule at 30 mg. Participants were randomised 1:1 to receive vimseltinib in the Fed or Fasted state, followed by a 2-week washout period and crossover.
- Arm 3 was planned as a randomised, crossover design to compare the relative bioavailability of the clinical capsule (reference formulation) with a proposed commercial capsule (test formulation). The proposed commercial capsule was 30 mg strength, but was not conducted.

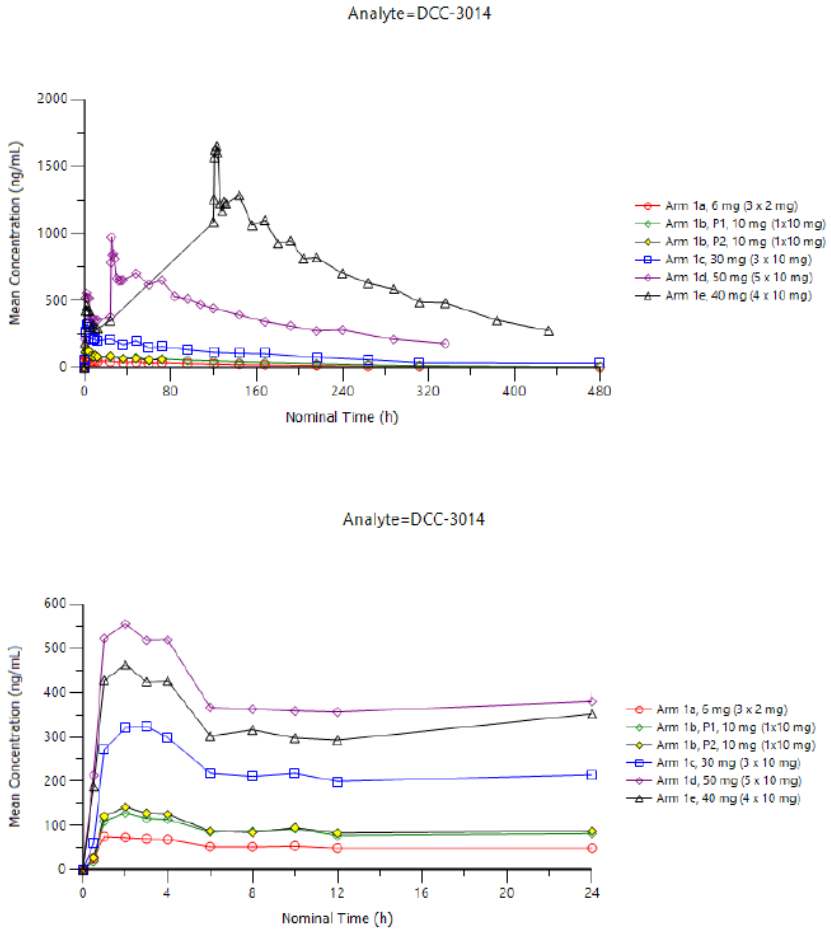
Figure 4. Study DCC-3014-01-002. Study design for DCC-3014 pharmacokinetics/food effect study



Abbreviations: PK=pharmacokinetics; QD=once daily; QTc=corrected QT interval; rBA=relative bioavailability.
Note: All arms are fasted and clinical capsule is used unless otherwise indicated.

Data from up to 96 participants (Arm 1: n=80, Arm 2: n=16) were included in the PK analysis. Concentration-time data for vimseltinib and in plasma after administration of ascending doses ranging from 6 mg to 50 mg are shown in Figure 5 (Arm 1a to 1e).

Figure 5. Study DCC-3014-01-002: mean plasma concentration-time profiles of vimseltinib (DCC-3014) after administration of 6 mg (Arm 1a, 3×2 mg), 10 mg (Arm 1b, 1×10 mg), 30 mg (Arm 1c, 3×10 mg), 50 mg (Arm 1d, 5×10 mg), and 40 mg (Arm 1e, 4×10 mg) vimseltinib on linear scale, PL evaluable set



Overall, the Cmax, AUC0-tlast, AUC0-inf of vimseltinib increased with increasing single doses of vimseltinib from 6 mg - 30 mg, and for Cmax and AUC0-24h between 6 mg - 50 mg. The same was shown for the metabolite DP-7005.

Arm 1b

Results of mean concentration-time profiles of vimseltinib and DP-7005 in arm 1b, see Figure 6. The intrasubject variability was less than 23% for both vimseltinib (intrasubject variability values were 14.28% for AUC0-72h and 20.86% for Cmax) and DP-7005 (intrasubject variability values were 21.02% for AUC0-72h and 22.60% for Cmax). The applicant concluded, that vimseltinib is not a highly variable drug. For results of the ANOVA, see Table 12.

Figure 6. Study DCC-3014-01-002: mean plasma concentration-time profiles of vimseltinib and DP-7005 after administration of 10 mg (Arm 1b, 1×10 mg) vimseltinib during periods 1 and 2 under fasted conditions on linear scale, PK evaluable set

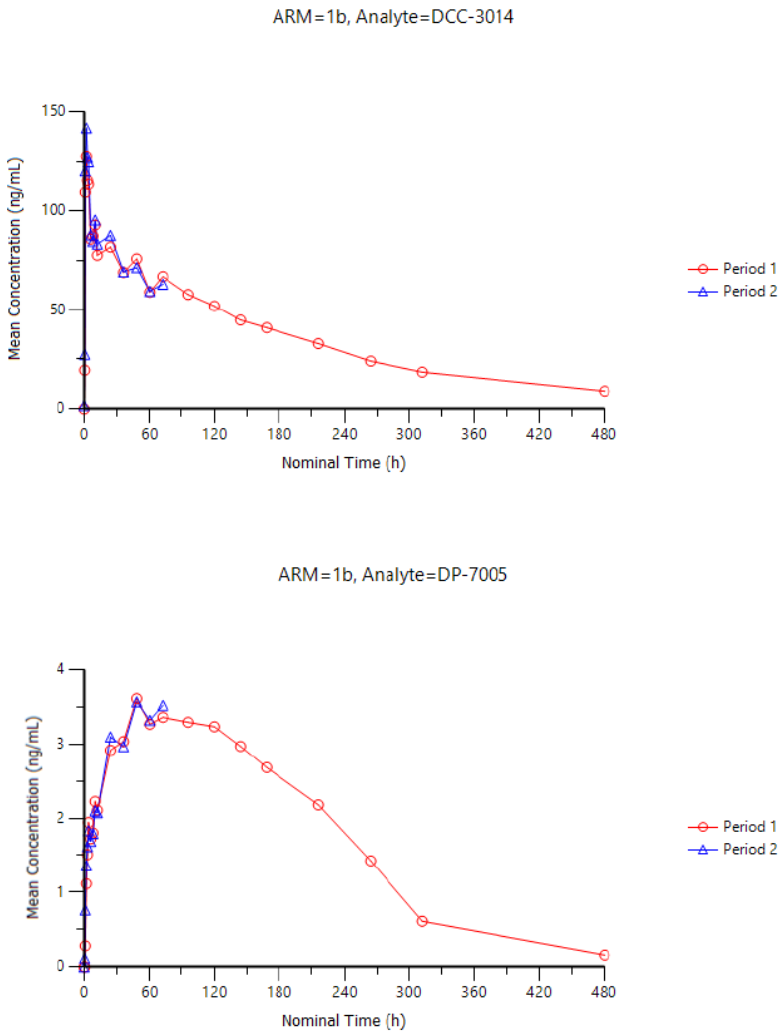


Table 12. Study DCC-3014-01-002: statistical analysis of the natural log-transformed systemic exposure parameters of vimseltinib comparing vimseltinib 10 mg (Arm 1b, 1×10 mg) administered in period 1 and period 2, PK evaluable set

Comparison	Dependent Variable	Test (n)[a]	Ref (n)[a]	GeoMean[b] Test	GeoMean[b] Ref	Ratio (%)[c] (Test/Ref)	90% CI Lower	90% CI Upper	p-value[d]	Intrasubject CV%
Period 2 vs Period 1	C_{max}	8	8	129	127	101.88	84.05	123.50	0.8593	20.86
	AUC_{0-72h}	8	8	4970	5040	98.73	86.44	112.76	0.8604	14.28

Abbreviations: AUC_{0-72h}=partial area under the concentration-time curve from time 0 to 72 hours; CI=confidence interval; C_{max}=maximum concentration; CV%=percent coefficient of variation; GeoMean=geometric mean; n=number evaluable; Ref=reference (Period 1); Test=Period 2.

a Five participants had predose concentrations >5% Cmax in Period 2; no data were available for two participants who discontinued after Period 1.
b Geometric Mean based on least square mean.
c Ratio(%)=Geometric Mean (Test)/Geometric Mean (Ref).
d P-value for the difference between treatments; significant difference defined *a priori* as p<0.05.

Influence of food

Figure 7. Study DCC-3014-01-002: mean plasma concentration-time profiles of vimseltinib and DP-7005 after administration of 30 mg vimseltinib (Arm 2, 3×10 mg) under fed (high-fat meal) and fasted conditions on linear scale, PK evaluable set

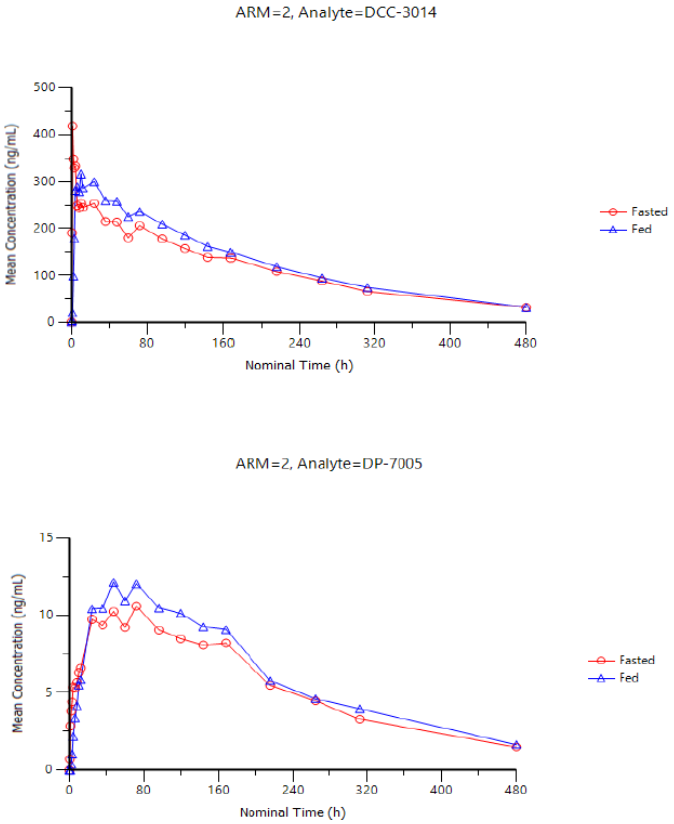


Figure 8. Study DCC-3014-01-002: mean plasma concentration-time profiles of vimseltinib after administration of 30 mg vimseltinib (Arm 2, 3 x 10 mg) under fed (high-fat meal) and fasted conditions on semi-logarithmic scales – PK evaluable set

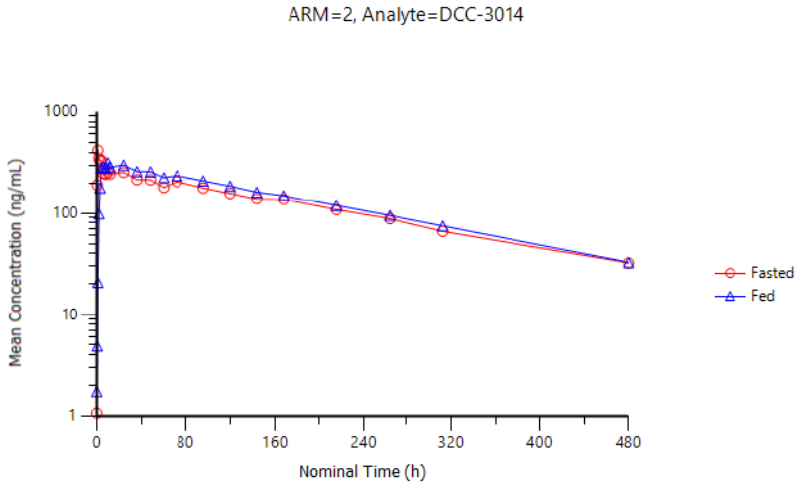


Table 13. Study DCC-3014-01-002: plasma pharmacokinetic parameters for vimseltinib after administration of 30 mg (Arm 2, 3×10 mg) vimseltinib capsule under fasted and fed (high-fat meal) conditions (food effect), PK evaluable set

Parameter	Vimseltinib					
	Fasted			Fed		
	n[a]	Geometric Mean	Geometric CV%	n[a]	Geometric Mean	Geometric CV%
t_{max} (h)	15	1.00 (0.500-4.00)		15	6.00 (3.00-25.4)	
C_{max} (ng/mL)	15	433	42.8	15	351	15.1
$AUC_{0\text{-}120h}$ (h*ng/mL)	15	23,800	39.6	15	28,100	15.9
$AUC_{0\text{-}480h}$ (h*ng/mL)	14[b]	51,300	41.8	15	58,700	25.6
$AUC_{0\text{-}tlast}$ (h*ng/mL)	15	48,500	48.5	15	58,900	25.8
$AUC_{0\text{-}inf}$ (h*ng/mL)	11[c]	59,100	23.2	15	65,000	29.8
AUC_{Extrap} (%)	11[c]	7.32	56.9	15	7.35	97.5
$t_{1/2}$ (h)	15	137	32.4	15	135	27.5
t_{last} (h)	15	480 (168-484)		15	482 (479-651)	
C_{last} (ng/mL)	15	29.5	70.6	15	24.5	94.7
CL/F (L/h)	11[c]	0.507	23.2	15	0.462	29.8
V_z/F (L)	11[c]	89.9	16.0	15	90.0	20.7

Abbreviations: $AUC_{0\text{-}x}$=partial area under the concentration-time curve from time 0 to time x; C_{max}=maximum concentration; C_{last}=last quantifiable concentration; CL/F=apparent total body clearance; CV%=percent coefficient of variation; n=number evaluable; $t_{1/2}$=observed terminal half-life; t_{last}=time to C_{last}; t_{max}=time to C_{max}; V_z/F=apparent volume of distribution.

a Three participants completed only the Fed period; two participants completed only the Fasted period; predose concentration for one participant (Fasted-Fed) in Period 2 (Fed) was >5% of Cmax.

b AUC0-48h could not be determined for one participant since λz criteria were not acceptable.

c AUCinf acceptance criteria not met for reporting parameter (AUCextrap>20%) for four participants under Fasted conditions; excluded from summary statistics and subsequent calculations or analysis.

Note: tmax and tlast presented as median (minimum – maximum)

In **study 01-001** all patients with MST were administered vimseltinib under fed conditions (high-fat meal) at Baseline (Day -7). The presence of a high-fat meal appeared to increase the median tmax from ~ 1 to 2 hours to ~ 4 to 6 hours under fed conditions.

Distribution

Plasma protein binding of vimseltinib was 96.7% at 1 µM and 96.5% at 10 µM; thus, the free fraction of vimseltinib was determined to be 3.3 - 3.5%, without concentration dependence. The bound percentage of DP-7005 was 94.3% at 1 µM and 92.4% 10 µM, i.e. free fraction of 5.7 – 7.6%. There was a weak concentration dependency in the plasma protein binding of DP-7005.

Mild hepatic impairment did not appear to affect vimseltinib PPB as geo-mean unbound vimseltinib fraction remained between ~6%-7%. The unbound fraction of DP-7005 remained at 13-15% regardless of hepatic function.

After a single 30 mg dose in Study 01-002, in HV the geo-mean (geoCV%) Vz/F of vimseltinib was 134 L (70.4%). The PopPK model estimated an apparent Vc/F of 88.0 L and Vp/F of 28.9 L. Covariate analysis

suggested that HV had a significantly lower Vc/F, and higher Vp/F, compared with TGCT patients, though steady-state exposure parameters were within 80% - 125% limits.

Based on $AUC_{0\text{-}inf}$, the geo-mean B:P ratio was 0.751.

In vivo study DCC-3014-03-0015 indicated that vimseltinib exhibits a significant 73% blood-brain-barrier (BBB) penetration based on AUC ratio (CNS/plasma) when given as a 1 mg/kg intravenous dose.

Elimination

Following single doses of 30 mg vimseltinib in HV in fasted state in study 01-002 (Arm 1c), the geo-mean total amount of vimseltinib excreted unchanged in urine during the confinement period of 168 hours was 0.0764 mg (76.4 µg), approximately < 1% of the dose indicating that CLr (geo-mean CLr=0.00333 L/h) represents a negligible pathway for vimseltinib elimination. This is supported by the greater geo-mean CLnr compared to CLr of vimseltinib (0.695 L/h vs 0.00333 L/h). In addition, geo-mean AURCu(0-tlast) of vimseltinib was lower compared to DP-7005 (0.0681 mg vs 0.109 mg) supporting CLnr as the predominant elimination pathway for vimseltinib. The geometric mean total amount of DP-7005 excreted in urine was greater compared to vimseltinib (0.119 mg vs 0.0764 mg).

Geo-mean CL/F ranged from 0.507 - 0.699 L/h. In the group of normal subjects of study 01-006 CL/F was 0.496 L/h. In the PopPK analysis for TGCT patients geo-mean CL (gCV) was estimated with 0.639 (45.1) L/h.

In HV, $t_{1/2}$ ranged from 134 - 137 hours. In patients after single doses of 6 - 50 mg in study 01-001, $t_{1/2}$ decreased from 153 hours to 113 hours. In the popPK analysis in TGCT patients, the geo-mean effective half-life (gCV) was 129 (35.9) hours, consistent with the $t_{1/2}$ observed in Study 002.

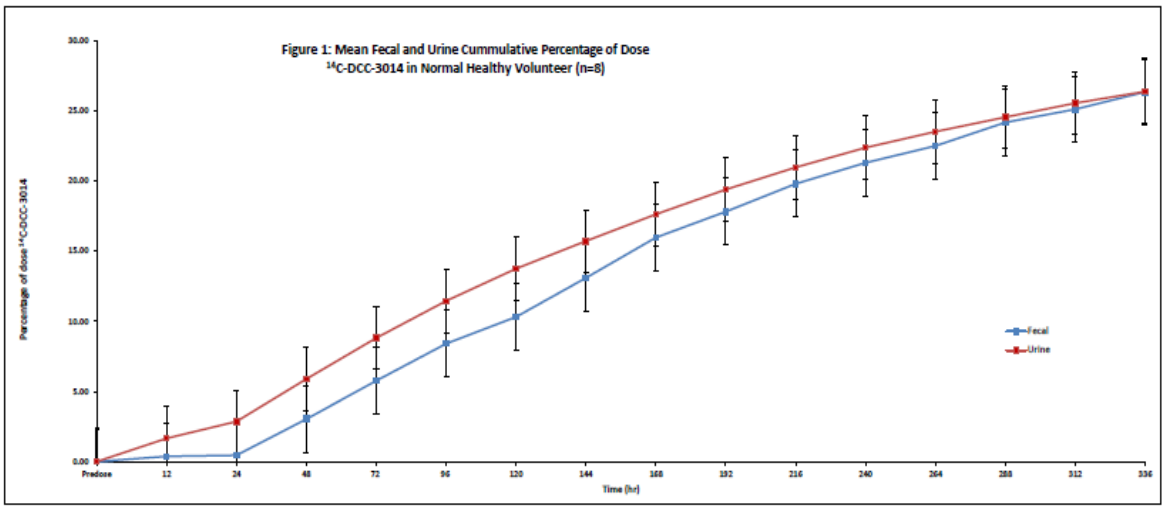
Mass balance (study 01-003) was investigated in 8 male HV after a single oral dose of 30 mg (approximately 72 µCi) ^{14}C-vimseltinib as a capsule formulation with neat drug substance (cold and hot material). Subjects were housed until day 15 (336 hours).

The observed mean total recovery of the administered radioactive dose in urine and faeces up to 50 days was 54.11 ± 13.71% (15.67 ± 3.92 mg). The estimated total recovery of radioactivity in excreta up to infinity was 80.4%.

The observed cumulative urinary excretion (Cumulative f_{eu} %(0-1200) (%); mean ± SD) was 26.96 ± 7.03% and 7.81 ± 2.02 mg. When extrapolated to infinity, the arithmetic mean amount recovered (Total A_{eu}) was estimated to 10.9 mg (37.5% of administered dose, Total $\%f_{eu}$).

The observed cumulative faecal excretion (Cumulative f_{ef} %(0-1200) (%)) was 27.15 ± 7.53% and 7.85 ± 2.15 mg. When extrapolated to infinity, the arithmetic mean amount recovered (Total A_{ef}) was estimated 12.4 mg (42.9% of administered dose, Total $\%f_{ef}$).

Figure 9. Mean cumulative faecal and urine excretion in percentage of dose



Note: Figure is only representative of continuous collection Days 1 through 15, Predose through 336 hours.

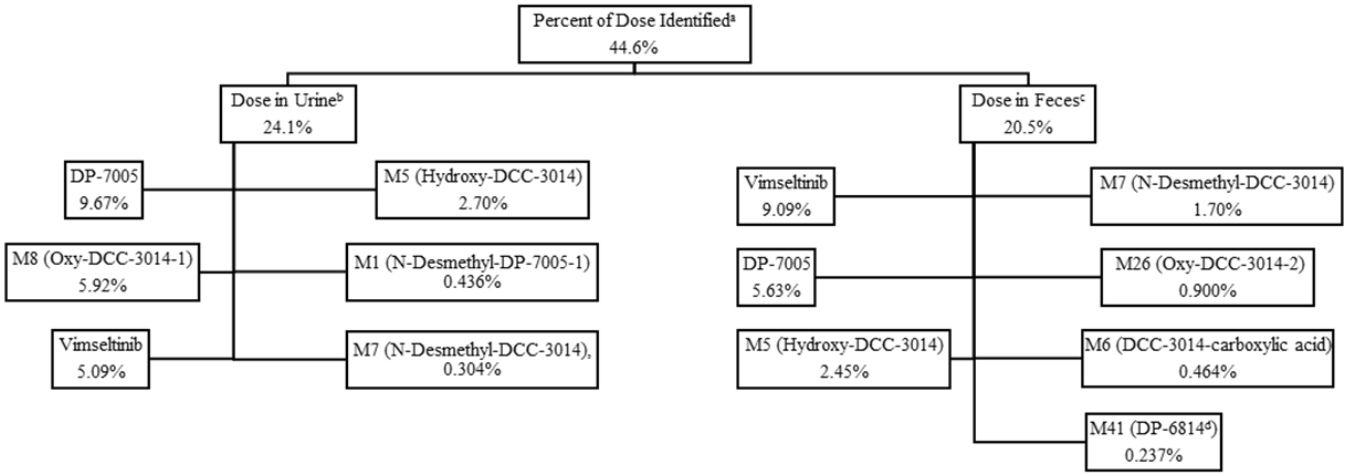
Table 14. Total percent of dose recovered in urine and feces

Subject	Observed Cumulative % Dose Excreted		Total % Recovered
	Urine (0-1200 hr)*	Feces (0-1200 hr)*	
[redacted]	30.86	35.98	66.84
[redacted]	18.43	13.32	31.75
[redacted]	24.05	25.48	49.53
[redacted]	33.43	34.46	67.89
[redacted]	25.00	24.53	49.53
[redacted]	26.60	32.14	58.74
[redacted]	18.71	21.47	40.18
[redacted]	38.61	29.85	68.46
Mean (n=8)	26.96	27.15	54.11
Std Dev	7.03	7.53	13.71

*After the first 15 days of confinement, samples were collected during weekly 24 hour visits.
Note: All calculations performed with machine precision of Microsoft Excel.

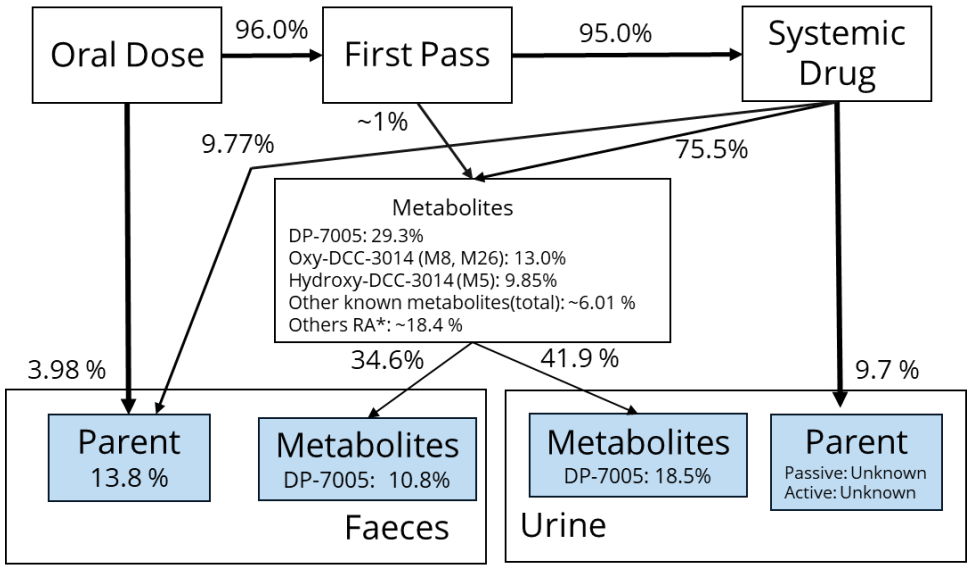
According to the applicant, the total recovery of radioactivity may have been underestimated since the recovery after participants were released from the clinical research facility after day 15 was based on the excretion rate determined from outpatient samples, rather than complete collection of all excreta. The excretion rate estimates were likely influenced by the time span of quantifiable radioactivity in urine and faeces at latter collection intervals; limited quantifiable data were observed after 29 days.

Figure 10. Mass balance study: summary of excretion of radioactivity



Abbreviation: DCC-3014=vimseltinib.
a All excreta were collected during the 336-hour interval after the administration of 14C-vimseltinib in which participants were confined to the clinical research unit. After participants were released from the clinical research facility, excreta were only collected at prespecified 24-hour intervals every week up to 1200 hours after administration.
b Four other metabolites were quantified in urine, but due to the absence of definitive molecular ion and product ion spectra, structures could not be proposed: M35 (0.773%), M37 (0.573%), M36 (0.209%), and M38 (0.0963%).
c Three other metabolites were quantified in faeces, but due to the absence of definitive molecular ion and product ion spectra, structures could not be proposed: M39 (0.388%), M40 (0.278%), and M42 (0.00906%).
d 3-desmethyl vimseltinib.

Figure 11. Elimination pathways for vimseltinib after a single oral dose



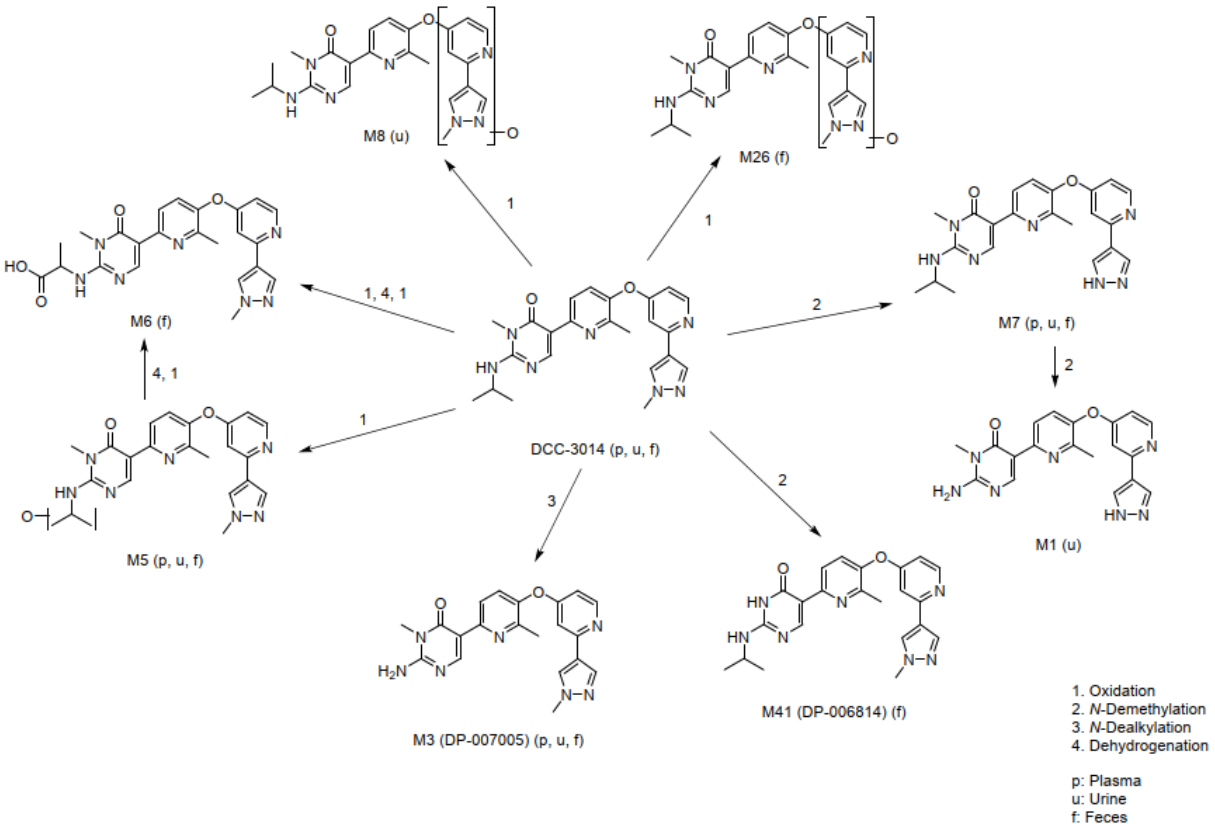
* Including unknown metabolites or %RA excreted but not quantitated

Metabolism

In vitro vimseltinib (1 µM) was incubated with human liver microsomes (1 mg protein/mL). In the presence of NADPH, after 60 min of incubation substrate loss was 1.5%. After incubation with human hepatocytes (1 million cells/ml) without NADPH the half-life of vimseltinib was ≥4 hours, as no substrate loss was observed after 240 minutes. Vimseltinib was metabolized in human hepatocytes and microsomes via oxidation, N-dealkylation, and dehydrogenation. No phase II conjugated metabolites were detected. In addition to unchanged vimseltinib (>90%), up to 7 metabolites were found, none was specific for human. DP-7005 accounted for <3%. Time course studies with microsomes and human CYP enzymes [CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5]) indicated minimal CYP-mediated metabolism, with no more than 22% loss of substrate.

As derived from the mass balance study vimseltinib was metabolised into 15 detectible metabolites, 8 of which were identified. The proposed biotransformation pathways are presented in Figure 12. No major circulating metabolites were detected.

Figure 12. Proposed biotransformation pathways of vimseltinib in humans



Quantifiable radioactivity was found in plasma and whole blood up to at least 336 hours for all participants. Total radioactivity (TRA) had a slightly longer geometric mean half-life in whole blood (158 hours vs 150 hours). When converted to similar units (1 mL plasma=1.024 g), exposures of vimseltinib in plasma and TRA in plasma were similar, indicating that parent makes up the majority of the TRA exposure in plasma.

The following PK parameter were derived for DP-7005 in TGCT patients of study 01-001 in steady-state at BIW 30 mg vimseltinib maintenance dose.

Table 15. PK parameters of DP-7005 in study 01-001 in TGCT patients in steady-state

AUC_{0-4h} (h•ng/mL)	AUC_{0-8h} (h•ng/mL)	AUC_{last} (h•ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max} (h)[b]	T_{last} (h)[b]
116 (37.8) [3]	211 (NC) [1]	155 (40.3) [4]	35.8 (33.9) [4]	32.6 (33.2) [4]	3.95 (1.10-4.10) [4]	4.10 (3.80-7.60) [4]
AUC_{0-4h} MPR	**AUC_{0-8h} MPR**	**AUC_{last} MPR**	**C_{max} MPR**			
0.0358 (38.6) [2]	0.0420 (NC) [1]	0.0438 (51.1) [2]	0.0402 (47.7) [4]			

In the mass balance the geo-mean MW-corrected metabolite:parent ratio for Cmax, AUC0-t, and AUC0-inf were 2.58%, 4.48%, and 5.01%, respectively.

Dose proportionality and time dependencies

Dose proportionality was concluded for vimseltinib C_{max} and AUC_{0-24h} from single oral doses between 6 - 50 mg since the slopes (β_1) in the linear regression were approximately 1 and the 90% CIs of included the value of 1. AUC_{0-inf} was dose proportional between 6 and 30 mg.

Table 16. Assessment of dose proportionality for vimseltinib following single-dose administrations – PK evaluable set (Study 002)

Dependent Variable	Dose Range	Model Variable	Slope Estimate (β_1)	90% CI Lower	90% CI Upper	p-value[a]	Rho1[b]
$ln(C_{max})$[c]	6-50 mg	ln(Dose)	0.9572	0.8464	1.0680	<0.0001	4.2747
$ln(AUC_{0-24h})$[c]	6-50 mg	ln(Dose)	0.9343	0.8376	1.0309	<0.0001	3.9518
$ln(AUC_{0-t})$[d]	6-30 mg	ln(Dose)	0.7953	0.6232	0.9673	<0.0001	1.8080
$ln(AUC_{0-inf})$[d]	6-30 mg	ln(Dose)	0.8804	0.6802	1.0805	<0.0001	2.0092

Abbreviations: AUC0-24h=area under the concentration-time curve from 0 to 24 hours; AUC0-inf=area under the concentration_time curve from time_zero extrapolated to infinity; AUC0-t=area under the concentration_time curve from time_zero to the time of the last quantifiable concentration; CI=confidence interval; Cmax=maximum concentration observed; inf=infinity; PK=pharmacokinetic(s).

a P-value for the slope estimate, β1.

b High/low-dose ratio in which dose proportionality can be demonstrated definitely, relative to the lowest dose in the analysis dataset.

c Range of doses used in analysis was from 6 mg (Arm 1a, 3×2 mg) to 50 mg (Arm 1d, 5×10 mg).

d Range of doses used in analysis was from 6 mg (Arm 1a, 3×2 mg) to 30 mg (Arm 1c, 3×10 mg) with PK sampling over 480 hours; Arms 1d and 1e were not included in the analysis due to once daily dosing and only 24-hour data after the first dose.

An additional analysis, showing dose proportionality between 6 mg and 30 mg for AUClast (480h) was provided. Vimseltinib AUC_{0-480h} was dose proportional following single oral doses of vimseltinib 6 mg to 30 mg, with linear regression slopes and 90% CI of 0.8722 (0.7045, 1.0398).

Table 17. Assessment of dose proportionality in AUC_{0-480h} following single dose administrations of 6 mg (Arm 1a, 3 x 2 mg), 10 mg (Arm 1b, 1 x 10 mg), 30 mg (Arm 1c, 3 x 10 mg) for vimseltinib under fasted conditions from Study DCC-3114-01-002

Model	Model Variable	Estimate (β_1)	P-value[a]	Lower CI[b]	Upper CI[b]	Rho1[c]
Power	ln(Dose)	0.8722	<.0001	0.7045	1.0398	2.1279
Quadratic	Intercept	7.2323	.	4.5973	9.8674	.
Quadratic	ln(Dose)*ln(Dose)	-0.0588	.	-0.4633	0.3456	.
Quadratic	ln(Dose)	1.1809	.	-0.9482	3.3100	.

Dose proportionality range was from 6 mg (Arm 1a, 3 x 2 mg) to 30 mg (Arm 1c, 3 x 10 mg)
[a]P-value is for the slope estimate, ß1
[b]90% confidence intervals (Lower and Upper)
[c]High/low dose ratio in which dose proportionality can be demonstrated definitely, relative to the lowest dose in the analysis dataset
Power Model: $\ln(PK)=\ln(\beta_0)+\beta_1*\ln(Dose)+e$, where PK is the pharmacokinetic parameter tested, $\ln(\beta_0)$ is the y-intercept, β_1 is the slope, and e is an error term

Time to reach steady state was estimated in the popPK in TGCT patients with 30.4 days for vimseltinib. According to the applicant, the simulated median time to steady-state was similar with or without 5 once daily 30 mg vimseltinib loading doses. For DP-7005, steady-state generally appeared to have been reached between C1D15 and C1D22.

In study 01-001 TGCT Cohort 5, exposure on C2D1 after 30 mg BIW was ~3.6-fold higher than after SD 30 mg. Simulations based on empirical Bayes estimates of the full analysis population showed that the 30 mg BIW regimen resulted in a median accumulation ratio of 2.59.

Pharmacokinetics in the target population

The Phase 1/2 **study 01-001** was open-label, multicentre, first-in-human, with dose escalation and expansion to determine safety, tolerability, the MTD, the recommended phase 2 dose (RP2D), preliminary efficacy and PK and PD effects in patients with MST and TGCT. The different treatments administered through the cohorts in the dose escalation phase are summarised in Table 18, and a dose was allowed to be taken ±1 day for BIW maintenance doses or ±2 days for weekly maintenance doses in repeated 28-day cycles. All participants in the expansion phase received vimseltinib at the RP2D (30 mg BIW on Day 1 and Day 5 with no loading dose). Vimseltinib was provided as 2-, 10-, and 50-mg hard gelatine capsules (clinical formulation) for oral administration.

Table 18. Treatments administered in the phase 1/2 study

Cohort	Vimseltinib Loading Dose	Vimseltinib Maintenance Dose	Number of Participants
Dose Escalation Phase			
1	Not applicable	10 mg once daily	7 participants with MST
2	10 mg once daily for 5 days	10 mg twice weekly	3 participants with MST
3	20 mg once daily for 5 days	20 mg once weekly	4 participants with MST
4	20 mg once daily for 5 days	20 mg twice weekly	4 participants with MST
5	30 mg once daily for 5 days	30 mg twice weekly	8 participants with TGCT 6 participants with MST
6	40 mg once daily for 5 days	40 mg twice weekly	5 participants with MST
7	50 mg once daily for 3 days	20 mg once daily	8 participants with MST
8	30 mg once daily for 3 days	10 mg once daily	12 participants with TGCT
9	20 mg once daily for 3 days	6 mg once daily	12 participants with TGCT
Expansion Phase			
N/A	N/A	30 mg twice weekly	65 participants with TGCT

Abbreviations: MST=malignant solid tumors; N/A=not applicable; TGCT=tenosynovial giant cell tumor.

Mean vimseltinib pre-dose data after MD in patients with MST and TGCT showed that steady state generally appeared to have been reached between C1D8 and D1D15. Most cohorts received loading doses, which likely affected time to reach steady state.

Vimseltinib exposure increased with dose in **patients with TGCT**. Following SD at C1D1, geo-mean AUC0-4 and Cmax increased from 442 h*ng/mL and 163 ng/mL with 20 mg in Cohort 9, respectively, to 904 h*ng/mL and 320 ng/mL, with 30 mg in Cohort 8 (AUC0-8 could not be assessed), respectively. Cohort 5 TGCT patients, at 30 mg, had comparable exposure to participants in Cohort 8 (AUC0-4, AUC0-8, and Cmax values of 745 h*ng/mL, 1130 h*ng/mL, and 273 ng/mL, respectively.

Following MD, geo-mean AUC0-4 and Cmax on C2D1 increased from 1210 h*ng/mL and 371 ng/mL, respectively, with 6 mg daily in Cohort 9 to 2450 h*ng/mL and 709 ng/mL, respectively, with 10 mg daily in Cohort 8.

After 30 mg loading doses in Cohorts 5 and 8, C2D1 exposure was comparable in TGCT patients on 30 mg BIW (Cohort 5) and those who received 10 mg QD (Cohort 8). Geo-mean AUC0-4 and Cmax were 2710 h*ng/mL and 838 ng/mL, respectively, in Cohort 5 versus 2450 h*ng/mL and 709 ng/mL, respectively, in Cohort 8.

In the expansion phase in all cohorts, vimseltinib concentrations appeared to reach steady state by C2D1, i.e. after 28 days of dosing and remained stable until Cycle 6. Based on the time to reach steady-state, vimseltinib half-life is estimated to be within a range of 67 to 134 hours in participants with TGCT.

The following PK parameter were derived for vimseltinib:

Table 19. PK parameters of vimseltinib in study 01-001 in TGCT patients on 30 mg BIW in steady-state, dose escalation phase

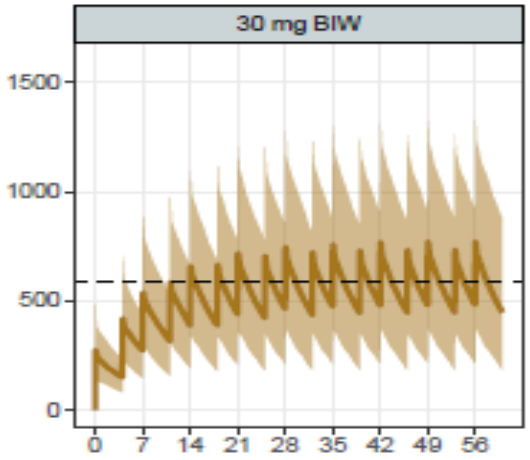
AUC_{0-4h} (h•ng/mL)	AUC_{0-8h} (h•ng/mL)	AUC_{last} (h•ng/mL)	C_{max} (ng/mL)	C_{min} (ng/mL)	T_{max} (h)[b]	T_{last} (h)[b]
2710 (48.2) [5]	4150 (48.5) [3]	3720 (34.0) [6]	838 (31.1) [6]	576 (69.4) [6]	2.00 (1.10-4.10) [6]	5.80 (3.80-7.60) [6]

The final dose recommendation of vimseltinib 30 mg twice weekly was investigated in the pivotal **phase III study DCC-3014-03-001 (MOTION)** in TGCT patients. A dose could be taken with or without food. Concentration data from the pivotal study were only analysed in the popPK model.

Table 20. Exposure metrics for 30 mg BIW based on EBEs from the final vimseltinib popPK model and analysis population, for a 76 kg, albumin 44 g/L, fasted, non-black or African American, TGCT patient

Cmax,ss (ng/mL) gMean (gCV, gCI)	Cavg,ss (ng/mL) gMean (gCV, gCI)	Cmin,ss (ng/mL) gMean (gCV, gCI)	$AUC_{T,ss}$ (mg*h/L) gMean (gCV, gCI)	AUC0-24h,ss (mg*h/L) gMean (gCV, gCI)
747 (39.4, 710 - 786)	559 (45.1, 527 - 592)	415 (57.9, 386 - 446)	46.9 (45.1, 44.3 - 49.7)	13.4 (45.1, 12.7 - 14.2)
AUC0-168h,ss (mg*h/L) gMean (gCV, gCI)	**CL (L/h) gMean (gCV, gCI)**	**Rac(AUC) gMean (gCV, gCI)**	**Time to steady state (days) gMean (gCV, gCI)**	**Effective half-life (h) gMean (gCV, gCI)**
93.8 (45.1, 88.6 - 99.4)	0.639 (45.1, 0.604 - 0.677)	2.52 (25.9, 2.44 - 2.61)	30.4 (32.8, 29.1 - 31.7)	129 (35.9, 123 - 135)

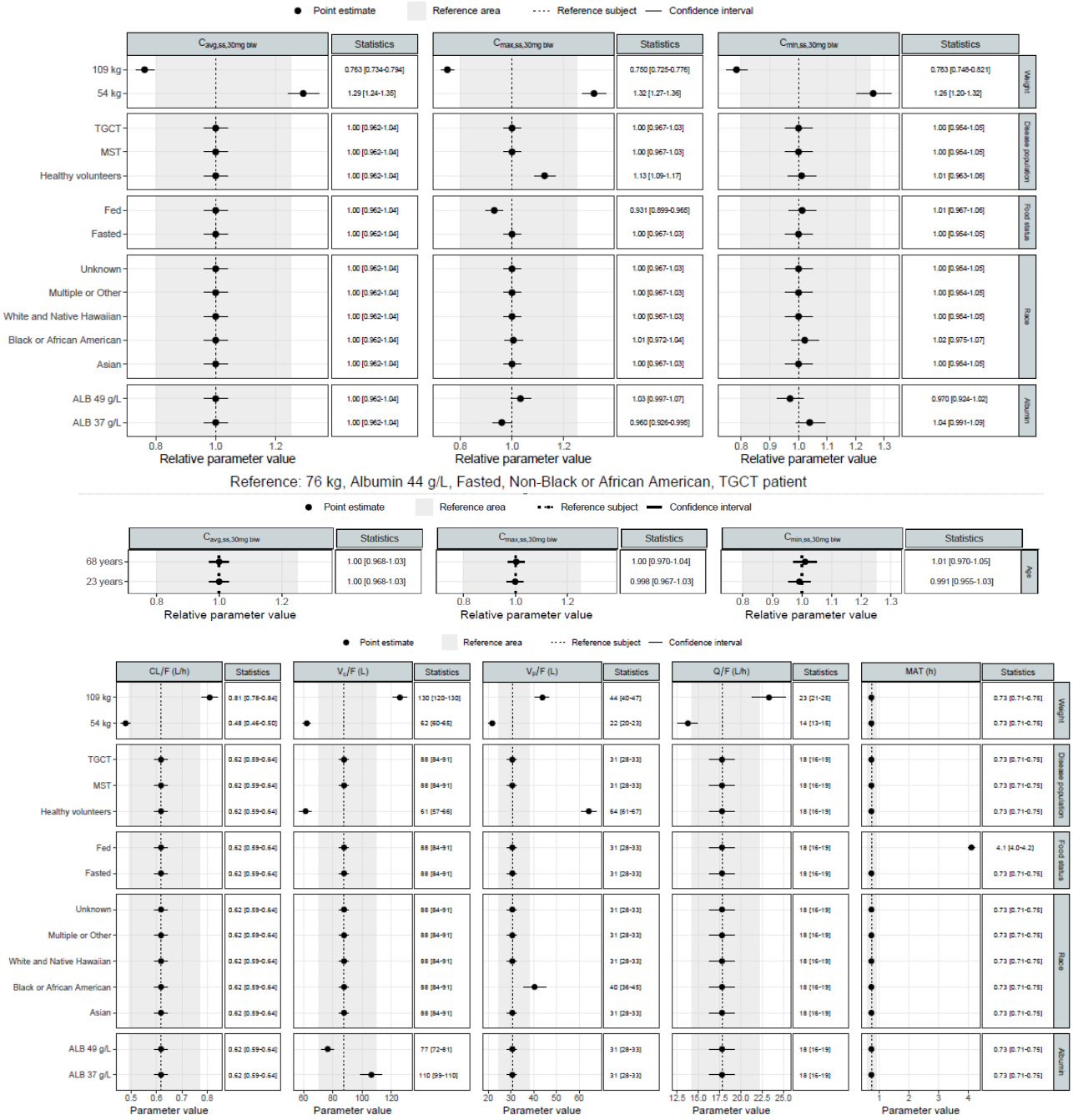
Figure 13. Simulated vimseltinib concentrations vs. time after first dose based on the EBEs from subjects in the analysis population (n=349). The horizontal black line indicates the Cavg,ss for the 30 mg BIW dosing regimen



Special populations

A summary of relative covariate effects in special populations is given in Figure 14:

Figure 14. Forest plots illustrating the relative effects of covariates on vimseltinib PK parameters at steady-state based on the final vimseltinib PK model, for a 76 kg, albumin 44 g/L, fasted, non-black or African American, TGCT patient



Exposure metrics stratified by gender demonstrated that females have an overall ~19% higher steady-state exposure of vimseltinib than males due to their lower body weight. Exposure metrics were also calculated for patients ≤ 52 kg and ≥ 115 kg bodyweight (5th and 95th percentiles), for the proposed dose of 30 mg BIW and the recommended dose reductions to 20 mg and 14 mg BIW and used for exposure-response-modelling.

Renal impairment

The PopPK analysis included 3 studies of which mean eGFR was 101 (range 37.7-144 ml/min/1.73m²), the lowest values (moderate RI) were obtained from the phase I/II study 01-001. There were no moderate renal impairment patients in the TGCT cohorts in study DCC-3014-01-001 dose escalation part whereas all 5 moderate renal impairment (RI) patients were the study participants with MST. eGFR was not identified as a covariate in the popPK, and no relevant differences in steady-state exposure were anticipated by the applicant for mild and moderate renal function (eGFR ≥37.7 mL/min/1.73 m^2). From the limited number of subjects with moderate RI treated in the clinical studies, the median $C_{max,ss}$ and $C_{avg,ss}$ (or $AUC_{\tau,ss}$) in participants with moderate RI was about 8% and 27% higher than with normal renal functions, respectively.

Hepatic impairment

Study DCC-3014-01-004 is an ongoing Phase I study to compare PK after 10 mg vimseltinib in subjects with hepatic impairment (HI) (as of Child-Pugh criteria) to healthy controls. The study consists of 3 parts: part 1 compared mild vs. normal and preliminary PK results were submitted, part 2 for moderate and part 3 for severe HI were not yet completed and/or started. When classified according to NCI-ODWG criteria, 3 of 8 subjects with Child-Pugh A had "mild" abnormal liver function, the other 5 were classified as "normal".

Total vimseltinib exposure was not significantly increased with mild HI.

There were no discernible trends between baseline **liver function tests** (albumin, alkaline phosphatase, ALT, AST, and bilirubin) and unbound vimseltinib exposure for the groups tested.

Gender was evaluated as covariate in the popPK model but not included in the final popPK model. The new exposure metrics stratified by gender demonstrated that females have an overall ~19% higher steady-state exposure of vimseltinib as males due to their lower body weight (data not shown).

The median **age** of patients included in the popPK was 45 years (range 20-91 years), and in the pivotal study 44 years (range 20-78). Exposure metrics, such as Cmax,ss, Cavg,ss, Cmin,ss, and CL were generally comparable across 3 age groups (<65 years, 65-74 year, and ≥75 years), with up to 21% differences.

Gender and age were evaluated as covariates but not retained in the final popPK model.

In the PopPK analysis, an exploratory covariate-parameter relationship was identified for participants of Black or African American **race,** who had an approximately 1.3-fold higher V_p/F, but the effect on steady-state exposure was within 80%-125% limits.

The effect of **body weight** was included using allometric scaling with fixed exponents. For a TGCT patient of 109 kg bodyweight $C_{ave,ss}$, $C_{max,ss}$ and $C_{min,ss}$ were reduced to approximately 75-78% of the exposure, whereas a 54 kg patient had an increase to 126-132% of this exposure.

Pharmacokinetic interaction studies

CYP enzyme interaction

In vitro, vimseltinib and DP-7005 exhibited IC_{50} values >40 µM for all CYP isoforms studied (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5; 40 µM highest concentration studied for DP-7005), and IC_{50} values >100 µM were exhibited by vimseltinib for 5 out of 7 CYP isoforms. Neither vimseltinib nor DP-7005 exhibited time-dependent or metabolism-dependent inhibition of any CYP isoform.

In vitro, vimseltinib induced CYP2B6 and CYP3A4 at concentrations above 30µM and 50x$C_{max,u}$.

Transporter Interaction

Vimseltinib was a substrate of P-gp. The efflux ratio of vimseltinib (10 µM) across MDCKII-MDR1 (P-gp) cells was 2.62 and decreased to 1.48 in the presence of P-gp inhibitor valspodar (10 µM). Vimseltinib was not a substrate of the other transporters examined (i.e., BCRP, BSEP, OATP1B1, OATP1B3 OAT1, OAT3 and OCT2) with efflux or uptake ratios of < 2.

Vimseltinib was an inhibitor of P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2-mediated transport of probe substrate resulting in IC_{50} values of 4.35, 0.556, 10.6, 10.4, 28.8, 51.5, 23.7 and 0.456 µM, respectively, meaning that for P-gp, BCRP and OCT2 potential for clinical interaction exists. The IC_{50} values of vimseltinib were 7.58 µM for MATE1, 23.3 µM for MATE2K, 9.21 µM for OATP1B1, and 10.1 µM for OATP1B3.

DP-7005 inhibited P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3 and OCT2 transporters by < 35% when tested at 10 µM. The IC50 values of DP-7005 were greater than 22.0 µM for MATE1 and MATE2K, greater than 27.0 µM for OATP1B1, and 19.4 µM for OATP1B3.

The vimseltinib PBPK model was used prospectively to simulate the extent of the drug-drug interaction between vimseltinib 30 mg BIW and bupropion (a CYP2B6 substrate), digoxin and dabigatran (P-gp substrates), rosuvastatin (a BCRP and OATP1B1/3 substrate), and metformin (an OCT2 substrate). Sensitivity analyses were included to account for "worst-case" scenarios of potentially inaccurate CYP induction parameters and transporter competitive inhibition constant estimates from in vitro experiments. The PBPK model should not be used to justify dosing recommendations as the platform is not regarded qualified to predict interactions based on P-gp, BCRP and OCT2.

Weak to moderate interaction was predicted for co-administration of dabigatran or rosuvastatin with vimseltinib 30 mg BIW and the applicant concluded that the results showed that the predicted drug-drug interaction effects on rosuvastatin are mainly driven by BCRP inhibition, but not OATP1B1/3 inhibition. No interaction was predicted for co-administration of bupropion, digoxin, or metformin. In **Study 01-006**, the effects of P-gp inhibition and gastric acid suppression on the single-dose PK of vimseltinib in HV were investigated. C_{max} was comparable with the P-gp inhibitor itraconazole and $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$ were ~ 17% to 22% higher. This suggests that itraconazole had a weak effect on total exposure to vimseltinib. With the PPI rabeprazole C_{max} and AUC were ~ 21% to 26% lower, suggesting that rabeprazole had a weak effect on vimseltinib absorption. The geo-mean metabolite to parent ratios were similar across all 3 treatments for Cmax, AUC0-t, and AUC0-inf, ranging from 0.02-0.3 for Cmax and 0.04-0.06 for AUC.

2.6.2.2. Pharmacodynamics

Mechanism of action

Colony stimulating factor 1 receptor (CSF1R) kinase is a member of the receptor protein tyrosine kinase (rPTK) family of growth factor receptors, which includes several known proto-oncogenes. CSF1R is expressed predominantly on monocytes and macrophages and its signalling plays a vital role in the differentiation of monocytes. CSF1R kinase activity is highly regulated by phosphorylation, upon which in its inhibitory juxtamembrane (JM) domain, CSF1R becomes catalytically active and can phosphorylate protein substrates (kinase activity). Further phosphorylation of the activation loop of the CSF1R further stabilizes the kinase in an active conformation. Overexpression of the cytokine ligand, CSF1, promotes proliferation and accumulation of CSF1R expressing cells in the synovium.

Vimseltinib is a selective, reversible small-molecule TKI that targets CSF1R kinase. It has >100-fold selectivity for inhibition of CSF1R vs. all other kinases tested and >500-fold selectivity for other closely related type III RTKs. *In vitro* enzyme and cell-based assays have shown that vimseltinib inhibited CSF1R autophosphorylation and signalling induced by CSF1 ligand binding, as well as cellular function and proliferation of cells expressing CSF1R. Vimseltinib also inhibited CSF1R-expressing cells and blocked downstream signalling in preclinical models *in vivo*.

Vimseltinib exhibited a preference for the only JM-domain phosphorylated CSF1R with IC_{50} = 2.8 nM, a ~22-fold weaker affinity for unphosphorylated catalytically inactive CSF1R with a Kd = 79 nM, and an IC_{50} = 290 nM for fully phosphorylated CSF1R. The active metabolite, DP-7005, displayed a similar ~100-fold preference for JM-domain phosphorylated CSF1R, but was ~20-fold weaker than parent vimseltinib.

Biomarkers

The circulating nonclassical monocytes (NCM) in peripheral blood, characterized by expression of CD14lowCD16+ markers, express CSF1R and are known to be sensitive to anti-CSF1/CSF1R targeted therapies. CSF1 and IL-34 are the 2 ligands that can bind to CSF1R. Therefore, the circulating NCM population and plasma CSF1 levels were investigated as biomarkers (BM) to study vimseltinib target engagement.

Primary and Secondary pharmacology

Primary pharmacodynamics

In the phase I/II **study 01-001** the percentage change from baseline in NCM and fold changes in the levels of CSF1 in plasma were summarized across TGCT and MST cohorts up to Week 25.
Vimseltinib demonstrated a dose-dependent decrease in the levels of circulating NCM from 10 to 40 mg twice weekly doses (Dose Escalation Cohorts 2, 4, 5, and 6) and from 6 to 20 mg daily doses (Dose Escalation Cohorts 9, 8, and 7). The maximum NCM reduction was reached by C2D1 (Week 5) for most cohorts and was maintained throughout the dosing period.

Plasma cytokines

Increased levels of CSF1 in plasma were observed across all cohorts. The mean fold changes over baseline CSF1 levels at C2D1 appeared to have a steep increase from 20 mg twice weekly dose (Cohort 4) to 30 mg twice weekly (Cohort 5) or from 6 mg daily dose (Cohort 9) to 10 mg daily dose (Cohort 8). The fold changes in CSF1 levels in participants with TGCT in Cohorts 5, 8, A, and B were in a similar range, while that in the lower dose cohort—6 mg daily dose (Cohort 9)—was relatively small. Similar to the NCM changes, the maximum fold changes in CSF1 levels across the cohorts were reached by C2D1 (Week 5).

PD data from the **pivotal MOTION study** showed the maximum reduction in mean NCM levels in the vimseltinib arm was reached by C2D1 (Week 5) and was maintained throughout the collection period in part 1 of the study. The longitudinal data showed that CSF1 levels in plasma continued to increase during the displayed 9-week collection period.

Secondary pharmacodynamics

Of the 127 subjects in HV study 01-002 having received one or two doses of vimseltinib 28 reported an TEAE of SOC skin and subcutaneous tissue disorders, mainly pruritus (n=26), and rash, which also lead to concomitant medication (antihistamines, corticosteroids) in several participants. 2 of 3 TEAEs that lead to treatment discontinuation were pruritus.

Similarly, in study 01-006 in HV, after a single dose of 30 mg 27% of vimseltinib-only subjects had a TEAE pruritus, 40% with itraconazole and 30% with rabeprazole (plus rash and urticaria which are known ADRs of rabeprazole) and needed antihistamines as concomitant medications.

The healthy participants (see study 002, arm 1d & 1e) were administered vimseltinib daily at 40 or 50 mg for 5 or 2 days, respectively, for characterisation of cardiac repolarisation as measured by prolongation of the QTc interval and encompassed plasma concentrations greater than 2-fold the high clinical exposure expected at a therapeutic dose (30 mg twice weekly). The high clinical exposure was 776 ng/mL (Pop PK modelling), based on the mean maximum plasma concentration at steady-state produced by administering vimseltinib 30 mg twice weekly in participants with TGCT.

The results of concentration QTcF modelling based on healthy participants, along with the predicted ΔΔQTcF (heart rate-corrected QT interval using Fridericia's method) results were provided (not shown). The concentration QTc model depicts a shallow and statistically significant slope (0.0032 ms per ng/mL [90% CI:0.00078 to 0.00564]), with a small intercept of 0.55 ms (90% CI: -1.863 to 2.961). A QTcF effect (ΔΔQTcF) exceeding 10 ms can be excluded for plasma concentrations of vimseltinib, up to 1774 ng/mL, greater than 2-fold the high clinical exposure expected at vimseltinib 30 mg twice-weekly dosing.

Pharmacokinetics-Pharmacodynamics (PK/PD)

An exposure-response analysis was performed for efficacy and safety. The suitability of the investigated dosing regimen of vimseltinib 30 mg twice weekly was also evaluated.

For **efficacy** as of $C_{ave,ss}$ and ORR per RECIST v1.1 and TVS at Week 25 there was no clear association within the 30 mg group between exposure and response (data not shown).

On basis of the popPK predicted geometric mean of $C_{avg,ss}$ of ~560 ng/ml (adjusted for PPB) in the target population additional exposure-response analyses were performed. At this C_{avg}, the CSF1 receptor can be almost fully inhibited, with about 92.5% inhibition of CSF1 receptors.

Comparing to 30 mg BIW dosing over 49 weeks, the predicted median change from baseline (% CFB) of tumour size per RECIST v1.1 reduced about 5% in the dose reduction group in the 95th percentile weight groups (≥115 kg) (Table 21). It is noted that no TGCT patients with WT of ≥115 kg in the MOTION study reduced their dose to 14 mg BIW.

Table 21. Predicted median % change from baseline of tumour size per RECIST v1.1 and per TVS at Week 49 for TGCT with ≤ 52 kg and ≥ 115 kg, following vimseltinib dosing with and without dose reductions

Weight/Endpoint	Without dose reduction [a]	With dose reduction [b]
52 kg (N=100)		
Tumour size per RECIST v1.1 (% CFB)	-43.7	-38.1
Tumour size per TVS (% CFB)	-49.9	-49.4
115 kg (N=100)		
Tumour size per RECIST v1.1 (% CFB)	-25.3	-20.7
Tumour size per TVS (% CFB)	-45.3	-43.5

[a]30 mg BIW for 49 weeks
[b]30 mg BIW for 25 weeks, followed by dose reduction to 20 mg BIW until Week 37, and then 14 mg BIW until Week 49

Furthermore, additional PKPD models explored clinically relevant PD biomarker, such as non-classic monocytes (NCM).

The relationship of percent change in NCM with percent change in tumour size and the relationship of percent change in NCM with ORR per RECIST v1.1, based on Independent Radiologic Review by week 25, were analysed separately for large and small joints. No relationship between either efficacy endpoints and NCM changes was established (data not shown).

For all **safety** endpoints the final model was a Cox proportional hazards model where the hazard for the event of interest increased with increasing $C_{max,ss}$. With vimseltinib 30 mg BIW, the median predicted proportion of events at Week 25 were 75.1%, 49.3%, 93.8%, and 31.5%, for periorbital oedema, rash, AST elevation, and ALT elevation, respectively.

As shown in Kaplan-Meier curves of event-free probability, most events happened at the beginning of treatment with less events in the placebo group. For periorbital oedema, rash, and AST elevation, there appeared to be less events in the low exposure group (q1), while the course of events appeared to be similar in the intermediate (q2) and high (q3) exposure groups. For ALT elevation, all exposure tertiles were overlapping (results not shown).

When comparing probabilities at week 25 of these ADRs for a 30 mg dose and a 20 mg dose, no relevant difference was predicted (data not shown).

Both efficacy and safety events at Week 25 were predicted to be similar across weight groups.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Methods

The bioanalytical methods were adequately described and the method validation reports supported their performance and acceptability. The methods used in the different studies were bridged satisfactorily. One method, which was utilised for most of the clinical studies' analyses, also tested the interference and supported its utilisation under presence of common concomitant medications. Circulating NCMs, plasma CSF1

levels and plasma IL-34 levels were investigated as biomarkers, the respective method validation reports confirmed the validity. Common methods were utilised for pharmacokinetic analyses for parent vimseltinib and metabolite DP-7005 in plasma, urine and faeces.

Population PK modelling

The final population PK model for vimseltinib provided a good description of the observed data considered overall as well as when analysed by disease populations and body weight subgroups. However, rather low number of patients included from the target population (n=214 for TGCT) is regarded as limitation of the model. Diagnostic plots indicated an adequate model performance as they generally show a good agreement between the observed and predicted vimseltinib concentrations. Shrinkage for IIV of CL/F and Vc/F was low, the use of the exposure metrics for subsequent exposure-response analyses is supported. For the decision which dosing regimen could be optimal, simulations were performed showing only a small difference between 30 mg 5 days QD and BIW after compared to 30 mg BIW only. This is not completely agreed, especially because the therapeutic window is not defined clearly. The therapeutic window proposed by the Applicant ranges from 150 to 1400 ng/mL based on MEC and MTC which is regarded as a rather broad approximation. The Applicant preferred to work with the observed concentration range at the steady state for 10 mg to 30 mg BIW. A loading dose was not considered necessary as TGCT is non-malignant, non-life-threatening disease.

PBPK Modelling

The applicant concluded from the PBPK that the interaction potential of vimseltinib as a perpetrator for P-gp, BCRP and OCT2 could be reduced by staggering the concomitant intake but especially for rosuvastatin a DDI risk remains even with dose staggering due to the long half-life of vimseltinib and the potentially persistent inhibitory effect on BCRP. The Applicant accepted the negative assessment regarding PBPK modelling for BCRP and OCT2 related DDI and will investigate DDI in clinical studies for vimseltinib perpetrator DDI assessments with rosuvastatin (BCRP substrate) and metformin (OCT2 substrate) proposing the date of final CSR submission for these two studies as December 2026 (RECs). For P-gp further sensitivity analyses were submitted to prove the appropriateness of the PBPK model. It was proposed to mitigate the DDI risk resulting from co-administration of vimseltinib and P-gp by dosing P-gp substrates 4 hours after vimseltinib. This is not agreed as the modelling results rely on a platform that is not qualified for the intended purpose and inappropriate. The applicant committed to conduct a clinical DDI study for the vimseltinib DDI study with P-gp substrates as September 2027 (REC).

Exposure-response Modelling

The suitability of the investigated dosing regimen of 30 mg vimseltinib BIW (twice a week) is difficult to interpret as no other dose was included in the ORR analysis and the patient number was rather low with one observation per patient. No clear E-R relationship was shown, following 30 mg BIW dosing, ORR per RECIST v1.1 and ORR per TVS at Week 25 were predicted to be 41.4% and 68.5%, respectively.

Due to limited data, the predictions based on E-R modelling are associated with large statistical uncertainty (high RSE) and should be interpreted with caution.

Absorption

Permeability was investigated in a validated Caco-cell model and showed higher permeability than the standard minoxidil. Vimseltinib has a pH-dependent solubility, highly soluble at all pH values < 3.5 and low soluble > pH 3.5. Based on this, BCS class 2 was concluded by the applicant.

In arm 1d and 1e of Study 01-002, participants were blinded and randomly assigned 2:1 to vimseltinib or placebo to evaluate cardiac safety. Higher doses of vimseltinib (50 mg QD for 2 days and 40 mg QD for 5 days) were given compared with a placebo control.

The bioequivalence study arm 3 of study 01-002 was not performed as no bioequivalence study was considered necessary by the applicant at that time as the proposed commercial capsule formulations are compositionally identical to the 10 mg vimseltinib drug product used during clinical development and are manufactured using the same process.

Vimseltinib was rapidly absorbed, with a Tmax 1-2h depending on studies. The PK results show increasing Cmax and AUC0-t or AUC0-inf with increasing doses after single oral doses of 6 to 30 mg vimseltinib.

An analysis with participants who completed both phases (fasted and fed) was provided, resulting in a less variability (C_{max} (Fasted: 25.9% and Fed: 12.9%), AUC_{last} (Fasted: 32.2 % and Fed: 24.8%), and AUC_{inf} (Fasted: 24.5 % and Fed: 29.5%)). The new determined variability showed lower variability in the fed state for Cmax and AUClast, but not for AUCinf. Therefore, no conclusion can be drawn whether the fed state generally leads to reduced variability or not and the applicant's statement that the PK variability is reasonable under both fasted or fed state can be followed.

The chosen wash-out phase was 14 days, which is considered a relatively short time frame in view of the t1/2 (T1/2 was 137 in fasted and 135 hours in fed state; 5x137 h = approximately 28 days). One participant had higher 5% of Cmax predose concentrations. The applicant explained that the "wash-out" phase (10 – 14 days) mentioned in the protocol was the period after the last in-clinic visit before crossover to period 2, so the actual time between the two treatments was 31 to 35 days (740 to 840 h), which is appropriate.

Distribution

No concentration dependence was observed for vimseltinib in the tested range and a slight dependence for the metabolite DP-7005. As in the hepatic impairment study unbound fractions were 2-fold of those observed *in vitro* (vimseltinib 6-7% and DP-7005 13-15% in normal controls and mild HI), the applicant was asked to discuss the discrepancy to the *in vitro* results. Comparison of the two utilised methods for measure of PPB revealed potentially relevant differences, e.g. regarding temperature, concentration range, radiochemical impurities and method used. Mild HI did not appear to affect vimseltinib plasma protein binding as geometric mean unbound vimseltinib fraction remained between approximately 6% and 7% in participants regardless of hepatic function.

Volume of distribution (Vz/F) was observed in HV with ~134 L, which is comparable to the estimations in the popPK for central (88.0 L) plus peripheral (~29L) V/F. Covariate analysis suggested that healthy participants had a lower Vc/F, and higher Vp/F, compared to participants with TGCT. However, the effect on steady state exposure parameters was within the 80% to 125% limits. The high VoD corroborates the lipophilicity of vimseltinib.

The geometric mean whole blood-to-plasma total radioactivity ratio was 0.751, indicating no appreciable red blood cell partitioning.

Vimseltinib crosses the BBB with exposures of 73% of plasma levels in animals.

Metabolism / Elimination

The elimination half-life was quite variable between studies and within one study seemed to decrease with increasing single doses between 6 and 50 mg. Geometric mean vimseltinib t1/2 ranged from 130 hours (study 01-002 Arm 1e, 40 mg, Day 5) to 153 hours (Arm 1a, 6 mg). In the target TGCT population with

30 mg in steady state, $t_{1/2}$ was estimated in the popPK with 129 hours, and 174 hours in solid tumour patients.

CL/F was about 0.6 L/h. Accumulation is expectable and was observed in TGCT patients under multiple dosing also in a BIW schedule being ~3.6-fold.

Max 69% of TRA were recovered in excreta up to day 50. As discussed by the applicant, probably the long outpatient time (35 days) without complete collection of excreta impaired the data and hence the reliability of the extrapolation of total recovery of radioactivity.

The applicant estimated about 80% total TRA recovery in excreta when extrapolating to infinity, of this 37.5% of the dose being excreted in urine and 42.9% in faeces; however, data are lacking to support the extrapolation. Faecal and urinary elimination fractions are hence considered comparable, with no clearly main elimination pathway.

Metabolic profiling as part of Study 003 in male healthy participants determined that primary metabolism occurred by oxidation, N-demethylation, and N-dealkylation; secondary biotransformation pathways included N-demethylation, dehydrogenation, and oxidation.

The requirement of EMA Guideline on the investigation of drug interactions CPMP/EWP/560/95/Rev. 1 Corr. 2 appendix 5 is a recovery in excreta of >90% and identification of 80% of recovered TRA. This was not achieved. A recent publication was referenced by the applicant for the observation that a recovery of less than recommended was often seen for products with a long half-life. However, acknowledging the low recovery as an indication for tissue accumulation, the SmPC was amended to include corresponding information from the non-clinical studies in section 5.3.

Metabolism was investigated *in vitro*. In presence of NADPH, no relevant metabolism was observed in human microsomes. *In vitro* metabolism occurred via oxidation, N-dealkylation, and dehydrogenation with only minimal CYP-enzyme-related metabolism and no detection of phase II conjugated metabolites.

In TGCT patients, the metabolite:parent ratio was between 3.6 and 4.4% (2.58 and 5.01% in HV) for plasma exposure parameters Cmax and AUC and independently from food intake, indicative of DP-7005 being a minor metabolite of vimseltinib. Therefore, and although DP-7005 is active at the target CSF1R, but with a ~20-fold higher IC_{50} in comparison to parent vimseltinib, its relevance for efficacy (or safety) can be considered minor.

Dose proportionality

Linear regression dose proportionality for Cmax and AUC0-24h after single oral doses of vimseltinib 6 mg - 50 mg can be concluded. Additionally, vimseltinib AUC0-inf was dose proportional between 6 mg and 30 mg. Upon request, a further analysis of AUC0-24h after single dose of vimseltinib 6 – 30 mg was provided, only including those results of the different study arms with similar tlast values (480 h).

Time-dependency based on enzyme induction or inhibition was not observed.

Variability

The intra-subject variability for both vimseltinib and DP-7005 was < 23% supporting that vimseltinib is not a highly variable drug. Inter-subject variability in TGCT patients in steady state was estimated with up to 45.1% for AUC_{ss}, 39% for $C_{max,ss}$ and ~58% for $C_{min,ss}$ (data not shown).

PK in the target population

Study 01-001 was a phase 1/2 in patients with MST and TGCT. After oral administration of a 30 mg dose of vimseltinib on Cycle 1 Day 1 to patients with TGCT in dose escalation, median T_{max} and mean C_{max} were consistent with the results from study 002 in HV: median T_{max} ranged from 1.60 to 1.70 hours and C_{max} ranged from 273 to 320 ng/mL.

Time to reach steady state was shortened to approximately 15 days with the administration of loading doses. It was clarified that the same steady-state levels will be reached with and without a loading dose, even though the attainment of the steady state PK exposure will take longer if no loading dose is given. The prolonged time to reach effective concentrations of about 14 days is acceptable, as TGCT is often a slowly progressing non-malignant, and non-life-threatening disease. The dosing scheme of cohort 5 was further investigated in the expansion phase instead of a dosing regimen from e.g. cohort 8, despite showing more stable Cmin values over time. At the time of dose selection cohorts 5 and 8 had similar PK profiles at C2D1; however, considering safety, Cohort 8 had a slightly higher incidence of adverse events. Consequently, 30 mg BIW without a loading dose was chosen as the RP2D, which can be followed.

PK from the target TGCT patients from pivotal phase III study was only analysed by popPK. PopPK estimates for 30 mg in steady-state were lower (<30%) than NCA-based actual PK values. The applicant's argumentation can be followed that the results from the model may be more reliable as NCA was based on limited data. Exposure was slightly higher, as clearance CL/F was slightly lower, in patients with malignant solid tumours.

SmPC section 4.2 recommends dose reductions to 20 mg or 14 mg in case of toxicities, as was performed in the phase III study and maintenance phase of phase I/II study and included in the popPK data set. Exposure metrics for dose reductions to 20 and 14 mg were provided upon request. With a 14 mg dose, a $C_{ave,ss}$ of 287 ng/ml would result in ~86% CSF1R inhibition or ~70% reduction of NCM (data not shown).

Special populations

No dedicated **renal impairment** study was performed. It is acknowledged that only a small amount of total dose is eliminated as parent vimseltinib and its main metabolite DP-7005, but overall the applicant estimated total excretion via urine to ~37.5%. eGFR was not identified as a covariate in the popPK, and no relevant differences in steady-state exposure were anticipated by the applicant for mild and moderate renal function (eGFR ≥37.7 mL/min/1.73 m^2). No clinical data is available in patients with severe renal impairment; a recommended dose of vimseltinib has not been established in patients with severe renal impairment. Accordingly, in the SmPC section 4.2, no dose adjustment is currently recommended for patients with mild or moderate renal impairment, together with a corresponding update of section 5.2.

Results of part 1 of the dedicated **hepatic impairment** study in healthy volunteers were submitted, covering mild HI according to Child-Pugh classification compared to normal hepatic function controls. No data are currently available for moderate and severe hepatic impairment.

Although any conclusion is currently preliminary, the impact of mild HI (Child-Pugh A) on total vimseltinib exposure can be considered clinically relevant as the point estimates were lower than common 80-125% confidence limits. Also the unbound vimseltinib exposure was lower with mild HI. Exposure of the metabolite was less affected (data not shown).

In contrast, PK parameters between the groups re-classified according to NCI-ODWG criteria seemed to be affected in the opposite direction, i.e. increasing exposures of parent and metabolite in the "mild group". It

was argued by the applicant that the comparison between the NCI groups was unbalanced as these were no matched pairs anymore.

As of to date, no reliable conclusions can be drawn from these preliminary results and the results of the moderate and severe groups and the completed CSR have to be awaited.

Additional exposure response evaluations were conducted to show that the lower exposure would not impair efficacy outcomes. Based on this, no dose adjustment is deemed necessary in patients with mild HI. However, a reduction to 14 mg twice weekly in patients with mild HI may result in reduced response (see section 4.2 of the SmPC). The final results of the ongoing hepatic impairment study are awaited to further inform the use of vimseltinib in patients with hepatic impairment.

Gender and **age** were evaluated as covariates but not retained in the final popPK model.

Patients of black or African American **race** had a ~1.3-fold higher Vp/F compared to non-black or African American participants. However, the effect on steady state exposure parameters was within the 80% to 125% limits effect of body weight. Therefore, race was not considered to have a clinically meaningful impact on the PK of vimseltinib.

The popPK model revealed that a 30 mg BIW dose resulted in significantly lower exposure in high **body weight** (109 kg) patients and in significantly higher exposure in low-weight (54 kg) patients. The estimated $C_{avg,ss}$ for 54 and 105 kg bodyweight (5% and 95% percentiles) were ~76% and 129% of subjects with reference body weight. Although the ER analysis did not predict a difference in efficacy or safety outcomes based on body weight, simulations for change from baseline for tumour response indicated that the dose reduction to 14 mg could lead to reduced efficacy in heavier patients. Specifically, reducing the dose to 14 mg in high-weight individuals was associated with up to 20% less tumour size reduction compared to the 30 mg BIW regimen. As a result, section 4.2 and 5.2 of the SmPC include a statement noting that dose reductions to 14 mg BIW in patients weighing more than 115 kg have not been studied, and efficacy in this subgroup has not been established.

Drug interactions

- As a victim

The *in vitro* studies showed that vimseltinib is metabolically stable and suggest minimal CYP-mediated metabolism. Given the minor role of CYP enzymes in the human phase 1 metabolism of vimseltinib the risk for drug-drug-interactions with CYPs modulator could be ruled out.

In vitro studies found that vimseltinib is not a substrate for the transporters BCRP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, or BSEP, based on uptake and efflux ratios near 1. In vitro studies showed that vimseltinib is a substrate for the transporters P-gp. However, the drug's high absorption (89%) and dose-proportional pharmacokinetics suggest that P-gp does not significantly affect its absorption, likely due to the drug's high permeability, this was confirmed in a clinical DDI study (see clinical study paragraph below). Therefore, the risk for drug-drug-interactions with these transporters modulators could be ruled out.

- As a perpetrator

Vimseltinib induction effect on CYP1A2, 2B6, 3A4 was assessed using cryopreserved human primary hepatocytes (3 donors) in the DCC-3014-03-0009 study (see section 2.6, Table 7).The results demonstrated that vimseltinib reduced CYP1A2 mRNA levels by less than 50% in a concentration-dependent manner (results not shown). The absence of cytotoxic effects, as indicated by unchanged cellular morphology at these concentrations, as reported by the applicant, indicates that this reduction is unlikely to be due to general

cytotoxicity. Hence, these findings suggest a potential down-regulation of CYP1A2 expression by vimseltinib. A short cautionary note was added to section 5.2 of the SmPC. This aligns with EMA guidance regarding situations when the in vitro signal suggests a possible clinical impact but definitive conclusions cannot currently be drawn.

With regard to CYP3A4, the results showed that CYP3A4 mRNA levels increased by more than 2-fold in two of three hepatocyte donors treated with 1 µM vimseltinib and in one donor treated with 3 µM vimseltinib but this increase was not concentration dependent and representing 1.49% and 1.37% relative to the positive control (data not shown). Therefore, it was agreed that the potential for CYP3A4 induction by vimseltinib could be considered low.

Concentration-dependent increases in CYP2B6 mRNA were not observed, with maximal increases greater than 2-fold observed at 0.1 to 10 vimseltinib (data not shown). The DDI risk with CYP2B6 substrates could be ruled out.

The inhibitory potential of vimseltinib and its metabolite (DP-7005) on several transporters (P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, and OCT2) was evaluated *in vitro* (Study DCC-3014-03-0006). From the results potential DDIs between vimseltinib and substrates of P-gp, BCRP, and OCT2 cannot be ruled out. However, the inhibitory effects of vimseltinib on BSEP, OATP1B1, OATP1B3, OAT1, and OAT3 substrates are not expected to be clinically significant, as their IC50 values exceed the worst-case concentrations at systemic, hepatic, and renal levels (i.e. 2.94 µM, 3.22 µM, and 27.8 µM, respectively).

Regarding its metabolite, a potential metabolite of vimseltinib , inhibited all of these transporters by < 35% when tested at 10 µM. Therefore, no IC50 was detected and the inhibitory effect on these transporters could be ruled out.

PBPK modelling was used to evaluate the potential for CYP-mediated and transporter-mediated DDIs (P-gp, BCRP and OCT2) with vimseltinib as a perpetrator. However, the PBPK platform is not considered as qualified to predict interactions with transporters as it is still showing some limitations. The applicant commits to conducting a DDI study with P-gp, BCRP and OCT2 substrates (RECs). The final clinical study report for the DDI study with these transporters is expected to be submitted by December 2026 for BCRP and OCT2 substrates and by September 2027 for P-gp substrate. Pending the study results, it is recommended in section 4.5 of the SmPC that the concomitant use of P-gp, BCRP and OCT2 substrates should be avoided and to refer to the product information of these substrates for dose modifications if concomitant use cannot be avoided.

Since vimseltinib has a teratogenic effect. The applicant commits to conducting a DDI study with an oral contraceptive. The final clinical study report for the DDI study with the oral contraceptive is expected to be submitted by September 2027 (REC). Pending the study results, it is recommended in section 4.5 and 4.6 of the SmPC that women of childbearing potential taking vimseltinib use a barrier method of contraception.

A clinical study (Study DCC-3014-01-006) was conducted to assess the impact of itraconazole, a P-gp inhibitor, and rabeprazole, a proton pump inhibitor (PPI), on the PK of vimseltinib and its metabolite. The results showed that, while the peak exposure (Cmax) of vimseltinib was similar whether administered alone or with itraconazole, total exposure (AUC) increased by 17% to 22% in the presence of itraconazole, indicating a weak effect. Conversely, rabeprazole reduced both peak and total exposures by 21% to 26%, also suggesting a weak impact on vimseltinib absorption.

Upon request the applicant discussed that a potential different impact of PPIs on PK in fed state was improbable, which can be followed.

Pharmacodynamics

Primary pharmacodynamics

For the biomarker analyses from study 01-001 results for NCM, CSF1 and IL-34 were presented. From the results in MST and TGCT patients it might be derived that upon administration of vimseltinib the levels of NCM decrease and the levels of CSF1 and IL-34 ligands in plasma increase within the first cycle until C2D1. A slight dose-dependency might be observed, though the sensitivity seems different for the 3 biomarkers

The PD data of the pivotal study 03-001 demonstrated a longitudinal effect on the abundant NCM (i.e., % CD14lowCD16+ monocytes of total monocytes) over the time course of the blinded part 1 of the study, in contrast to no change with placebo treatment. Decrease of NCM levels was observable from week 3 of treatment ongoing. A similar trend was observed in the longitudinal data plot with values of CSF1 of which levels increased while mean CSF1 levels remained stable in the placebo arm.

Secondary pharmacodynamics

Single doses of vimseltinib resulted in adverse events (AEs) as pruritus and rash, with need for concomitant treatment with antihistamines or corticoids. The applicant discussed that pruritus, oedema, and xerosis (dry skin) are common AEs among patients with cancer treated with antibody or small-molecule inhibitors of CSF1R.

The results from the cardiodynamic evaluation of the 40 and 50 mg doses in healthy participants demonstrated that vimseltinib has no clinically relevant effect on heart rate or on cardiac conduction (the PR and QRS intervals). There was no clinically meaningful effect on the QTc interval and an effect on ΔΔQTcF exceeding 10 ms can be excluded within the observed ranges of plasma concentrations of vimseltinib, up to 1774 ng/mL. One single subject showed an increase of 10.3 ms.

As a result of study 001 in TGCT patients, mean ΔQTcF varied across dose levels between −25.3 ms and 23.6 ms, but mean ΔQTcF was below 20 ms at all post-baseline time points across doses with the exception of 2 timepoints from 2 subjects.

Exposure-response relationship

The applicant provided an ER report for efficacy and safety where the PK exposure metrics used in this analysis were calculated based on empirical Bayes estimates obtained from the vimseltinib PopPK model.

For efficacy, a flat relationship between $C_{ave,ss}$ and ORR by RESIST and TVS was predicted, i.e. increased exposure between 300-1100 ng/ml did not provide benefit in terms of response. The most relevant covariate for ORR by RECIST was tumour size, with decreasing probability with size.

For the safety parameters the evaluated ADRs periorbital oedema, rash, AST and ALT elevations start early after treatment initiation and only minimal exposure-dependence of probability between $C_{max,ss}$ tertiles (lowest vs. mid/highest tertiles) could be observed from the simulations.

Dose justification / therapeutic window

30 mg BIW without a loading dose achieved steady state after ~ 1 cycle (28 days) compared to a loading dose with ~ 15 days. Considering no immediate need of tumour size reduction in a non-malignant, non-life-threatening condition, this is acceptable to reduce Cmax.

As regards efficacy, it was stated that the geo-mean $C_{min,ss}$ achieved with this dosing was above the *in vitro* IC_{50}. New calculations revealed sufficient average exposure for target engagement and PD response.

As regards safety, a MTD was not reached in the dose escalation studies. The highest observed concentrations for the QTc study arm of study 01-002 did not cross the modelled threshold of concern for QTc prolongation (1774 ng/mL). Early onset of certain ADRs may, however, be dose limiting and their probability increased with increasing C_{max}.

The applicant provided a detailed PK-PD justification of the therapeutic window, and used PK simulation to show that $C_{av,ss}$ and $C_{min,ss}$ is expected to be below the maximum tolerable concentration and the maximum concentration excluding a QTc effect.

2.6.4. Conclusions on clinical pharmacology

From the submitted clinical pharmacology package it can be concluded that pharmacokinetics and pharmacodynamics of vimseltinib and its metabolite DP-7005 are sufficiently characterised.

2.6.5. Clinical efficacy

For evaluation of efficacy one pivotal trial DCC-3014- 03-001 long-term MTD (MOTION) was submitted; additional supportive data is available from the Phase I/II trial DCC 3014-01-001 as detailed in the Table below:

Table 22. Clinical studies relevant for efficacy and safety evaluation

Study Identifier/ Type of Study	Number of Study Centres and Location	Objec-tives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled[a]	Healthy Participants or Diagnosis of Patients / Age	Duration of Treatment	Study Status; Type of Report
PHASE I / II (supportive)								
DCC-3014-01-001 Phase 1/2 (Safety and Efficacy)	25 centres in Australia, Canada, France, Italy, Netherlands, Poland, Spain, United Kingdom, and United States	Safety, PK, Efficacy	Open label, multicentre, dose escalation and expansion Part 1: 3+3 Dose Escalation to determine RP2D in patients with advanced MSTs or TGCT Part 2: Dose expansion to evaluate safety, tolerability, preliminary tumour	Vimseltinib; Oral Administration <u>Cohort 1:</u> LD=none; MD=10 mg QD for 28 days until Commercialisation.(UC) <u>Cohort 2:</u> LD=10 mg QD×5 days; MD=10 mg twice weekly for 28 days (UC) <u>Cohort 3:</u> LD=20 mg QD×5 days; MD=20 mg once a week for 28 days (UC) <u>Cohort 4:</u> LD=20 mg QD×5 days; MD=20 mg twice a week for 28 days (UC) <u>Cohort 5:</u> LD=30 mg QD×5 days; MD=30 mg twice weekly for 28 days (UC)	Total: 135 (37 MST patients; 98 TGCT patients)	Patients with Histologically confirmed MST or TGCT Age: ≥18 years	Repeated 28-day cycles Until disease progression, lack of clinical benefit, un-acceptable toxicity, withdrawal by partici-pant, physician's decision, or commercial availability	Enrolment complete; Ongoing; Interim CSR

Study Identifier/ Type of Study	Number of Study Centres and Location	Objec-tives of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Enrolled[a]	Healthy Participants or Diagnosis of Patients / Age	Duration of Treatment	Study Status; Type of Report
			activity in patients with TGC	Cohort 6: LD=40 mg QD×5 days; MD=40 mg twice weekly for 28 days (UC) Cohort 7: LD=50 mg QD×3 days; MD=20 mg QD for 28 days (UC) Cohort 8: LD=30 mg QD×3 days; MD=10 mg QD for 28 days UC Cohort 9: LD=20 mg QD×3 days; MD=6 mg QD for 28 days UC **Expansion** Cohort A and B: 30 mg twice weekly for 28 days UC				
PHASE III (pivotal)								
DCC-3014-01-001 MOTION Phase 3 (Efficacy and Safety)	30 centres in United States, Italy, Spain, France, Germany, United Kingdom, Australia, Canada, Hong Kong, Netherlands, Norway, Poland, and Switzerland	Efficacy PK/PD, safety	Randomized, multicentre, placebo-controlled, double-blind study Part 1: double-blind, placebo-controlled Part 2: open-label, placebo crossover to vimseltinib	Vimseltinib 30 mg or matching placebo twice weekly Oral administration	Total: 123 randomised 2:1 (N=83 vimseltinib; N=40 placebo)	Patients with a histologically confirmed diagnosis of TGCT Age: ≥18 years	Repeated 28 day-cycles Until disease progression, lack of clinical benefit, unacceptable toxicity, withdrawal by participant, physician's decision, or commercial availability	Enrolment complete; Ongoing; Full CSR[d]

2.6.5.1. Dose response study(ies)

DCC-3014-01-001

"A Multicenter Phase 1/2, Open-label Study of DCC-3014 to Assess the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics in Patients with Advanced Tumours and Tenosynovial Giant Cell Tumour

Dose-finding was the most relevant aim of the Phase I/II trial DCC-3014-01-001. In this trial the dose for the pivotal MOTION trial was established for a schedule using vimseltinib 30 mg twice weekly based on an acceptable and manageable safety profile and the objective responses observed, see also section 2.6.5.4. . Effects of an additional loading dose was also investigated.

PK data were collected from 9 cohorts, in each cohort, participants received vimseltinib for TGCT and MST. Dose escalation was based on a pharmacologically guided 3+3 study design in participants with MST and TGCT. A minimum of 3 patients was enrolled in each dose level cohort.

Following multiple daily, weekly, or twice weekly administrations of vimseltinib in participants with MST and TGCT with or without loading doses, the following PK trends were observed:

In the absence of any loading doses, steady state for vimseltinib was achieved within 28 days of dosing in participants with TGCT indicating a half-life of 67 to 134 hours. Administration of a loading dose shortened the time to reach steady state to approximately 15 days with the administration of loading doses.

However considering that TGCT is a non-malignant, non-life-threatening disease this approach was not necessary, since accumulation (up to 3-fold) was observed in participants with TGCT following multiple administrations of vimseltinib with or without loading doses.

The exposure-efficacy analysis based on data from MOTION did not show an association between vimseltinib exposure and ORR per RECIST v1.1 or TVS and a flat exposure-efficacy relationship was identified across the exposure range for the evaluated dosing regimen.

In summary, the 30 mg twice weekly posology was used in the pivotal trial MOTION (see below). Insofar, most evidence on efficacy and safety was generated with this dose.

For more information regarding the details of this trial please refer to section 2.6.5.4. Supportive study of this AR.

2.6.5.2. Main study

MOTION: Phase 3, Randomized, Placebo-controlled, Double-blind Study of Vimseltinib to Assess the Efficacy and Safety in Patients with Tenosynovial Giant Cell Tumor

Table 23. Study identifiers

Study code	DCC-3014-03-001 (MOTION)
EU CT number	2020-004883-25
NCT number	NCT05059262
ISRCT number	Not reported
Other identifier(s)	MOTION Trial

Methods

MOTION Trial was a multicentre, randomized, placebo-controlled study of vimseltinib in patients with tenosynovial giant cell tumour (TGCT), consisting of 2 parts: Part 1 was double blind and Part 2 was open label.

The study evaluated efficacy, safety, clinical outcome assessments, pharmacokinetics (PK), and pharmacodynamics of vimseltinib.

The study consisted of a 42-day screening period prior to the first dose of study drug, a Part 1 double-blind treatment period of 24 weeks (referred to in 28-day cycles) and a Part 2 open-label period until Week 49. Participants continued treatment after Week 49 during the extension period.

There was an End-of-Treatment Visit within 7 days after the decision to stop study drug, a Safety Follow-up Visit 30 days (±5 days) after the last dose of study drug, and a Disease Follow-up period of up to 2 years after the last dose of study drug or until initiation of new TGCT treatment or surgery, whichever occurred first. Participants were allowed to undergo surgical resection only after completion of Part 1.

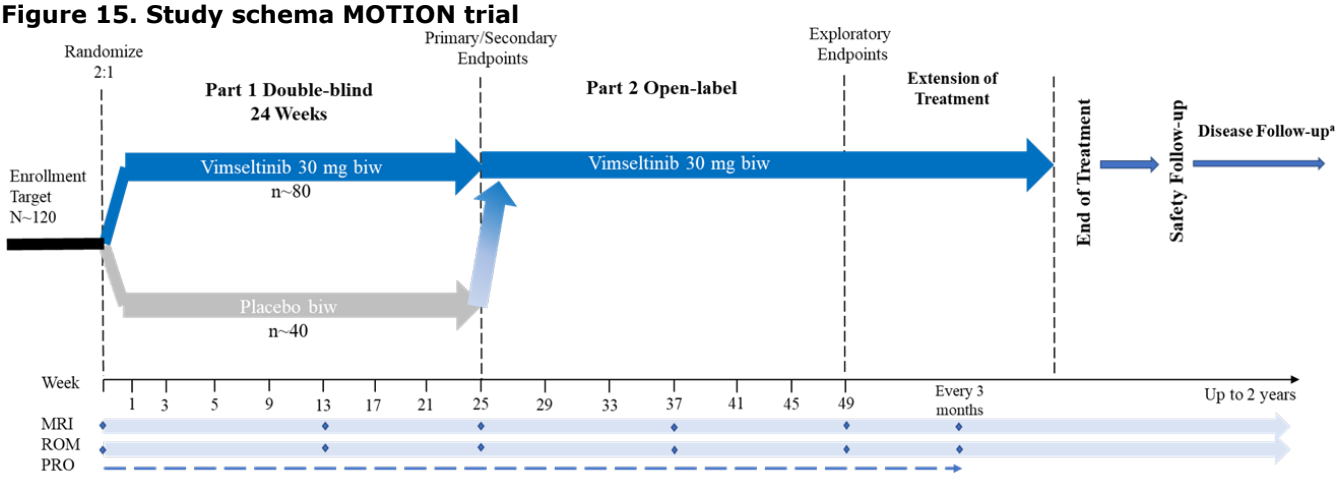
Participants were randomized in a 2:1 ratio to receive either vimseltinib at the dose of 30 mg twice weekly or placebo for 24 weeks. Randomisation was stratified for tumour location (lower limb/all other) and region (U.S./non-U.S.).

At Week 25, the primary and secondary endpoints were assessed, and participants randomized to placebo in Part 1 had the option to cross over and receive open label vimseltinib in Part 2 upon completion of Part 1. Participants randomized to placebo in Part 1 with confirmed disease progression using RECIST v1.1 by blinded IRR before Week 25 were eligible for early entry into Part 2.

Participants randomized to vimseltinib in Part 1 with confirmed disease progression by IRR before Week 25 were discontinued from study, while those without confirmed disease progression by IRR before Week 25 continued to receive vimseltinib in Part 2 upon completion of Part 1.

Anti-tumour activity was assessed by RECIST v1.1. Tumour volume score and mRECIST were used as additional assessments of anti-tumour activity. Range of motion assessments were performed, and PRO measures were collected. Safety was assessed using Common Terminology Criteria for Adverse Events v5.0. Correlation between efficacy or safety with PK and pharmacodynamics were planned.

Figure 15. Study schema MOTION trial



Patient population:
- Histologically confirmed, symptomatic tenosynovial giant cell tumors
- Surgical resection will potentially cause worsening functional limitations or severe morbidity
- No prior use of systemic therapy targeting CSF1 or CSF1R (except imatinib and nilotinib)

Study Participants

Participants must meet all of the following criteria to be eligible to enrol in the study.

1. Male or female participants ≥18 years of age.
2. Histologically confirmed diagnosis of TGCT (formerly known as pigmented villonodular synovitis [PVNS] or giant cell tumour of the tendon sheath [GCT-TS]). Tumour biopsy to confirm TGCT diagnosis will be required if no histology/pathology is available. Participants should have TGCT in a single joint and must have TGCT in joints where ROM assessments can be assessed.
3. Disease for which surgical resection will potentially cause worsening functional limitation or severe morbidity as judged by surgical consultation or a multidisciplinary tumour board.
4. Symptomatic disease with at least moderate pain or at least moderate stiffness (defined as a score of 4 or more, with 10 describing the worst condition) within the screening period and documented in the medical record.
5. Participants should complete 14 consecutive days of questionnaires during the screening period and must meet minimum requirements outlined in the Schedule of Patient-reported Outcome Assessments of the study protocol**.**
6. An analgesic regimen, if used, needs to be stable (i.e., no change in dose) as judged by the Investigator for at least 2 weeks prior to the first dose of study drug.
7. Measurable disease per RECIST v1.1 with at least one lesion having a minimum size of 2 cm, as assessed from magnetic resonance imaging (MRI) scans by a central radiologist.
8. Adequate organ function and bone marrow reserve as indicated by the following laboratory assessments performed within 21 days prior to the first dose of study drug:
    a. Bone marrow function: absolute neutrophil count (ANC) ≥1500/μL; haemoglobin ≥10 g/dL; platelet count ≥lower limit of normal (LLN)
    b. Hepatic function: total serum bilirubin ≤upper limit of normal (ULN); serum aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ULN
    c. Renal function: creatinine clearance ≥50 mL/min based either on urine collection or Cockcroft-Gault estimation
    d. Electrolytes ≥LLN for: potassium, magnesium, and calcium
9. Able to take oral medication.
10. Participants of reproductive potential must:
    a. Have a negative serum beta-human chorionic gonadotropin (β-hCG) pregnancy test at screening (female participants).
    b. Agree to follow the contraception requirements outlined in the protocol.
11. The participant is capable of understanding and complying with the protocol and has signed the informed consent form (ICF). A signed ICF must be obtained before any study-specific procedures are performed.
12. Willing and able to complete the PRO assessments on an electronic device.

Exclusion Criteria:

Participants meeting any of the following criteria will be excluded from the study.

1. Previous use of systemic therapy (investigational or approved) targeting CSF1 or CSF1R including vimseltinib; previous therapy with imatinib and nilotinib is allowed.
2. Treatment for TGCT, including investigational therapy, during the screening period
3. NOTE: Participants may not be part of an ongoing or have prior participation in a non-TGCT investigational drug study within 30 days of screening. Ongoing participation in a noninterventional study (including observational studies) is permitted.
4. Known metastatic TGCT or other active cancer that requires concurrent treatment (exceptions will be considered on a case-by-case basis depending on tumour type, stage, location, planned treatment, and expected recovery after discussion and approval by Sponsor)
5. Baseline prolongation of the QT interval corrected by Fridericia's formula (QTcF) based on repeated demonstration of QTcF >450 ms in males or >470 ms in females or history of long QT syndrome
6. Receive concurrent treatment with any prohibited medications
    - Acetaminophen usage exceeding 3 g/day
    - Proton-pump inhibitors taken within 4 days prior to the first dose of study drug
    - Medications that are breast cancer resistance protein (BCRP) or organic cation transporter 2 (OCT2) substrates taken within at least 4 days or 5×half-life (whichever is longer) prior to the first dose of study drug
    - Medications with a known risk of prolonging the QT interval within at least 14 days or 5×half-life (whichever is longer) prior to the first dose of study drug (see SP Appendix 1)
    - Prophylactic use of myeloid growth factors (e.g., granulocyte colony-stimulating factor [G-CSF], granulocyte macrophage-colony-stimulating factor [GM-CSF])
7. Major surgery within 14 days of the first dose of study drug; following major surgeries >14 days prior to the first dose of study drug, all surgical wounds must be healed and free of infection or dehiscence
8. Any clinically significant comorbidities, such as significant concomitant arthropathy not related to TGCT in the affected joint, or any other serious medical or psychiatric condition(s), known current alcohol abuse, which in the judgment of the Investigator, could compromise compliance with the protocol, interfere with the interpretation of study results, or predispose the participant to safety risks.
9. Active liver or biliary disease including non-alcoholic steatohepatitis (NASH) or cirrhosis Malabsorption syndrome or other illness that could affect oral absorption as judged by the Investigator
10. Known active human immunodeficiency virus (HIV), acute or chronic hepatitis B, acute or chronic hepatitis C, or known active mycobacterium tuberculosis infection
11. If female, the participant is pregnant or breastfeeding
12. Known allergy or hypersensitivity to any component of the study drug.

Treatments

Vimseltinib 30 mg or matching placebo twice weekly were administered as oral capsules on repeated 28-day cycles. Participants were instructed to take their assigned dose of vimseltinib or matching placebo orally at the same time each day according to the assigned schedule

Vimseltinib or matching placebo capsules were administered orally on Day 1 and Day 5 each week at approximately the same time of day. The study drug was taken on an empty stomach, at least 1 hour before and no sooner than 2 hours after ingestion of food. Each dose was taken within 24 hours of the scheduled dosing time (±1 day window), with at least 24 hours between doses. If a participant missed the scheduled dose, then that dose was skipped. The next required dose was taken at the next scheduled time and the participant did not double the dose to make up for an earlier missed dose. Should a participant vomit after dosing, the study drug was not re-administered.

Objectives

Primary Objective

• To evaluate anti-tumour activity of vimseltinib using RECIST v1.1 by blinded IRR

Key secondary objectives

- To assess anti-tumour activity of vimseltinib using TVS and mRECIST by blinded IRR
- To assess the effects of vimseltinib on ROM
- To assess the effects of vimseltinib on physical function, worst stiffness, worst pain, and QoL using PRO measures
- To assess safety and tolerability of vimseltinib

Outcomes/endpoints

Primary Endpoint

• ORR (including CR and PR) per RECIST v1.1 at Week 25

The primary efficacy estimand had the following attributes:

Estimand Attribute		
Population	Participants with TGCT who meet all inclusion and exclusion criteria, who are randomised to receive either vimseltinib 30mg or placebo twice weekly.	
Treatment	Vimseltinib 30 mg twice weekly vs placebo twice weekly	
Variable	Objective response at Week 25, which is defined as overall response of CR or PR at Week 25 based on independent radiologic review per RECIST v1.1	
Population-level summary	Difference in ORR at Week 25 (proportion of randomised participants meeting CR or PR per RECIST v1.1 at Week 25) between the two arms and associated 95% CI using a stratified Mantel-Haenszel method with stratification factors based on randomisation stratification factors.	
Intercurrent Event	**Strategy**	**Description**

Lack of adherence to study drug	Treatment Policy	Adherence is not considered. Data on the main outcome are continued to be collected.
Use of a Subsequent TGCT Therapy/Surgery	Composite Policy	Assessments after subsequent TGCT therapy/surgery are not collected; missing data is considered a non-response.
End of Part 1 Unblinding prior to assessment at Week 25	Composite policy	Assessments after unblinding are not considered; missing data is considered a non-response
Any other events leading to missing evaluation including discontinuation of study prior to Week 25 visit	Composite	Missing data at baseline or at Week 25 is considered a non-response

Key Secondary Endpoints

- ORR per TVS at Week 25
- Change from baseline in active ROM of the affected joint, relative to a reference standard, at Week 25
- Change from baseline in the PROMIS-PF score at Week 25
- Change from baseline in the Worst Stiffness NRS score at Week 25
- Change from baseline in EQ-VAS at Week 25
- Response of at least a 30% improvement in the mean BPI Worst Pain NRS score without a 30% or greater increase in narcotic analgesic use at Week 25

Other Secondary Endpoints

- ORR per RECIST v1.1
- ORR assessed by mRECIST at Week 25
- DOR (time from first PR or CR to disease progression or death) assessed using RECIST v1.1, TVS, and mRECIST
- Incidence of TEAEs, treatment-emergent SAEs, related TEAEs, dose reductions, dose interruptions, and discontinuation of study drug due to AE
- Changes from baseline in laboratory parameters, ECGs, and vital signs

Sample size

The sample size selection of approximately 120 participants with TGCT (n~80 vimseltinib, n~40 placebo) was based on considerations for powering the analyses of the primary endpoint, key secondary endpoints, detection of rare safety events and overall exposure to vimseltinib, assuming 15% participant dropout. Participants were randomized in a 2:1 ratio of vimseltinib versus placebo.

This sample size had 98% power to detect a statistically significant difference between treatment groups, assuming true ORRs of 35% and 5% in the vimseltinib arm and the placebo arm, respectively, using a two-sided Fisher's exact test at a 5% type I error rate level.

Randomisation and Blinding (masking)

Participants were randomized in a 2:1 ratio to receive either vimseltinib 30 mg twice weekly or placebo in the double-blind portion of the study (Part 1). Randomisation was stratified by tumour location (lower limb or all other) and regions (U.S./Non-U.S).

Interactive response technology was used to randomise and assign study drug.

Blinding Part 1: In Part 1 of the study, participants and all site personnel, including the Investigator, the site monitor, and the study team were blinded to study drug treatment.

Blinding Part 2: After completion of part 1 assessments, participants who wish to continue to the open label past of this study (Part 2) will be unblinded. Participants randomized to placebo will crossover to receive vimseltinib and participants initially randomized to vimseltinib will continue to receive vimseltinib in Part 2.

Statistical methods

The analyses were aligned to the pre-specifications of the protocol and the SAP. The protocol was not aligned to ICHE9(R1), that is, no estimands were pre-specified for the primary analysis nor the analyses of the key-secondary endpoints.

Between-group comparisons will focus on the comparative performance of vimseltinib versus placebo. All statistical tests will be conducted at a 2-sided significance level of 0.05.

Analyses sets

Screen Set: The Screen Set consisted of all participants who signed the ICF.

Intent-to-Treat Set: The ITT Set consisted of participants who were randomized to a study treatment regimen. Analysis was performed according to the allocated treatment regimen. The ITT Set was the primary analysis set for all the efficacy endpoints analyses.

Per Protocol Analysis Set:

The PP Analysis Set consisted of participants in the ITT Set with at least 1 post-baseline IRR tumour assessment who had no IPDs. Participants with IPDs that resulted in exclusion from the PP Set were identified and documented prior to database lock and could include violations of key inclusion/exclusion criteria, noncompliance with study treatment, participant taking the wrong study treatment, or participant receiving prohibited concomitant medications or therapies.

The efficacy analyses performed on the PP Set were supportive and treatment group was based on actual treatment received.

Safety Analysis Set: The SAF Set consisted of participants who received at least 1 dose of study treatment. Analysis was performed according to the treatment regimen actually received.

Pharmacokinetic Set: The PK Set consisted of participants who received at least 1 dose of vimseltinib and had at least 1 non-missing PK concentration in plasma reported for vimseltinib or DP-7005.

PRO Set: The PRO Set consisted of participants in the ITT Set who had valid baseline and at least 1 post-baseline PRO assessment.

Regarding the primary endpoint

Objective response rate (ORR) per RECIST v1.1 at Week 25 was defined as the proportion of participants with a CR or a PR as the Week 25 Tumour Response (as defined in Table 2) based on IRR per RECIST v1.1. ORR at Week 25 was compared between the 2 treatment groups using a two-sided Cochran-Mantel-Haenszel (CMH) test stratified by the randomisation stratification factors. The test was performed at a 0.05 alpha level on the ITT Set. A 95% CI for the proportion in each arm using the Clopper-Pearson method as well as the difference in proportion and its associated Wald 95% CI were presented. The ITT set on which the primary analysis is based, consists of participants who have been randomized to a study treatment regimen. Analysis were performed according to the allocated treatment regimen. The ITT Set was the primary analysis set for all the efficacy endpoints analyses.

Regarding the key secondary endpoints

Multiple secondary endpoints were analysed using a mixed model for repeated measurements (MMRM) using the sandwich estimator to estimate the variance-covariance matrix. The dependent variable was the change from baseline. Each of these models includes fixed effects for treatment group, timepoint, treatment group by timepoint interaction, stratification factor for region (U.S. versus non-U.S.), stratification factor for tumour location (lower limb vs. all other), and the baseline value of the corresponding endpoint. Statistical comparisons between treatment groups were made at the specified timepoint. For the analysis of ROM only, tumour location was replaced with joint type (knee, ankle, or other). An unstructured variance-covariance matrix was used. If the unstructured variance-covariance matrix failed to converge, then alternative structures were to be utilized. Statistical comparisons between treatment groups were made based on a contrast statement at Week 25.

Interim Analyses

No interim analyses were planned, intended or conducted.

Multiplicity control

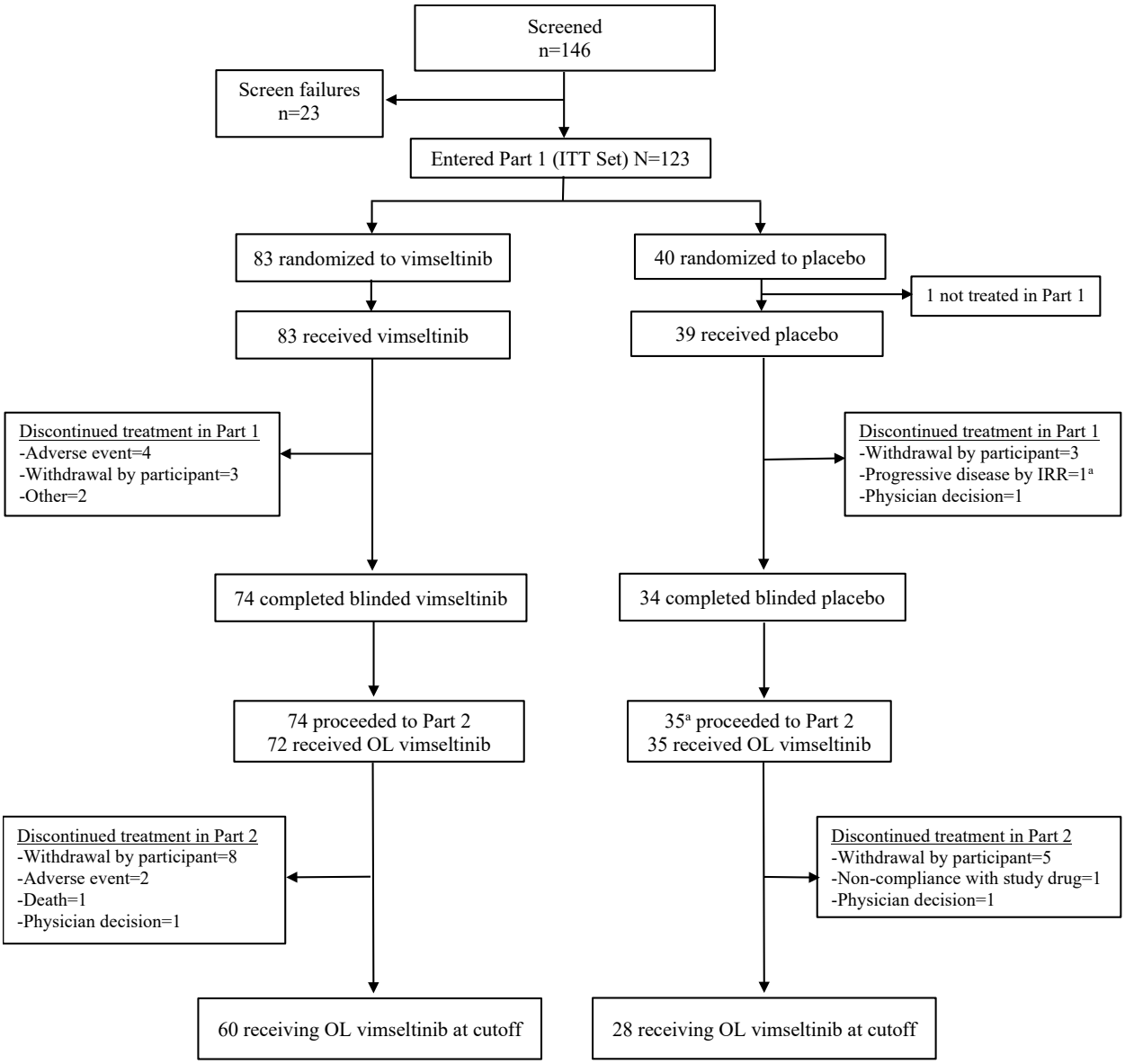
To control overall type I error, a hierarchical testing procedure was utilised. Statistical testing was performed for the analysis of primary (1st bullet point) and key secondary (2nd to 7th bullet point) endpoints in the following order at a 2-sided 0.05 alpha level for each:

1. ORR per RECIST v1.1 at Week 25
2. ORR per TVS at Week 25
3. Mean change from baseline in active ROM at Week 25
4. Mean change from baseline in the PROMIS-physical function score at Week 25
5. Mean change from baseline in the worst stiffness NRS score at Week 25
6. Mean change from baseline in EQ-VAS at Week 25
7. Proportion of responders based on BPI-30 (worst pain) NRS score and narcotic analgesic use at Week 25

Results

Participant flow

Figure 16. Participant disposition in MOTION, ITT set



Abbreviations: IRR=independent radiological review; ITT=intent-to-treat; N/n=sample size; OL=open-label.
a One participant experienced progressive disease by IRR and crossed over early to Part 2.
Data cutoff date: 22 Aug 2023.

Participant disposition for Part 1 is presented in Table 24.

Table 24. Participant disposition during Part 1, ITT set

Participants, n (%)	Vimseltinib N=83	Placebo N=40	Total N=123
Entered double-blind treatment period (Part 1) [a]	83 (100.0)	40 (100.0)	123 (100.0)
Not treated in Part 1[a]	0	1 (2.5)	1 (0.8)
Treated in Part 1 [a]	83 (100.0)	39 (97.5)	122 (99.2)
Completed treatment [b]	74 (89.2)	34 (87.2)	108 (88.5)
Ongoing on treatment [b]	0	0	0
Discontinued treatment [b]	9 (10.8)	5 (12.8)	14 (11.5)
Primary reason for treatment discontinuation [b]			
Progressive disease by IRR	0	1 (2.6)c	1 (0.8)
Adverse event	4 (4.8)	0	4 (3.3)
Withdrawal by participant	3 (3.6)	3 (7.7)	6 (4.9)
Physician decision	0	1 (2.6)	1 (0.8)
Other	2 (2.4)	0	2 (1.6)
Completed study in Part 1 [a]	75 (90.4)	35 (87.5)	110 (89.4)
Ongoing on study in Part 1 [a]	1 (1.2)d	0	1 (0.8)
Discontinued from study in Part 1 [a]	7 (8.4)	5 (12.5)	12 (9.8)
Primary reason for study discontinuation in Part 1 [a]			
Subsequent TGCT therapy and/or surgery	3 (3.6)	0	3 (2.4)
Withdrawal by participant (withdrawal of consent)	3 (3.6)	3 (7.5)	6 (4.9)
Physician decision	1 (1.2)	1 (2.5)	2 (1.6)
Other	0	1 (2.5)	1 (0.8)

Abbreviations: IRR=independent radiological review; ITT=intent-to-treat; n=number of participants in a category; N=sample size; TGCT=tenosynovial giant cell tumour.
a Percentage was based on number of participants in ITT Set.
b Percentage was based on number of treated participants in Part 1.
c Participant discontinued treatment early and crossed over to Part 2.
d Participant was planned to discontinue study ahead of data cutoff, but was delayed due to relocation to a different country.
Note: Data cutoff date was 22 Aug 2023.

Open-label Period (Part 2)

Participant disposition for Part 2 at data cutoff date is presented in Table 25. Majority of participants who continued to Part 2 remained on treatment (82.2%) at data cutoff. The most common reason for treatment discontinuation in Part 2 was withdrawal by participant (12.1%).

At data cutoff, most participants who had continued to Part 2 (96.3%) were ongoing on the study in Part 2. One death unrelated to study drug occurred in Part 2 (see section 2.6.8.3.). The most common reason for study discontinuation in Part 2 was lost to follow up (1.8%).

Table 25. Participant disposition during Part 2, ITT set

Participants, n (%)	Vimseltinib N=83	Placebo N=40	Total N=123
Proceeded or crossed over to open-label treatment period (Part 2) [a]	**74 (89.2)**	**35 (87.5)**	**109 (88.6)**
Not treated in Part 2[b]	2 (2.7)	0	2 (1.8)
Treated in Part 2[b]	72 (97.3)	35 (100.0)	107 (98.2)
Completed treatment [c]	0	0	0
Ongoing on treatment [c]	60 (83.3)	28 (80.0)	88 (82.2)

Participants, n (%)	Vimseltinib N=83	Placebo N=40	Total N=123
Discontinued treatment [c]	12 (16.7)	7 (20.0)	19 (17.8)
Primary reason for treatment discontinuation[c]			
Non-compliance with study drug	0	1 (2.9)	1 (0.9)
Adverse event	2 (2.8)	0	2 (1.9)
Death	1 (1.4)	0	1 (0.9)
Withdrawal by participant	8 (11.1)	5 (14.3)	13 (12.1)
Physician decision	1 (1.4)	1 (2.9)	2 (1.9)
Completed study in Part 2[b]	0	0	0
Ongoing on study in Part 2[b]	73 (98.6)	32 (91.4)	105 (96.3)
Discontinued from study in Part 2[b]	1 (1.4)	3 (8.6)	4 (3.7)
Primary reason for study discontinuation in Part 2[b]			
Death	1 (1.4) [d]	0	1 (0.9)
Withdrawal by participants (Consent withdrawn)	0	1 (2.9)	1 (0.9)
Lost of follow up	0	2 (5.6)	2 (1.8)

Abbreviation: ITT=intent-to-treat; n=number of participants in a category; N=sample size.

[a] Percentage was based on number of participants in ITT Set.

[b] Percentage was based on number of proceeded or crossed over to open-label treatment period (Part 2) participants.

[c] Percentage was based on number of treated participants in Part 2.

[d] One participant (vimseltinib arm) died in Part 2 due to a fall unrelated to study drug. Note:
Data cutoff date was 22 Aug 2023.

Recruitment

Study Centres and Countries: This multicentre study was conducted at 7 sites in the United States; 5 sites in Italy; 4 sites in Spain; 3 sites in France; 2 sites each in Germany and United Kingdom; 1 site each in Australia, Canada, Hong Kong, Netherlands, Norway, Poland, and Switzerland.

Studied Period (years):

Date first participant enrolled:15 Oct 2021

The analyses presented are based on the Week 25 primary endpoint data with cutoff date of 22 Aug 2023.

Conduct of the study

Three amendments with several local amendments were performed. Amendment 3 introduced several changes affecting several secondary endpoints.

Protocol deviations: Protocol deviations were reported for 97 participants (78.9%). There were 6 participants (4.9%) with IPDs who were excluded from the PP Set for efficacy analyses.

Baseline data

Demographic and Baseline Characteristics

Demographic and baseline characteristics of participants are presented in Table 26 for the ITT set.

Table 26. Demographic characteristics and baseline characteristics, ITT set

Participants, n (%)	Vimseltinib N=83	Placebo N=40	Total N=123
Age at informed consent (years)a			
Mean (STD)	43.8 (13.92)	42.5 (13.67)	43.4 (13.80)
Median	45.0	43.0	44.0
Min, max	20, 78	21, 72	20, 78
Age group (years), n (%)[b]			
18 to <50	54 (65.1)	27 (67.5)	81 (65.9)
50 to <65	24 (28.9)	9 (22.5)	33 (26.8)
65 to <75	3 (3.6)	4 (10.0)	7 (5.7)
75 to <85	2 (2.4)	0	2 (1.6)
Sex, n (%)[b]			
Male	37 (44.6)	13 (32.5)	50 (40.7)
Female	46 (55.4)	27 (67.5)	73 (59.3)
Race, n (%)[b]			
Asian	1 (1.2)	4 (10.0)	5 (4.1)
Black or African American	4 (4.8)	0	4 (3.3)
White	59 (71.1)	21 (52.5)	80 (65.0)
Not reported	18 (21.7)	13 (32.5)	31 (25.2)
Unknown	1 (1.2)	2 (5.0)	3 (2.4)
Ethnicity, n (%)[b]			
Hispanic or Latino	3 (3.6)	1 (2.5)	4 (3.3)
Not Hispanic or Latino	62 (74.7)	23 (57.5)	85 (69.1)
Not reported	17 (20.5)	15 (37.5)	32 (26.0)
Unknown	1 (1.2)	1 (2.5)	2 (1.6)
Baseline BMI (kg/m^2)			
n	81	40	121
Mean (STD)	27.52 (5.919)	27.08 (6.148)	27.37 (5.974)
Median	26.20	25.90	26.20
Min, max	18.8, 46.0	17.2, 44.6	17.2, 46.0
Region, n (%)[b]			
U.S.	9 (10.8)_	4 (10.0)	13 (10.6)
Non-U.S.	74 (89.2)	36 (90.0)	110 (89.4)
Tumour location based on IRT, n (%)[b]			
Lower limb	73 (88.0)	36 (90.0)	109 (88.6)
All other	10 (12.0)	4 (10.0)	14 (11.4)

Abbreviations: BMI=body mass index; IRT=interactive response technology; ITT=intent-to-treat; n=number of participants in a category; max=maximum; min=minimum; n=number of participants in a category; N=sample size; STD=standard deviation.
a Age at informed consent (years) was calculated as (year of informed consent – year of birth) if not collected on the case report form.
b Percentage was based on number of participants in ITT Set.
Note: Data cutoff date was 22 Aug 2023.

Characteristics were similar between treatment arms. The mean (STD) age of participants was 43.4 (13.80) years. The participants were generally White (65.0%), non-Hispanic (69.1%), and female (59.3%). The mean (STD) baseline BMI was 27.37 (5.974) kg/m2. Majority of participants were non-U.S. (89.4%) and presented with tumour in the lower limb (88.6%) as recorded per IRT.

Medical and Disease History

The most frequently reported medical history PTs in the ITT Set included hypertension (18.7%), arthralgia (17.9%), tumour biopsy (11.4%), and depression (10.6%).

Disease history for TGCT participants is provided in Table 27. Most participants had diffuse TGCT (69.1%), and the knee was the most common primary affected joint (67.5%). The mean (STD) time from original diagnosis to first dose of study drug was 5.54 (5.10) years. Over half (56.1%) of participants experienced Grade 2 baseline signs and symptoms for TGCT (Table 14.1.4.2.1).

The most frequently reported TGCT signs and symptoms at baseline included arthralgia (69.9%), joint range of motion decreased (22.0%), joint stiffness (18.7%), mobility decreased (15.4%), and joint swelling (12.2%).

Table 27. TGCT disease history, ITT set

Participants, n (%)	Vimseltinib N=83	Placebo N=40	Total N=123
Disease subtype, n (%)			
Diffuse TGCT	57 (68.7)	28 (70.0)	85 (69.1)
Localized TGCT	26 (31.3)	10 (25.0)	36 (29.3)
Missing	0	2 (5.0)	2 (1.6)
Primary affected joint, n (%)			
Knee	56 (67.5)	27 (67.5)	83 (67.5)
Ankle	9 (10.8)	6 (15.0)	15 (12.2)
Hip	11 (13.3)	1 (2.5)	12 (9.8)
Foot	1 (1.2)	3 (7.5)	4 (3.3)
Wrist	2 (2.4)	1 (2.5)	3 (2.4)
Hand	2 (2.4)	0	2 (1.6)
Shoulder	1 (1.2)	1 (2.5)	2 (1.6)
Elbow	1 (1.2)	0	1 (0.8)
Other	0	1 (2.5)	1 (0.8)

Abbreviations: ITT=intent-to-treat; n=number of participants in a category; N=sample size; TGCT=tenosynovial giant cell tumour.
Note 1: TGCT disease history was reported by the Investigator. Percentage is based on number of participants in ITT Set.
Note 2: Data cutoff date was 22 Aug 2023.

Prior and Concomitant Procedures, Medications, and Therapies

The majority of participants (74.0%) reported at least 1 prior TGCT surgery or procedure. In addition, 22.8% reported receiving a prior TGCT systemic therapy, which included imatinib (18.7%) and nilotinib (4.9%), and 8.9% reported prior TGCT radiation therapy.

The majority of participants received at least 1 prior or concomitant medication. Common prior medications included paracetamol (25.4%) and ibuprofen (18.9%). Common concomitant medications in the double blind period included paracetamol (43.4%) and ibuprofen (28.7%).

Measurements of Treatment Compliance

Mean (STD) RDI in the double-blind period was 81.25% (18.207%) for vimseltinib and 91.62% (11.226%) for placebo. Median (min, max) RDI in the double-blind period was 87.5% (14.6%, 102.1%) for vimseltinib and 95.8% (50.0%, 100.0%) for placebo

Numbers analysed

- Efficacy analyses were performed on the ITT Set unless otherwise specified.
- Exploratory PRO analyses were performed on the PRO Set,

Table 28. Summary of populations

Populations	Vimseltinib (N=83) n (%)	Placebo (N=40) n (%)	Total (N=123) n (%)
ITT Set	83 (100.0)	40 (100.0)	123 (100.0)
PP Set	82 (98.8)	34 (85.0)	116 (94.3)
Safety Set	83 (100.0)	39 (97.5)	122 (99.2)
PK Set	83 (100.0)	34 (85.0)	117 (95.1)
PRO Set	83 (100.0)	39 (97.5)	122 (99.2)

For definition of analyses sets, see Statistical methods.

Outcomes and estimation

Primary endpoint: Objective Response Rate per RECIST v1.1 at Week 25

Determination of an overall response for each timepoint was based on the combination of responses for target lesions, and the presence or absence of 1 or more new lesions per RECIST v1.1.

Table 29. Definitions of response for the primary efficacy endpoint in MOTION

Timepoint Response at Week 13	Timepoint Response at Week 25	End of Part 1 (Week 25) Tumour Response Status (Primary Efficacy Endpoint)
CR or PR	CR	Response (CR)
CR or PR	PD	Nonresponse (PD)
PR	Non-CR/non-PD/non-NE[a]	Response (PR)[b]
SD	CR or PR	Response (CR or PR)
SD	SD	Nonresponse (SD)
SD	PD	Nonresponse (PD)[c]
CR, PR, SD, and NE	NE	Nonresponse (NE)
PD	Any	Nonresponse (PD)
NE	CR or PR	Response (CR or PR)
NE	SD or PD	Nonresponse (SD or PD)

Abbreviations: CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

[a] Neither sufficient shrinkage to qualify for CR nor sufficient increase to qualify for PD, taking as reference the nadir at Week 13.

[b] A tumour that has achieved the criteria of PR will be considered an ongoing PR until PD is objectively documented.

c To be considered SD, the tumour must achieve the criteria for SD at the Week 25 visit; shorter duration SD will not be considered SD at the End of Part 1.

Table 30. Objective response rate per RECIST v1.1 at week 25 (double-blind period) based on IRR, ITT set

Parameter	Vimseltinib N=83	Placebo N=40
Overall response at Week 25 (End of Part 1 Visit), n1[a]	83	40
CR, n (%)	4 (4.8)	0
PR, n (%)	29 (34.9)	0
SD, n (%)	42 (50.6)	33 (82.5)
PD, n (%)	0	0
NE, n (%)	8 (9.6)	7 (17.5)
Reason for NE, n (%)		
No post-baseline scan available	0	2 (5.0)
Week 25 scan outside analysis window	3 (3.6)	2 (5.0)
Discontinued Part 1 prior to Week 25	5 (6.0)	2 (5.0)
No adequate scan at Week 25	0	1 (2.5)
Objective response rate (CR+PR), n (%)	33 (39.8)	0
95% exact CI[b]	(29.2, 51.1)	(0.0, 8.8)
Difference in objective response rate (vimseltinib vs placebo), % (95% CI)		
Stratified Mantel-Haenszel with stratification factors based on IRT[c]	39.0 (28.4, 49.6)	
Unstratified Wald	39.8 (29.2, 50.3)	
Unstratified Exact	39.8 (28.8, 51.1)	
CMH test p-value stratified by stratification factors based on IRT (primary analysis)[c]	<0.0001	
Chi-square test p-value (sensitivity analysis)	<0.0001	
Fisher exact test p-value (sensitivity analysis)	<0.0001	

Abbreviations: CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CR=complete response; IRR=independent radiological review; IRT=interactive response technology; ITT=intent-to-treat; n=number of participants in a category; N=sample size; NE=not evaluable; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.

a n1=all participants in the ITT Set who reached the timepoint for which data were being summarized or discontinued from the study prior to Week 25 (End of Part 1 Visit). Percentage was based on n1. The determination of the tumour response status for each participant at Week 25 (End of Part 1 Visit) with respect to the primary efficacy endpoint was based on Table 8.

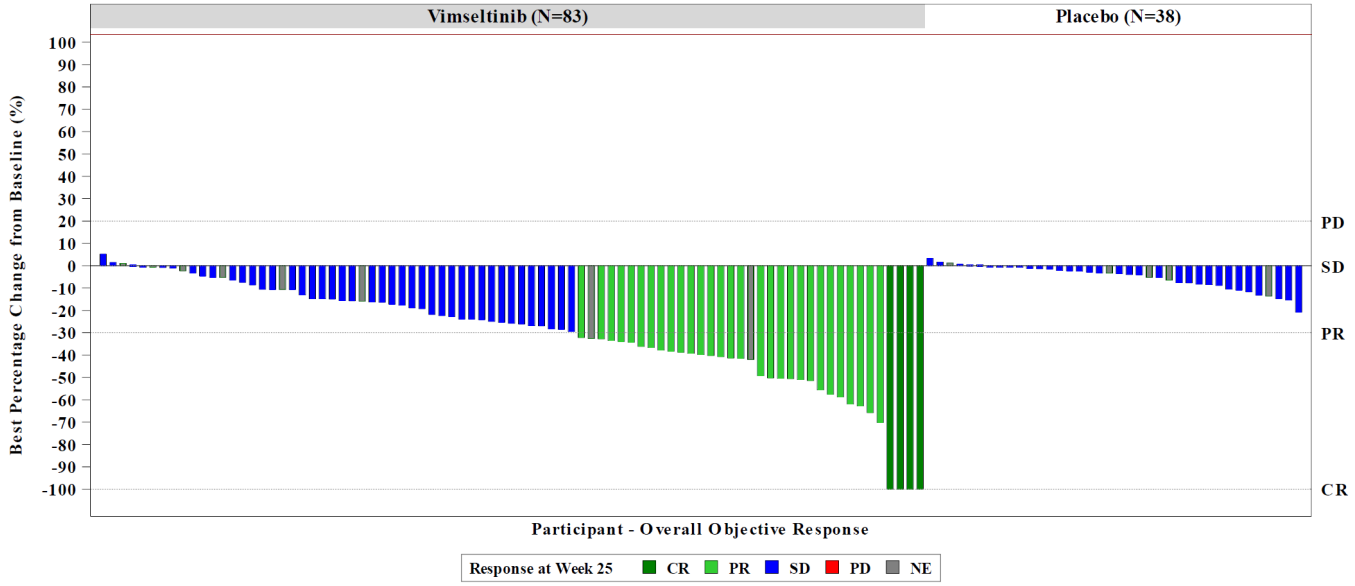
b Two-sided 95% exact CI for the proportion in each arm was computed using the Clopper-Pearson method.

c Stratified by tumour location (lower limb/all other) and region (U.S./non-U.S.) based on IRT.

Note 1: Participants who did not have an End of Part 1 assessment for any reason or whose Week 25 assessment was after the first dose in the open-label extension or outside of the visit window of ±14 days were assessed as NE and a non-responder.

Note 2: A participant who had a scan performed in visit window but was not evaluable by IRR was NE due to "No adequate scan at Week 25".

Figure 17. Waterfall plot of overall objective response in target lesions per RECIST v1.1 at week 25 (double-blind period) based on IRR, ITT Set (2:1 randomisation)



Abbreviations: CR=complete response; IRR=independent radiological review; ITT=intent-to-treat; N=sample size; NE=not evaluable; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumors; SD=stable disease.
Note: Participants with target lesion(s) at baseline and at least 1 post-baseline assessment were shown. Baseline was defined as the most recent non-missing measurement prior to the first administration of study drug

Table 31. Sensitivity analysis of objective response rate per RECIST v1.1 up to week 25 (double-blind period) based on IRR, ITT set

Parameter	Vimseltinib N=83	Placebo N=40
Overall response up to Week 25 (End of Part 1 Visit), n1[a]	83	40
CR, n (%)	4 (4.8)	0
PR, n (%)	31 (37.3)	0
SD, n (%)	48 (57.8)	38 (95.0)
PD, n (%)	0	0
NE, n (%)	0	2 (5.0)
Reason for NE, n (%)		
No post-baseline scan available	0	2 (5.0)
Objective response rate (CR+PR), n (%)	35 (42.2)	0
95% exact CI[b]	(31.4, 53.5)	(0.0, 8.8)
Difference in objective response rate (vimseltinib vs placebo), % (95% CI)		
Stratified Mantel-Haenszel with stratification factors based on IRT[c]	41.4 (30.8, 52.1)	
Unstratified Wald	42.2 (31.5, 52.8)	
Unstratified Exact	42.2 (31.2, 53.5)	
CMH test p-value stratified by stratification factors based on IRT (primary analysis)c	<0.0001	
Chi-square test p-value (sensitivity analysis)	<0.0001	
Fisher exact test p-value (sensitivity analysis)	<0.0001	

Abbreviations: CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CR=complete response; IRR=independent radiological review; IRT=interactive response technology; ITT=intent-to-treat; n=number of participants in a category; N=sample size; NE=not evaluable; PD=progressive disease; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; SD=stable disease.

a n1=all participants in the ITT Set who reached the timepoint for which data were being summarized or discontinued from the study prior to Week 25 (End of Part 1 Visit). Percentage was based on n1. Any participant who met the criteria for response at least once up to, and including, Week 25 would be counted as a responder.
b Two-sided 95% exact CI for the proportion in each arm was computed using the Clopper-Pearson method.
c Stratified by tumour location (lower limb/all other) and region (U.S./non-U.S.) based on IRT.
Note 1: Participants who did not have an End of Part 1 assessment for any reason or whose Week 25 assessment was after the first dose in the open-label extension or outside of the visit window of ±14 days were assessed as NE and a non-responder.
Note 2: A participant who had a scan performed in visit window but was not evaluable by IRR was NE due to "No adequate scan at Week 25".

Key Secondary Efficacy Outcome

a.) Objective Response Rate per TVS at Week 25

Table 32. Objective response rate per TVS at week 25 (double-blind period) based on IRR, ITT set

Parameter	Vimseltinib N=83	Placebo N=40
Overall response at Week 25 (End of Part 1 Visit), n1[a]	83	40
CR, n (%)	4 (4.8)	0
PR, n (%)	52 (62.7)	0
SD, n (%)	19 (22.9)	34 (85.0)
PD, n (%)	0	1 (2.5)
NE, n (%)	8 (9.6)	5 (12.5)
Reason for NE, n (%)		
No post-baseline scan available	0	2 (5.0)
Week 25 scan outside analysis window	3 (3.6)	2 (5.0)
Discontinued Part 1 prior to Week 25	5 (6.0)	1 (2.5)
Objective response rate (CR+PR), n (%)	56 (67.5)	0
95% exact CI[b]	(56.3, 77.4)	(0.0, 8.8)
Difference in objective response rate (vimseltinib vs placebo), % (95% CI)		
Stratified Mantel-Haenszel with stratification factors based on IRT[c]	67.2 (57.0, 77.3)	
Unstratified Wald	67.5 (57.4, 77.5)	
Unstratified Exact	67.5 (56.1, 77.4)	
CMH test p-value stratified by stratification factors based on IRT (primary analysis)[c]	<0.0001	
Chi-square test p-value (sensitivity analysis)	<0.0001	
Fisher exact test p-value (sensitivity analysis)	<0.0001	

Abbreviations: CI=confidence interval; CMH=Cochran-Mantel-Haenszel; CR=complete response; IRR=independent radiological review; IRT=interactive response technology; ITT=intent-to-treat; n=number of participants in a category; N=sample size; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease; TVS=tumour volume score.
a n1=all participants in the ITT Set who reached the timepoint for which data were being summarized or discontinued from the study prior to Week 25 (End of Part 1 Visit). Percentage was based on n1. The determination of the tumour response status for each participant at Week 25 (End of Part 1 Visit) with respect to the primary efficacy endpoint was based on Table 8.
b Two-sided 95% exact CI for the proportion in each arm was computed using the Clopper-Pearson method. c Stratified by tumour location (lower limb/all other) and region (U.S./non-U.S.) based on IRT.
Note 1: Participants who did not have an End of Part 1 assessment for any reason or whose Week 25 assessment was after the first dose in the open-label extension or outside of the visit window of ±14 days were assessed as NE and a non-responder.
Note 2: A participant who had a scan performed in visit window but was not evaluable by IRR was NE due to "No adequate scan at Week 25".

ORR by TVS at Week 25 was as key secondary endpoint for tumour response, in addition to the single dimension measurements per RECIST v1.1 used as the primary endpoint, considering the irregular tumours shapes in TGCT .

b.) Active Range of Motion Relative to Reference Standard at Week 25

Table 33. Change from baseline at week 25 in active ROM per AMA standard with MMRM model in double-blind period, ITT set

Parameter	Vimseltinib (N=83)	Placebo (N=40)
n at baseline [a]	79	38
Mean (STD)	63.0 (29.37)	62.9 (32.22)
Median	71.1	66.7
Min, max	0, 107	0, 111
n at Week 25	73	33
Mean (STD)	83.6 (28.12)	68.3 (35.31)
Median	88.9	77.8
Min, max	0, 150	0, 126
Change from baseline [a]		
Mean (STD)	19.3 (31.48)	4.2 (25.57)
Median	11.1	0.0
Min, max	-30, 150	-61, 100
MMRM model (vimseltinib vs placebo) [b]		
LS mean (SE)	18.4 (6.46)	3.8 (7.19)
95% CI of LS mean	(5.6, 31.2)	(-10.5, 18.0)
Difference (95% CI) in LS mean	14.6 (4.0, 25.3)	
p-value	0.0077	

Abbreviations: AMA=American Medical Association; CI=confidence interval; ITT=intent-to-treat; LS=least square; max=maximum; min=minimum; MMRM=mixed model repeated measures; n=number of participants in a category; N=sample size; ROM=range of motion; STD=standard deviation; SE=standard error.
a Baseline was defined as the most recent non-missing measurement prior to the first administration of study drug.
b Model included treatment+visit+treatment by visit interaction+stratification factor for region (U.S. versus non-U.S.)+joint type (knee, ankle, or other)+the most impaired ROM baseline value.

Measurement of the affected and contralateral, non-affected joint were assessed using a goniometer. The measurement (in degrees) of the affected joint was used to derive a relative ROM obtained through normalisation to the measurement from a reference standard value provided by the AMA per motion and type (active or passive).

If the missing data for all participants were imputed based on the mean value using multiple imputations for participants that received placebo, then the difference in LS mean (95% CI) in change from baseline in active ROM per AMA standard at Week 25 was 13.0% (2.7%, 23.3%) with a p-value of 0.0131.

Based on the Minimal clinically important difference (MCID) threshold of an improvement of at least 10% points, 48.2% of participants on vimseltinib versus 20.0% of participants on placebo experienced a clinically meaningful improvement with an estimated difference (95% CI) of 28.7% (12.2%, 45.2%).

c.) Change from Baseline in PROMIS-PF at Week 25

Fifteen questions from the PROMIS-PF item bank were asked regardless of tumour location for the individual participant. The questions use one of two 5-point verbal rating scales: either 1="unable to do", 2="with much difficulty", 3="with some difficulty", 4="with a little difficulty", and 5="without any difficulty"; or 1="cannot do", 2="quite a lot", 3="somewhat", 4="very little", and 5="not at all." There was no specified recall period. The subset of questions used for scoring was based on the location of the tumour (upper or lower body) based on Gelhorn et al, 2016.

Table 34. Change from baseline at week 25 in PROMIS-PF with MMRM model in double-blind period, ITT set

Parameter	Vimseltinib (N=83)	Placebo (N=40)
n at baseline [a]	83	40
Mean (STD)	39.0 (6.14)	38.5 (5.98)
Median	39.0	38.5
Min, max	23, 51	24, 61
n at Week 25	63	30
Mean (STD)	43.7 (6.13)	40.7 (6.74)
Median	43.0	39.0
Min, max	32, 62	29, 61
Change from baseline [a]		
Mean (STD)	4.6 (6.27)	1.1 (4.15)
Median	3.0	0.5
Min, max	-8, 29	-5, 10
MMRM model with stratification factor based on IRT (vimseltinib vs placebo) [b]		
LS mean (SE)	4.6 (0.96)	1.3 (0.88)
95% CI of LS mean	(2.7, 6.5)	(-0.5, 3.0)
Difference (95% CI) in LS mean	3.3 (1.4, 5.2)	
p-value	0.0007	

Abbreviations: CI=confidence interval; IRT=interactive response technology; ITT=intent-to-treat; LS=least square; max=maximum; min=minimum; MMRM=mixed model repeated measures; n=number of participants in a category; N=sample size; PROMIS-PF=Patient-reported Outcomes Measurement Information System-Physical Function; STD=standard deviation; SE=standard error.
a Baseline was defined as the most recent non-missing measurement prior to the first administration of study drug.
b Model included treatment+visit+treatment by visit interaction+stratification factor for region (U.S. versus non- U.S.) and tumour location (lower limb/all other) based on IRT+PROMIS-PF baseline value.

d.) Change from Baseline in Worst Stiffness Numeric Rating Scale (NRS) at Week 25

The main analysis of Worst Stiffness NRS in the past 24 hours consisted of a comparison between treatment groups of the mean change from baseline at Week 25 using a MMRM. The different timepoints included in the model were Weeks 5, 9, 13, 17, 21, and 25, which respectively correspond to Day 1 of Cycles 2, 3, 4, 5, 6, and 7.

Table 35. Change from baseline at week 25 in worst stiffness NRS with MMRM model in double-blind period, ITT set

Parameter	Vimseltinib (N=83)	Placebo (N=40)
n at baseline [a]	83	40
Mean (STD)	5.1 (2.00)	5.2 (1.81)
Median	5.3	5.6
Min, max	0, 8	1, 8
n at Week 25	63	27
Mean (STD)	2.9 (2.07)	4.3 (1.90)
Median	2.6	4.1
Min, max	0, 8	0, 7
Change from baseline [a]		
Mean (STD)	-2.2 (2.07)	-0.6 (1.47)
Median	-2.1	-0.4
Min, max	-8, 3	-4, 3
MMRM model with stratification factor based on IRT (vimseltinib vs placebo) [b]		
LS mean (SE)	-2.1 (0.24)	-0.3 (0.28)
95% CI of LS mean	(-2.5, -1.6)	(-0.8, 0.3)
Difference (95% CI) in LS mean	-1.8 (-2.5, -1.1)	
p-value	<0.0001	

Abbreviations: CI=confidence interval; IRT=interactive response technology; ITT=intent-to-treat; LS=least square; max=maximum; min=minimum; MMRM=mixed model repeated measures; n=number of participants in a category; N=sample size; NRS=numeric rating scale; STD=standard deviation; SE=standard error.
a Baseline was defined as the most recent non-missing measurement prior to the first administration of study drug.
b Model included treatment+visit+treatment by visit interaction+stratification factor for region (U.S. versus non- U.S.) and tumour location (lower limb/all other) based on IRT+Worst Stiffness NRS baseline value.

e.) Change from Baseline in EQ-5D-5L VAS at Week 25

The main analysis of the EQ-VAS consisted of a comparison between treatment groups of the mean change from baseline at Week 25 using a MMRM. The different timepoints included in the model were Weeks 5, 9, 13, 17, 21, and 25, which respectively correspond to Day 1 of Cycles 2, 3, 4, 5, 6, and 7. Values for analysis were the earliest collected value in each cycle.

The observed value and change from baseline in EQ-VAS were summarized with descriptive statistics by timepoint and treatment group.

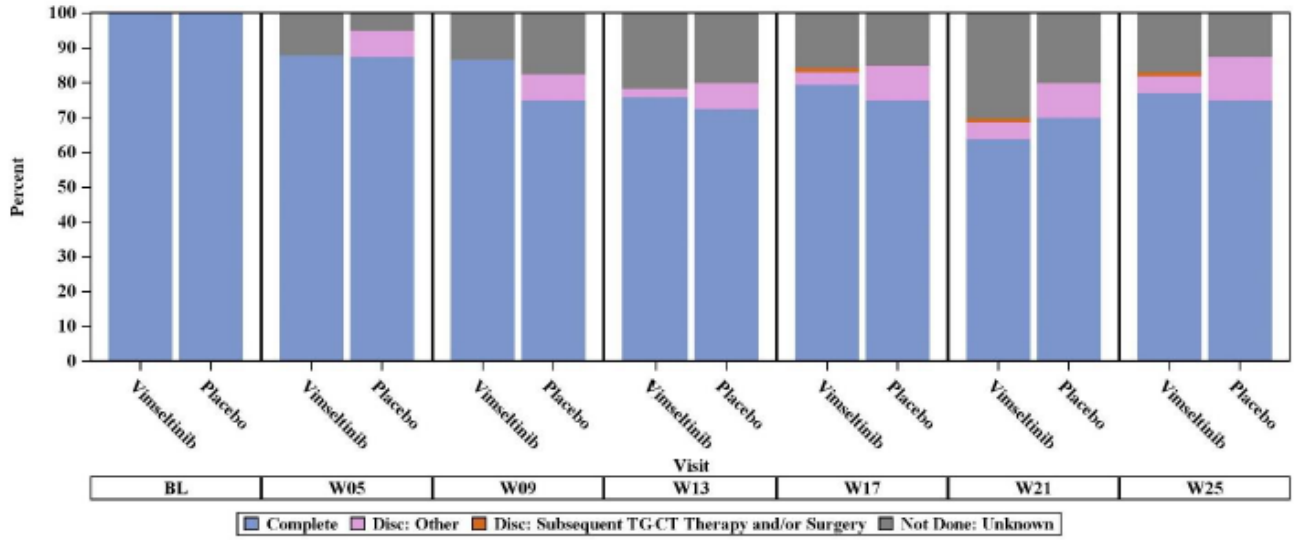
Table 36. Change from baseline at week 25 in EQ-5D-5L VAS with MMRM model in double-blind period, ITT set

Parameter	Vimseltinib (N=83)	Placebo (N=40)
n at baseline [a]	83	40
Mean (STD)	61.4 (19.53)	60.2 (20.63)
Median	65.0	63.0
Min, max	10, 95	15, 92
n at Week 25	64	30
Mean (STD)	74.1 (14.99)	67.5 (15.94)
Median	75.0	70.5
Min, max	40, 98	40, 92
Change from baseline [a]		
Mean (STD)	12.0 (19.92)	4.0 (17.29)
Median	6.0	2.0
Min, max	-44, 75	-29, 60
MMRM model with stratification factor based on IRT (vimseltinib vs placebo) [b]		
LS mean (SE)	13.5 (2.35)	6.1 (2.85)

Parameter	Vimseltinib (N=83)	Placebo (N=40)
95% CI of LS mean	(8.9, 18.2)	(0.5, 11.8)
Difference (95% CI) in LS mean	7.4 (1.4, 13.4)	
p-value	0.0155	

Abbreviations: CI=confidence interval; IRT=interactive response technology; ITT=intent-to-treat; LS=least square; max=maximum; min=minimum; MMRM=mixed model repeated measures; n=number of participants in a category; N=sample size; STD=standard deviation; SE=standard error; VAS=Visual Analogue Scale.
a Baseline was defined as the most recent non-missing measurement prior to the first administration of study drug.
b Model included treatment+visit+treatment by visit interaction+stratification factor for region (U.S. versus non-U.S.) and tumour location (lower limb/all other) based on IRT+VAS baseline value.
Note: Week 25 included result

Figure 18. Available data rate for EQ-5D-5L VAS in double-blind period, ITT set



Abbreviations: BL=baseline; Disc=discontinuation; ITT=intent-to-treat; TGCT=tenosynovial giant cell tumour; VAS=Visual Analogue Scale; W=Week.

f.) Brief Pain Inventory – BPI Worst Pain NRS Response at Week 25

A responder analysis based on the BPI Worst Pain NRS item and analgesic use was performed. A responder was defined as a participant who: (i) experienced a decrease of at least 30% in the mean BPI Worst Pain NRS item and (ii) did not experience a 30% or greater increase in narcotic analgesic use. The change in BPI Worst Pain NRS for responder assessment was assessed by comparing data collected during a 14-day period prior to the current visit with baseline values collected prior to the first dose of study drug. This was referenced as BPI-30 response.

Table 37. BPI-30 worst pain NRS response rate with CMH test at week 25, ITT set

Parameter	Vimseltinib N=83	Placebo N=40
Patients with valid mean Worst Pain NRS at baseline and Week 25, n (%)	68 (81.9)	31 (77.5)
Patients with decrease of at least 30% in the mean Worst Pain NRS item, n (%)	40 (48.2)	9 (22.5)
Patients without a 30% or greater increase in narcotic analgesic data, n (%)	81 (97.6)	38 (95.0)
Number of responders [a]	40	9
Responder rate (%)	48.2	22.5
95% exact CI [b]	(37.1, 59.4)	(10.8, 38.5)
Difference in responder rate (vimseltinib vs placebo), % (95% CI)		
Stratified Wald with stratification factors based on IRT [c]	26.2 (9.5, 42.8)	
Unstratified Wald	25.7 (8.9, 42.5)	
Unstratified Exact	25.7 (4.1, 41.6)	
CMH test p-value stratified by stratification factors based on IRT (primary analysis)c	0.0056	
Chi-square test p-value (sensitivity analysis)	0.0064	
Fisher exact test p-value (sensitivity analysis)	0.0101	

Abbreviations: BPI=Brief Pain Inventory; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; IRT=interactive response technology; ITT=intent-to-treat; n=number of participants in a category; N=sample size; NRS=numeric rating scale.
a A responder was defined as a participant who: (i) experienced a decrease of at least 30% in the mean BPI Worst Pain NRS item and (ii) did not experience a 30% or greater increase in narcotic analgesic use.
b Two-sided 95% exact CI for the proportion in each arm was computed using the Clopper-Pearson method.
c Stratified by tumour location (lower limb/all other) and region (U.S./non-U.S.) based on IRT.

Responder rate was 48.2% (95% CI: 37.1%, 59.4%) for the vimseltinib arm and 22.5% (95% CI: 10.8%, 38.5%) for the placebo arm. The stratified difference in Worst Pain response rate was 26.2% (95% CI: 9.5%, 42.8%; p=0.0056) based on IRT.

In the responders patients who achieved at least 30% reduction in BPI Worst Pain NRS, there was no increase reported in narcotic analgesic use.

g.) Duration of Response

Duration of response was defined as the time from the first documented objective response (CR or PR) until the time of disease progression or death by any cause, whichever occurred earlier.

DOR was summarized in 2 sets of participants, firstly for participants with an objective response at Week 25 and secondly for those who achieved CR or PR as BOR on study to the study treatment in the ITT Set.

Table 38. Duration of response for objective responders at week 25 based on IRR per RECIST v1.1 and TVS by treatment, ITT set

Categories	RECIST v1.1		TVS	
	Vimseltinib N=83	Placebo N=40	Vimseltinib N=83	Placebo N=40
Participants with objective response (CR+PR), n (%)[a]	33 (39.8)	0	56 (67.5)	0
Time to response (CR+PR) (weeks)[b]				
n	33	0	56	0
Mean (STD)	16.7 (5.96)	-- (--)	13.5 (4.00)	-- (--)
Median	12.7	--	12.0	--
Min, max	11, 26	--, --	11, 24	--, --
Number of participants with event, n (%)[c]	1 (3.0)	0	1 (1.8)	0
Progressive disease	1 (3.0)	0	0	0
Death	0	0	1 (1.8)	0
Number of participants censored, n (%)[c]	32 (97.0)	0	55 (98.2)	0
Last evaluable radiological assessment prior to 2 consecutive NE/missing	1 (3.0)	0	1 (1.8)	0
Last evaluable radiological assessment	31 (93.9)	0	54 (96.4)	0
Kaplan-Meier estimates of DOR in responders (Weeks)[d]				
Median (95% CI)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)	NE (NE, NE)
Min, max	0.1+, 50.9+	NE, NE	0.1+, 60.4+	NE, NE
Kaplan-Meier estimates of duration of follow-up (Weeks)[e]				
Median (95% CI)	24.14 (13.29, 35.29)	NE (NE, NE)	28.14 (24.14, 36.14)	NE (NE, NE)
DOR (months) by category, n (%)c				
<6 months	19 (57.6)	0	27 (48.2)	0
≥6 to <12 months	14 (42.4)	0	27 (48.2)	0
≥12 to <18 months	0	0	2 (3.6)	0

Abbreviations: CI=confidence interval; CR=complete response; DOR=duration of response; IRR=independent radiological review; ITT=intent-to-treat;
max=maximum; min=minimum; n=number of participants in a category; N=sample size; NE=not evaluable; PR=partial response; RECIST=Response Evaluation
Criteria in Solid Tumors; SAP=Statistical Analysis Plan; STD=standard deviation; TVS=tumour volume score.
a Percentage is based on participants in ITT Set.
b Time to response was defined as the time in weeks from Cycle 1 Day 1 to achieving first CR or PR.
c Percentage was based on participants with responders in ITT Set.
d Duration of response was defined as the time from the first documented objective response (CR or PR) until the time of disease progression or death by any cause, whichever occurred earlier. The DOR in weeks was calculated as (earlier of date of progressive disease or death, or censoring–date of first response+1)/7. Participants who did not have disease progression (per radiological assessment) or death were censored according to the rules in SAP v2.0. The plus (+) sign for the min or max indicated that the participant was still in response.
e Summary based on reverse Kaplan-Meier method reversing the event/censoring flag as specified in Schemper and Smith, 1996.
Note: Data cutoff date was 22 Aug 2023.

Table 39. Duration of response for objective responders at week 25 based on IRR per RECIST v1.1 and TVS by treatment, ITT set - updated analysis

Categories	RECIST v1.1		TVS	
	Vimseltinib N=83	Placebo N=40	Vimseltinib N=83	Placebo N=40
Kaplan-Meier estimates of duration of follow-up (Weeks)[a]				
Median (95% CI)	48.57 (36.14, 58.29)	NE (NE, NE)	48.43 (38.86, 59.86)	NE (NE, NE)
DOR (months) by category, n (%)c				
<6 months	5 (15.2)	0	8 (14.3)	0
≥6 to <12 months	16 (48.5)	0	25 (44.6)	0
≥12 to <18 months	10 (30.3)	0	20 (35.7)	0
≥18-<24 months	2 (6.1)	0	3 (5.4)	0

[a] Summary based on reverse Kaplan-Meier method reversing the event/censoring flag as specified in Schemper and Smith, 1996.
Data cutoff date: 22 Feb 2024

Twelve months from last participant randomized, i.e., 6 months of additional follow-up from the primary analysis.

Second DoR update:

The median DOR was not reached for responders on study using RECIST v1.1 (maximum DOR of 134 weeks with response ongoing) and for responders on study using TVS (maximum DOR of 144 weeks with response ongoing).

Table 40. Duration of response based on IRR per RECIST v1.1 and TVS for objective responders at week 25 (ITT set)

Categories	RECIST v1.1	TVS
	Vimseltinib (N=83)	Vimseltinib (N=83)
Number of participants with objective response (CR+PR) at Week 25, n (%)	33 (39.8)	56 (67.5)
Number of participants with events (PD or death), n (%)[1]	3 (9.1)	6 (10.7)
PD	3 (9.1)	5 (8.9)
Death	0	1 (1.8)
Number of participants censored	30 (90.9)	50 (89.3)
K-M estimate of DOR in responders, weeks[2]		
Median (95% CI)	NE (NE, NE)	NE (NE, NE)
Min, max	11.0+, 134.4+	10.4+, 143.7+
DOR (months) by category, n (%)[1]		
<6 months	5 (15.2)	8 (14.3)
≥6-<12 months	4 (12.1)	9 (16.1)
≥12-<18 months	3 (9.1)	7 (12.5)
≥18-<24 months	8 (24.2)	10 (17.9)
≥24-<36 months	13 (39.4)	22 (39.3)
Median (95% CI) duration of follow-up, weeks[3]	96.14 (74.29, 108.71)	96.29 (73.43, 108.71)

Abbreviations: CI=confidence interval; CR=complete response; DOR=duration of response; IRR=independent radiological review; ITT=Intent-to-Treat; K-M=Kaplan-Meier; max=maximum; min=minimum; n=number of participants in the category; N=sample size; NE=not evaluable; PD=progressive disease; PR=partial response; RECIST v1.1=Response Evaluation Criteria in Solid Tumors v1.1; SAP=statistical analysis plan; TVS=tumour volume score.
Note 1: Data cutoff was 22 Feb 2025.
[1] Percentage is calculated among participants in the ITT Set with an objective response at Week 25.
[2] DOR is defined as the time from the first documented objective response (CR or PR) until the time of disease progression or death by any cause, whichever occurs earlier. DOR in weeks is calculated as (earlier of date of PD or death, or censoring–date of first response+1)/7. Participants who do not have disease progression (per radiologic assessment) or death are censored according to the rules in SAP. The plus (+) sign for the Min or Max indicates that the participant is still in response.
[3] Summary based on reverse K-M method reversing the event/censoring flag as specified in Schemper and Smith, 1996.

Characterisation of the Complete responses:

Of the 4 participants with CR at Week 25 per RECIST v1.1, 2 participants were still in CR at their last radiological assessment prior to the latest data cutoff, 22 Feb 2025; 1 participant's last radiological assessment was at Cycle 19 (~18 months on study), which was still a CR; and the final participant in CR had no further evaluable scans after Week 25 since they discontinued at Week 25.

Table 41 shows the analysis of the time to CR and DOCR for the 19 out of 83 participants (2.9%) with a BOR of CR. The median time to CR was 50.1 weeks for the 19 participants randomized to vimseltinib who experienced a CR. The median follow-up and corresponding 95% CI were 36.9 (12.1, 71.3) weeks.

The mean (SD) tumour size at baseline for participants who achieved a CR was 49.6 (29.22) mm compared with 69.1 (42.56) mm for all participants randomized to vimseltinib.

Table 41. Summary of time to CR and DOCR based on independent radiological review per RECIST v1.1 (ITT set), MOTION at Week 97 (cut-off date:22 Feb 2025)

Category	Vimseltinib (N=83)
Participants with CR, n (%)[a]	19 (22.9)
Baseline tumour size of target lesions for participants with BOR of CR, mm	
n	19
Mean (SD)	49.60 (29.217)
Median	36.20
Min, max	22.1, 120.9
Time to CR, weeks[b]	
n	19
Mean (SD)	65.7 (42.40)
Median	50.1
Min, max	11, 146
Number of participants with event, n (%)[c]	0
PD	0
Death	0
Number of participants censored, n (%)[c]	19 (100.0)
Last evaluable radiological assessment prior to the start of new anticancer therapy	1 (5.3)
Last evaluable radiological assessment prior to the 2 consecutive NE/missing assessments	0
Last evaluable radiological assessment	18 (94.7)
KM estimate of DOCR, weeks	
Median (95% CI)	NE (NE, NE)
Min, max	0.1^{+}, 133.7^{+}
Median (95% CI) duration of follow-up, weeks[d]	36.86 (12.14, 71.29)

Abbreviations: CI=confidence interval; CR=complete response; DB=double-blind; DOCR=duration of complete response; ITT=Intent-to-treat; KM=Kaplan-Meier; max=maximum; min=minimum; OL=open-label; PD=progressive disease; RECIST=Response Evaluation Criteria in Solid Tumors; SAP=Statistical Analysis Plan; SD=standard deviation.

[a] Percentage is based on participants in the ITT set.

[b] Time to CR was defined as (Cycle 1 Day 1 date–date of first CR+1)/7.

[c] Percentage is based on participants with objective response in ITT set.

[d] Summary based on reverse Kaplan-Meier method reversing the event/censoring flag as specified in Schemper and Smith (1996).

Note 1: Data cutoff date was 22 Feb 2025.

Note 2: DOR is defined as the time from the first documented CR until the time of disease progression or death by any cause, whichever occurs earlier. DOCR in weeks is calculated as: (earlier of date of PD or death, or censoring–date of first CR+1)/7. Participants who do not have disease progression (per radiologic assessment) or death are censored according to the rules in SAP. The plus (+) sign for the min or max indicates that the participant is still in response.

Ancillary analyses

Table 42. Summary of treatment differences at week 25 by prior radiation use, ITT set

	Prior Radiation		No Prior Radiation	
	Vimseltinib (N=9)	**Placebo (N=2)**	**Vimseltinib (N=74)**	**Placebo (N=38)**
Overall Response at Week 25 per RECIST v 1.1	9	2	74	38
Complete Response (CR), n (%)	0	0	4 (5.4)	0
Partial Response (PR), n (%)	5 (55.6)	0	24 (32.4)	0
Stable Disease (SD), n (%)	4 (44.4)	2 (100.0)	38 (51.4)	31 (81.6)
Progressive Disease (PD), n (%)	0	0	0	0
Not Evaluable (NE), n (%)	0	0	8 (10.8)	7 (18.4)
Objective Response Rate (CR+PR), n (%)	5 (55.6)	0	28 (37.8)	0
[95% Exact CI] [1]	(21.2, 86.3)	(0.0, 84.2)	(26.8, 49.9)	(0.0, 9.3)
Difference in ORR (vimseltinib vs placebo), % (95% CI) [1]	55.6 (-31.1, 86.4)		37.8 (26.3, 49.9)	
Fisher's Exact p-value	0.4545		< 0.0001	
Overall Response at Week 25 per TVS	9	2	74	38
Complete Response (CR), n (%)	0	0	4 (5.4)	0
Partial Response (PR), n (%)	7 (77.8)	0	45 (60.8)	0
Stable Disease (SD), n (%)	2 (22.2)	2 (100.0)	17 (23.0)	32 (84.2)
Progressive Disease (PD), n (%)	0	0	0	1 (2.6)
Not Evaluable (NE), n (%)	0	0	8 (10.8)	5 (13.2)
Objective Response Rate (CR+PR), n (%)	7 (77.8)	0	49 (66.2)	0
[95% Exact CI] [1]	(40.0, 97.2)	(0.0, 84.2)	(54.3, 76.8)	(0.0, 9.3)
Difference in ORR (vimseltinib vs placebo), % (95% CI) [1]	77.8 (-13.0, 98.7)		66.2 (54.1, 76.8)	
Fisher's Exact p-value	0.1091		< 0.0001	
Mean change from baseline in active ROM at Week 25 [2]				
Baseline Mean	68.6	88.9	62.3	61.4
Number with data at Baseline and Week 25	8	2	65	31
LS Mean at Week 25 (95% CI)	7.8 (-3.9, 19.6)	-1.7 (-10.9, 7.6)	18.0 (4.3, 31.7)	1.4 (-13.8, 16.7)
Difference in LS Means (95%CI)	9.5 (-3.5, 22.5)		16.6 (4.7, 28.5)	
p-value	0.1250		0.0068	
Mean change from baseline in PROMIS-PF at Week 25 [2]				
Baseline Mean	39.9	43.0	38.8	38.2
Number with data at Baseline and Week 25	8	2	55	28
LS Mean at Week 25 (95% CI)	2.1 (-0.4, 4.6)	2.7 (-3.7, 9.1)	5.1 (3.3, 6.8)	1.1 (-1.0, 3.3)
Difference in LS Means (95%CI)	-0.6 (-7.7, 6.5)		3.9 (1.6, 6.2)	
p-value	0.8385		0.0010	
Mean change from baseline in Worst Stiffness NRS at Week 25 [2]				
Baseline Mean	4.5	3.8	5.2	5.3

	Prior Radiation		No Prior Radiation	
	Vimseltinib (N=9)	**Placebo (N=2)**	**Vimseltinib (N=74)**	**Placebo (N=38)**
Number with data at Baseline and Week 25	8	2	55	25
LS Mean at Week 25 (95% CI)	-1.6 (-2.8, -0.5)	-0.9 (-3.0, 1.3)	-2.4 (-3.1, -1.7)	-0.9 (-1.7, -0.1)
Difference in LS Means (95%CI)	-0.7 (-2.8, 1.3)		-1.5 (-2.3, -0.8)	
p-value	0.4239		0.0001	
Mean change from baseline in EQ-5D-5L VAS at Week 25 [2]				
Baseline Mean	65.6	67.0	60.9	59.9
Number with data at Baseline and Week 25	8	2	56	28
LS Mean at Week 25 (95% CI)	9.2 (1.3, 17.0)	19.4 (17.2, 21.5)	12.9 (6.9, 19.0)	4.5 (-2.8, 11.9)
Difference in LS Means (95%CI)	-10.2 (-18.5, -1.9)		8.4 (1.9, 14.9)	
p-value	0.0233		0.0119	
BPI Worst Pain NRS Responders [3]				
Responders (Response Rate), n (%)	5 (55.6)	0	35 (47.3)	9 (23.7)
[95% Exact CI] [1]	(21.2, 86.3)	(0.0, 84.2)	(35.6, 59.3)	(11.4, 40.2)
Difference in Responder Rate (vimseltinib vs placebo), % (95% CI) [1]	55.6 (-31.1, 86.4)		23.6 (2.6, 40.4)	
Fisher's Exact p-value	0.4545		0.0239	

AMA=American Medical Association; BPI=Brief Pain Inventory; CI=confidence interval; CR=complete response; EQ-5D-5L=5-level EQ-5D; ITT=Intent-to-Treat; LS=least-squares; MMRM=mixed model repeated measurement; NRS=numeric rating scale; PR=partial=response; PROMIS=Patient-Reported Outcomes Measurement Information System; ROM=range of motion; TVS=tumour volume score; VAS=Visual Analog Scale.

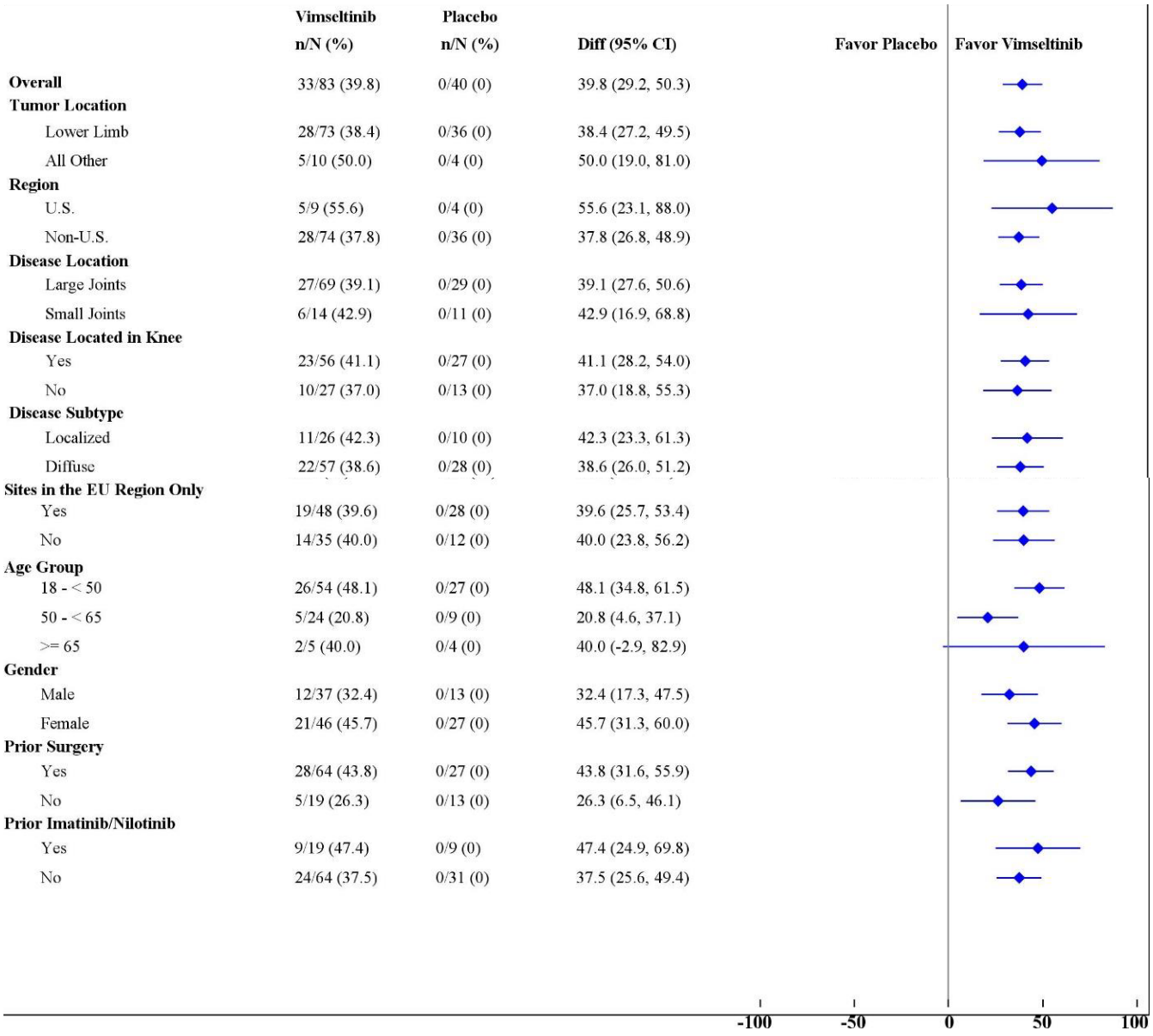
Note 1: Data cutoff 22 Aug 2023.

[1] Two-sided 95% exact confidence interval for the proportion in each arm is computed using the Clopper-Pearson method.

[2] Mean change from baseline was estimated from the MMRM for each corresponding endpoint. Baseline means presented include all participants and not only the ones with data at baseline and Week 25. Active ROM was normalized to the AMA reference standard.

[3] Response of at least a 30% improvement in the mean BPI Worst Pain NRS score without a 30% or greater increase in narcotic analgesic use at Week 25.

Figure 19. Forest plot of treatment difference in objective response rate (95% CI) per RECIST v1.1 at week 25 (double-blind period) based on IRR by subgroups, ITT set



Summary of main efficacy results

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

Table 43. Summary of efficacy for trial DCC-3014-03-001 (MOTION)

Title: A Phase 3, Randomized, Placebo-controlled, Double-blind Study of Vimseltinib to Assess the Efficacy and Safety in Patients with Tenosynovial Giant Cell Tumor			
Study identifier	DCC-3014-03-001 (MOTION) EudraCT No: 2020-004883-25 NCT No: NCT05059262		
Design	2-part, multicentre, randomized, placebo-controlled, double-blind Phase 3 study		
	Duration of Part 1: Duration of Part 2:		24 weeks (double-blind) 24 weeks (open label), Part 2 continues until all participants have either reached at least the Week 49 Visit or withdrew from the trial. Participants who completed Part 2 were allowed to continue vimseltinib treatment for longer efficacy
Hypothesis	Superiority		
Treatments groups	Vimseltinib		Part 1: 30 mg twice weekly, 24 weeks, N=83 Part 2: 30 mg twice weekly, 24 weeks Extension of treatment: 30 mg twice weekly, until radiological confirmation of disease progression as defined in the protocol, unacceptable toxicity, withdrawal by participant, physician's decision, or commercial availability of vimseltinib
	Placebo		Part 1: Matching placebo, 24 weeks, N=40 (1 participant not treated) Part 2: Vimseltinib 30 mg twice weekly, 24 weeks Extension of treatment: Vimseltinib 30 mg twice weekly, until radiological confirmation of disease progression as defined in the protocol, unacceptable toxicity, withdrawal by participant, physician's decision, or commercial availability of vimseltinib
Endpoints and definitions	Primary endpoint	ORR	Objective response rate (CR+PR) based on RECIST v1.1 at Week 25 (central blinded independent radiologic review (IRR); no confirmation)
	Secondary endpoint	ORR per TVS	ORR per Tumour Volume Score as defined by the proportion of participants with a CR or PR at Week 25
	Secondary endpoint	ROM	Mean change from baseline in active Range of Motion of the affected joint, relative to a reference standard, at Week 25

	Secondary endpoint	PROMIS-PF	Mean change from baseline in the Patient-reported Outcomes Measurement Information System Physical Function score at Week 25
	Secondary endpoint	Worst stiffness NRS	Mean change from baseline in the Worst Stiffness Numeric Rating Scale score at Week 25
	Secondary endpoint	EQ-5D-5L VAS	Mean change from baseline in EuroQol Visual Analogue Scale at Week 25
	Secondary endpoint	BPI-30 Worst Pain NRS response rate	Response of at least a 30% improvement in the mean Brief Pain Inventory Worst Pain Numeric Rating Scale score without a 30% or greater increase in narcotic analgesic use at Week 25
	Secondary endpoint	DOR	Duration of response (time from first PR or CR to disease progression or death) assessed using RECIST v1.1
Database lock	22 August 2023 (data cutoff date for primary analysis), 22 February 2024 (updated cutoff date for DOR only)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The ITT population defined as all participants who have been randomized to a study treatment regimen was the primary analysis set for all the efficacy endpoints analyses (N=123) The primary efficacy analyses were conduct at Week 25		
Descriptive statistics and estimate variability	Treatment group	Vimseltinib	Placebo
	Number of subjects	83	40
	CR per RECIST v1.1, n (%)	4 (4.8)	0
	PR er RECIST v1.1, n (%)	29 (34.9)	0
	ORR per RECIST v1.1, n (%) (95% exact CI)	33 (39.8) (29.2, 51.1)	0 (0.0, 8.8)
	ORR per TVS, n (%) (95% exact CI)	56 (67.5) (56.3, 77.4)	0 (0.0, 8.8)
	ROM, LS mean (SE) (95% CI of LS mean)	18.4 (6.46) (5.6, 31.2)	3.8 (7.19) (-10.5, 18.0)
	PROMIS-PF, LS mean (SE) (95% CI of LS mean)	4.6 (0.96) (2.7, 6.5)	1.3 (0.88) (-0.5, 3.0)

	Worst stiffness NRS, LS mean (SE) (95% CI of LS mean)	 -2.1 (0.24) (-2.5, -1.6)	 -0.3 (0.28) (-0.8, 0.3)
	EQ-5D-5L VAS, LS mean (SE) (95% CI of LS mean)	 13.5 (2.35) (8.9, 18.2)	 6.1 (2.85) (0.5, 11.8)
	BPI-30 Worst Pain NRS, Responder rate, % (95% exact CI)	 48.2 (37.1, 59.4)	 22.5 (10.8, 38.5)
	DOR (weeks)* KM median (95% CI) Min, Max	 NE (NE, NE) 11.0+, 84.4+	 NE (NE, NE) NE
Effect estimate per comparison	Primary endpoint: ORR	Comparison groups	Vimseltinib vs placebo
		Difference, %	40%
		(95% CI)	(28.4, 49.6)
		P-value (CMH 2-sided)	<0.0001
	Secondary endpoint: ORR per TVS	Comparison groups	Vimseltinib vs placebo
		Difference, %	67.2
		(95% CI)	(57.0, 77.3)
		P-value (CMH 2-sided)	<0.0001
	Secondary endpoint: ROM	Comparison groups	Vimseltinib vs placebo
		Difference, LS mean	14.6%
		(95% CI of LS mean)	(4.0, 25.3)
		P-value (MMRM 2-sided)	0.0077
	Secondary endpoint: PROMIS PF	Comparison groups	Vimseltinib vs placebo
		Difference LS mean (SE)	3.3
		(95% CI of LS mean)	(1.4, 5.2)
		P-value (MMRM 2-sided)	0.0007
	Secondary endpoint: Worst Stiffness NRS	Comparison groups	Vimseltinib vs placebo
		Difference, LS mean	-1.8
		(95% CI of LS mean)	(-2.5, -1.1)
		P-value (MMRM 2-sided)	<0.0001
	Secondary endpoint: EQ-5D-5L VAS	Comparison groups	Vimseltinib vs placebo
		Difference, LS mean	7.4
		(95% CI of LS mean)	(1.4, 13.4)
		P-value (MMRM 2-sided)	0.0155

	Secondary endpoint: BPI-30 Worst Pain NRS	Comparison groups	Vimseltinib vs placebo
		Difference, %	26.2
		(95% CI)	(9.5, 42.8)
		P-value (CMH 2-sided)	0.0056
Notes	*Updated data with data cutoff 22 February 2024		

2.6.5.3. 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	3/83	2/83	0/83
Non Controlled Trials	6/101	0/101	0/101

2.6.5.4. Supportive study(ies)

Phase I/II Trial DCC-3014-01-001

"A Multicenter Phase 1/2, Open-label Study of DCC-3014 to Assess the Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics in Patients with Advanced Tumors and Tenosynovial Giant Cell Tumor"

Study Sites – clinical	25 sites; Australia (1), Canada (2), France (2), Italy (3), the Netherlands (1), Poland (1), Spain (3), United Kingdom (1), United States (11).
Sponsor	Deciphera Pharmaceuticals, LLC 200 Smith Street Waltham, MA 02451 Phone: 781-209-6400
Clinical Phase Dates (first participant enrolled – last participant completed)	16 Feb 2017 - ongoing
Date of the Clinical Study Report	27 Jun 2023
Study Number	DCC-3014-01-001

Supportive data regarding efficacy and safety is claimed from Trial DCC-3014-01-001. This trial is a multicentre Phase 1 /2 uncontrolled, open-label trial investigating the safety, efficacy, pharmacokinetics, and pharmacodynamics in patients with advanced tumours and tenosynovial giant cell tumour.

This multicentre study was performed in 9 countries and included 25 centres that enrolled participants. This included 1 centre in Australia, 2 centres in Canada, 2 centres in France, 3 centres in Italy, 1 centre in the Netherlands, 1 centre in Poland, 3 centres in Spain, 1 centre in the United Kingdom, and 11 centres in the United States.

The study comprised 2 distinct parts; Dose Escalation (enrolled both malignant solid tumour (MST) and TGCT participants [Phase 1]) and Expansion (enrolled TGCT participants only [Phase 2] at RP2D).

The study consisted of a screening period conducted within 28 days (Dose Escalation Phase) or 42 days (Expansion Phase) prior to the first dose of study drug, a treatment period of 28-day cycles, an end-of-

treatment (EOT) visit, and a Follow-up Safety visit 30 days (±5 days) after the last dose of study drug. Participants were then followed in the Disease Follow-up period for up to 2 years after last dose of study treatment or until radiological progression, start of new subsequent therapy/surgery, or withdrawal of consent.

Dose Escalation Phase: Participants with solid tumours received vimseltinib, at an assigned dose level appropriate for their escalation cohort. Based on clinical experience from Cohort 1 (10 mg once daily (QD); no loading dose), subsequent cohorts (Cohort 2 and above) included loading doses followed by maintenance doses. Additional dosing schemes (including QD dosing) could be explored based on preliminary PK, pharmacodynamic, and safety data as well as discussion and agreement between the Sponsor and Investigators following safety and PK/pharmacodynamic readouts.

Dose escalation was based on a pharmacologically guided 3+3 study design in participants with MST and TGCT, a common design employed in Phase 1 dose-finding studies of chemotherapeutic agents.

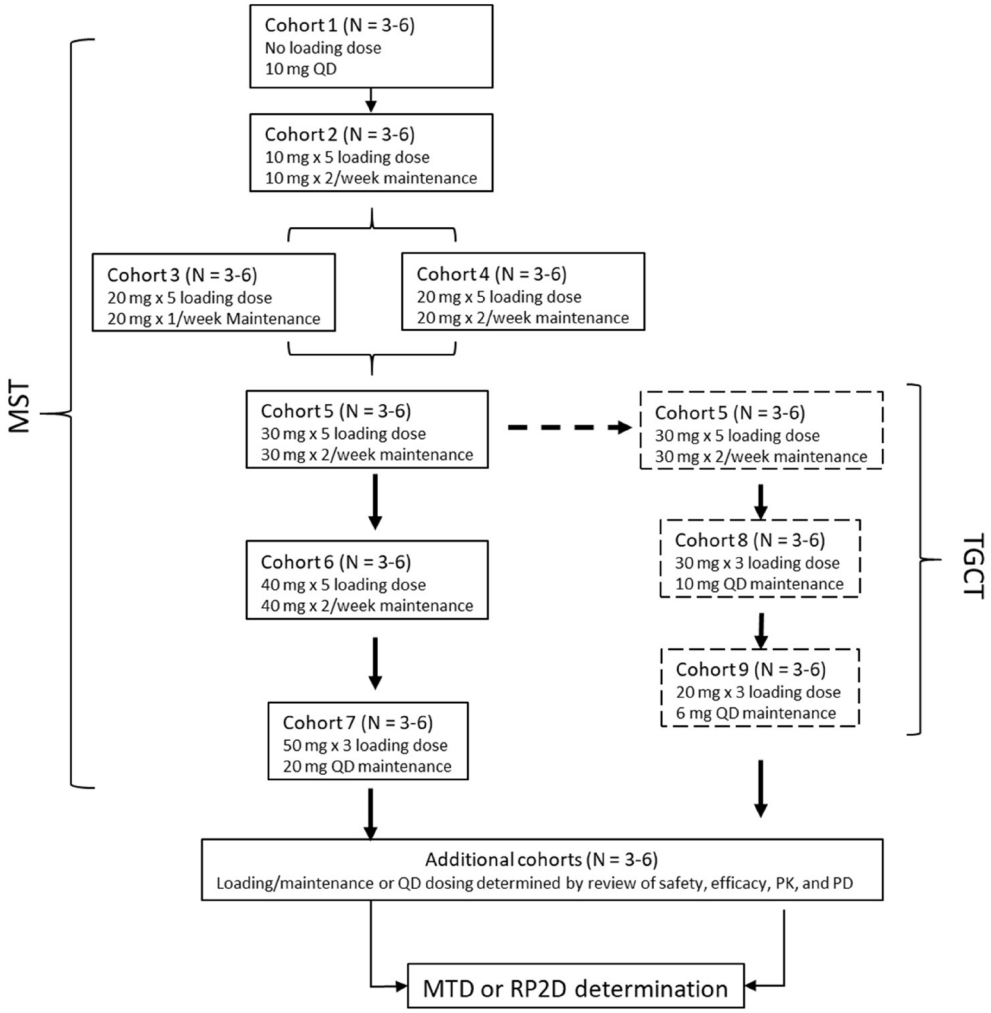
The MTD was defined as the highest dose level at which no more than 1 of 6 dose-limiting toxicity (DLT)-evaluable participants (<33%) experienced a DLT(s) in Cycle 1 during the Dose Escalation Phase. The RP2D may be the MTD or a biologically active or maximally feasible dose that is lower than the MTD.

Vimseltinib was administered at an appropriate dose for the participant's escalation cohort. A participant could start receiving vimseltinib at a higher dose level after the completion of Cycle 2.

Intra-participant dose escalation could occur based on agreement between the Sponsor and Investigator and was on the Day 1 visit of the next treatment cycle.

The dose escalation schema is provided in the figure below.

Figure 20. Dose escalation in trial DCC-3014-01-001



Abbreviations: MTD=maximum tolerated dose; N=sample size; PK=pharmacokinetics; RP2D=recommended Phase 2 dose; TGCT=tenosynovial giant cell tumour, MST=malignant solid tumour.

Note: Cohorts 3 and 4 were run simultaneously. Dose escalation continued by increasing the total dose in the first cycle up to 50% from that set in the previous cohort. An additional lower or intermediate dose level(s) and/or alternate dose schedule(s) could be explored to determine an RP2D in participants with TGCT. More than one cohort at lower dose levels could be run simultaneously. Additional participants could be enrolled to a dose escalation cohort for further evaluation of safety, efficacy, PK, and pharmacodynamics.

Expansion Phase: Upon determination of the RP2D, 2 expansion cohorts of TGCT participants were initiated for further evaluation of safety, tolerability, PK, pharmacodynamics, and efficacy to support any future study of vimseltinib in this population (Cohort A and Cohort B).

All participants in the Expansion Phase received vimseltinib at the RP2D (as determined in the Dose Escalation Phase), which was 30 mg twice weekly as oral capsules on Day 1 and Day 5 at the same time each week, with no loading dose.

A data monitoring committee monitored the safety and efficacy data in both phases of the study on a periodic basis to ensure the ongoing safety of study participants.

This multicentre study occurred in 9 countries and included 25 centres that enrolled participants. This included 1 centre in Australia, 2 centres in Canada, 2 centres in France, 3 centres in Italy, 1 centre in the Netherlands, 1 centre in Poland, 3 centres in Spain, 1 centre in the United Kingdom, and 11 centres in the United States.

Objectives:

Dose Escalation Phase Primary Objectives:

- To assess the safety and tolerability of vimseltinib
- To characterize the pharmacokinetic (PK) profile of vimseltinib
- To determine a maximum tolerated dose (MTD) of vimseltinib
- To determine recommended Phase 2 dose (RP2D) of vimseltinib

Expansion Phase Primary Objectives:

- To assess the safety and tolerability of vimseltinib
- To characterize the PK profile of vimseltinib
- To evaluate antitumor activity of vimseltinib using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 in tenosynovial giant cell tumour (TGCT) (Expansion Cohort A only)

Secondary Objectives (TGCT Expansion Cohort A only):

- To evaluate antitumor activity of vimseltinib using tumour volume score (TVS) and modified RECIST (mRECIST)
- To assess the effects of vimseltinib on range of motion (ROM)
- To assess the effects of vimseltinib on physical function, worst pain, and worst stiffness using patient-reported outcome (PRO) measures

Exploratory objectives are listed in the clinical study report (CSR)

Endpoints:

Primary Safety Endpoints: DLTs, treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), dose adjustments or discontinuation of study drug due to toxicity, physical examination findings, Eastern Cooperative Oncology Group (ECOG) performance status (PS), changes from baseline in laboratory parameters, electrocardiograms (ECGs), left ventricular ejection fraction (LVEF) via echocardiogram (ECHO)/multigated acquisition (MUGA) scans findings, and vital signs.

Primary Efficacy Endpoints (TGCT Expansion Cohort A Only):

- Objective Response Rate (ORR=complete response [CR]+partial response [PR]) assessed by independent radiological review (IRR) using RECIST v1.1 at Week 25 (Cycle 7 Day 1)
- Duration of response (DOR; time from PR or CR to disease progression or death)
- **Primary PK Endpoints:** The following PK endpoints, including but not limited to the following, will be evaluated for both vimseltinib and its metabolite, DP-7005, if detected:
- Time to maximum observed concentration (tmax)
- Maximum observed

- concentration (Cmax)
- Trough observed concentration (Cmin)
- Area under the concentration time curve (AUC)

Secondary Endpoints:

- ORR assessed by IRR using TVS and mRECIST at Week 25 (Cycle 7 Day 1)
- ROM: change from baseline in relative ROM at Week 25 (Cycle 7 Day 1)
- Response based on BPI worst pain NRS and narcotic analgesic use by BPI-30 at Week 25 (Cycle 7 Day 1)
- Patient-reported Outcomes Measurement Information System – Physical Function (PROMIS-PF) questionnaire: Change from baseline at Week 25 (Cycle 7 Day 1)
- Worst stiffness NRS: Change from baseline at Week 25 (Cycle 7 Day 1)

Number of Participants (planned and analysed): Approximately 60 participants each in the Dose Escalation Phase and Expansion Phase were planned.

A total of 151 participants were screened, and 134 were enrolled in the study prior to the data cutoff for this interim CSR; one additional participant was enrolled after the data cutoff and is not included

Diagnosis and Main Criteria for Inclusion:

The **Dose Escalation Phase** enrolled male or female adult participants (≥18 years of age)

- with advanced MST that had progressed after treatment with all available therapies known to confer clinical benefit or for which conventional therapy was not considered effective as judged by the Investigator, or
- with histologically confirmed diagnosis of TGCT (formerly known as pigmented villonodular synovitis [PVNS] or giant cell tumour of the tendon sheath [GCT-TS]), a tumour biopsy to confirm TGCT diagnosis was required if no histology/pathology was available at the time of screening.

The **Expansion Phase** enrolled male or female adult participants (≥18 years of age)

- with histologically confirmed diagnosis of TGCT (formerly known as PVNS or GCT-TS), a tumour biopsy to confirm TGCT diagnosis was required if no histology/pathology was available at the time of screening,
- with disease for which surgical resection would potentially cause worsening of functional limitation or severe morbidity, as determined by surgical consultation or a multidisciplinary tumour board, or
- with symptomatic disease with at least moderate pain per the Brief Pain Inventory (BPI) Worst Pain or at least moderate stiffness per Worst Stiffness numeric rating scale (NRS) item (defined as a score of 4 or more, with 10 describing the worst condition) within 30 days of the first dose documented in the medical record.

Participants in **Expansion Cohort A had not received** prior anti-colony stimulating factor 1 (CSF1) or anti-CSF1 receptor (CSF1R) treatment, with the exception of imatinib or nilotinib.

Participants in Expansion Cohort B had received prior systemic treatment with anti-CSF1 or anti-CSF1R therapy.

Duration of Treatment:

Vimseltinib was provided as 2-, 10-, and 50-mg hard gelatine capsules for oral administration. Participants were eligible to receive study drug until tumour progression, occurrence of unacceptable toxicity, withdrawal of consent, physician's decision, or commercialisation. Participants could continue receiving treatment after tumour progression if agreed upon by the Investigator and Sponsor if there were no other treatments

available. Additionally, treatment may have been extended by agreement between the Investigator and Sponsor for participants who exhibited evidence of clinical benefit and tolerability to the drug, and who adhered to the study procedures.

Statistical Methods:

Sample Size: In the Dose Escalation Phase, the sample size was based on a standard 3+3 design. Approximately 60 participants were planned to participate in the Escalation Phase to evaluate approximately 9 dose cohorts until determination of MTD or R2PD.

In Expansion Cohort A, the sample size of 40 TGCT participants was estimated based on the desired precision for the estimation of response rate. In Expansion Cohort B, the sample size of20 participants was used as in similar studies to further evaluate safety, PK, pharmacodynamic, and preliminary efficacy.

Analysis Populations:

- Enrolled population: The enrolled population included all participants who signed the informed consent form.
- Safety population: The safety population was primarily used for safety analysis and included all participants who received any study drug.
- Per-protocol population: The per-protocol population was the primary set for efficacy analyses and included participants in the safety population with at least one post-Baseline imaging efficacy evaluation obtained via IRR or local imaging.
- PK population: The PK population included all participants who received at least one dose of vimseltinib and had at least 1 non-missing PK concentration in plasma reported for vimseltinib or DP-7005.
- PRO population: The PRO population was the primary set for analysis of PRO data and included participants in the safety population with at least one post-Baseline PRO assessment available.

Dose-limiting toxicities (Dose Escalation Phase), the incidence, severity, seriousness, and causality of study treatment to TEAEs, dose adjustments or discontinuation of study drug due to toxicity, and by- participant findings in the participants' clinical laboratories, vital signs, ECOG PS, ECG, physical examination, ECHO/MUGA) findings, and ophthalmologic examinations were summarized.

Summary of Results:

Date first participants enrolled: 16 Feb 2017

(The analyses presented in this report are based on a data cutoff date of 27 Jun 2023.)

Demography and Baseline Characteristics: Overall, participants with TGCT were mainly White (85.6%), non-Hispanic (86.6%), and female (59.8%). The mean overall age of participants with TGCT was 45.4 years and mean body mass index (BMI) was 27.20 kg/m2. Participants with MST were mainly White (86.5%), non-Hispanic (89.2%), and female (64.9%). Mean overall age was 61.4 years and mean BMI was 28.77 kg/m^2.

Exposure: Median total treatment duration in participants with TGCT was 537.0 (range: 6 to 1427) days; median number of cycles was 20.0 (range: 1 to 51). Overall, 77.3% of participants had a dose modification of any sort. Median relative dose intensity was 75.00% (range: 25.0% to 106.3%) in participants with TGCT.

Median treatment duration in participants with MST was 43.0 (range: 1 to 234) days, median number of cycles was 2.0 (range: 0 to 9), and median relative dose intensity was 83.33% (range: 9.1% to 109.1%).

Efficacy Results:

- The Dose Escalation Phase met its primary endpoint of establishing the RP2D as 30 mg twice weekly with no loading dose in participants with TGCT with no prior specific anti-CSF1/CSF1R therapy (except imatinib or nilotinib); the MTD was not identified for vimseltinib in participants with MST or TGCT.
- Vimseltinib demonstrated efficacy in participants with TGCT with no prior specific anti-CSF1/CSF1R therapy (except imatinib or nilotinib) at the RP2D; the ORR by IRR using RECIST v1.1 was 37.8% (95% CI: 23.8%, 53.5%) at Week 25 (C7D1); 0 participants had achieved CR and 17 had achieved PR.
- During the entire treatment period to data cutoff, ORR in participants with TGCT in Cohort A was 64.4% by IRR using RECIST v1.1.
- Duration of response: Up to the data cutoff date (27 Jun 2023), the Kaplan-Meier estimated median DOR for responders to vimseltinib per RECIST v1.1 was not reached across all TGCT 30 mg twice weekly cohorts (Cohorts A, B, and 5), with responses lasting up to 196+ weeks; all responses were ongoing. Overall, most responses were maintained for at least 12 months. The median duration of follow-up ranged from 48.7 weeks to 56.1 weeks.
- Efficacy was comparable between assessments using TVS or mRECIST (ORR: 51.1%, 23 participants with PR for both assessments) at 30 mg twice weekly, in participants with TGCT with no prior specific anti-CSF1/CSF1R therapy (except imatinib or nilotinib).
- ORR based on best overall response (BOR) by IRR using RECIST v1.1 was 62.1% for all participants with TGCT; ORR based on BOR using TVS or mRECIST was comparable.
- ORR at Week 25 (C7D1) for all participants with TGCT was 40.7%, results by individual cohort ranged from 35.7% in Cohort B to 50.0% in Cohorts 5 and 9.
- Analysis of functional assessments showed a mean 19.74 percentage point increase in active relative ROM from Baseline in all participants with TGCT.
- Analysis of PRO endpoints showed an improvement in worst pain based on BPI, physical function based on PROMIS-PF, and worst stiffness NRS.
- No participants with MST showed an objective response using RECIST v1.1.

(Pharmacokinetic as well as Safety Results are discussed in the PK and Safety section of this report.)

2.6.6. Discussion on clinical efficacy

Vimseltinib is a highly selective small molecule TKI that targets CSF1R and>100-fold selectivity for inhibition of CSF1R versus all other kinases tested and >500-fold selectivity for other closely related type III receptor tyrosine kinases (KIT, PDGFRA/B, and FLT3). Vimseltinib is intended for the treatment of tenosynovial giant cell tumour (TGCT).

Design and conduct of clinical studies

Efficacy assessment for the applied broad TGCT indication is based on one pivotal trial (DCC-3014-03-001; MOTION), which was a multicentre, randomised, placebo-controlled study of vimseltinib in patients with TGCT.

The pivotal MOTION trial evaluated efficacy, safety, clinical outcome assessments, pharmacokinetics (PK), and pharmacodynamics of vimseltinib in 2 parts:

- Part 1 consists of a 24-week, double blinded placebo-controlled treatment comparison,
- Part 2 was an open label and offers placebo treated Phase 1 participants the option for cross-over to vimseltinib treatment.

Treatment durations after a 42-day screening period in which single baseline assessment for the ROM and PRO endpoints was performed prior to the first dose were 24 weeks (divided into 28-days or 4-weeks cycles) in Part 1 and 24 weeks in the open-label Part. Afterwards, participants could continue treatment in the extension period.

In principle, a controlled pivotal RCT trial like MOTION is explicitly welcomed in the rare TGCT orphan disease population and placebo is seen as adequate comparator in patients who are reliably not amenable to surgery. Considering that the 24 week duration of placebo controlled Part 1 was derived from the exploratory Phase 1/ 2 trial, a longer placebo-controlled phase would have been needed to reliably characterise efficacy and potential long-term toxicities for pivotal purposes. However, it is also acknowledged that compliance in placebo treatment may be worst over longer treatment periods.

The decision to randomise patients in a 2:1 ratio with vimseltinib against placebo seems critical regarding the outcome. While the rationale for this decision in an orphan disease population is fully understood, the mode of randomisation weakens the comparison with the placebo outcome in a very heterogeneous population such as TGCT. Randomisation was stratified for tumour location (lower limb/all other) and region (U.S/non-U.S.), and the absence of stratification by tumour size categories is considered to be one of the limitations of the study design.

Whether the study could be really conducted double-blind as planned may be challenged considering the very frequently occurring visible skin adverse events. The presence of such sign (periorbital oedema, rush etc.) is likely to have led to partial unblinding during the trial, which appears critical for the assessment of some key secondary endpoints reflecting PRO and QoL for which the assessment bears a more subjective component. However, a reliable double blinded assessment of these endpoints is essential for translation of the observed tumour ORR into a clinically relevant and meaningful benefit in the target population.

The studied population includes histologically confirmed TGCT subjects with localised single giant cell tumours of the tendon sheath [GCT-TS] and those with the diffuse type of TGCT [PVNS]. Participants had to have symptomatic TGCT with a minimum size of 2 cm in a single joint and must have had TGCT in joints where ROM assessments could be conducted. The target population was further characterised by the criterion that surgical resection would potentially cause worsening functional limitation or severe morbidity as judged by surgical consultation or a multidisciplinary tumour board. The majority of patients enrolled in MOTION (data not shown) were assessed as affected by TGCT that would require complex surgeries (e.g., two-incision open surgery) with a low to zero probability of an R0 resection and in the included population the expected probability of an R2 resection (residual macroscopic disease) would be also very high (72.3%). This outcome sufficiently explains the decision to avoid surgery

In general, the inclusion and exclusion criteria are acceptable to characterise an adequate TGCT target population for vimseltinib, but the resulting trial population is very heterogeneous. Particularly the mix-up of the prognostic different populations of localised and the more aggressive diffuse form and the time since first manifestation may contribute to heterogeneity. Such limitations can be considered inevitable in the context of the applied complex TGCT population.

Particularly in the diffuse TGCT (PVNS) population, additional radiation therapy is a treatment option recommended after surgery. Among the 11 patients with prior radiation use (9 in vimseltinib arm and 2 in placebo arm), the treatment outcomes did not appear to be affected by the exposure to prior radiation (Table 42).

The population was additionally restricted to symptomatic patients with at least moderate pain on stable analgesic regimen or at least moderate stiffness (defined as a score of 4 or more, with 10 describing the worst condition) at the single baseline assessment during the screening period.

Dose-finding was the most relevant aim of the Phase I/II trial DCC-3014-01-001. In this trial, the dose for the pivotal MOTION trial was established for a schedule using vimseltinib 30 mg twice weekly based on an acceptable and manageable safety profile and the objective responses observed.

The exposure-efficacy analysis based on data from MOTION did not show an association between vimseltinib exposure and ORR per RECIST v1.1 or TVS. A flat exposure-efficacy relationship was identified across the exposure range for the evaluated dosing regimen according to the submitted data. However, since the exposure-efficacy model could not predict ORR per RECIST v1.1 or TVS outside of the 30 mg twice weekly dosing regimen, the degree of uncertainty regarding the dose finding remains high. Whether a potentially higher efficacy could be achieved with a different posology (as reported from Cohorts 5 and 9 in DCC-3014-01-001 in Phase 1) cannot be assessed in the context of the current MAA procedure.

The claim of treatment effects is based on the results from the primary analysis after 25 weeks (end of placebo and cross-over option for placebo arm). Duration of response is partially evaluable from a later cut-off date (22 Feb 2024) and was recently reported for the last cut-off data (25 Feb 2025).

With respect to the efficacy outcome assessment, the endpoints used were agreed with the CHMP during an EMA Protocol assistance. ORR per RECIST v1.1 is an established outcome measure in cancer tumours and hence can be accepted in principle as primary endpoint in a non-malignant tumour. However, it needs to be considered that it is not per se a measure of patients' benefit. It general, relevance of ORR alone in a benign tumour has not the same relevant impact as in malignant tumours. Complete response could have more clinical relevance.

The assessment of the key secondary endpoint ORR by TVS at Week 25 was included as an additional assessment of tumour response. Volumetric measurements such as TVS may show more impressive reduction in tumours with complex shape and irregular borders like TGCT than the single longitudinal measurement used in RECIST v1.1, as the primary endpoint. However, currently the value of TVS measurement is under discussion and the benefits are not as generally accepted as ORR according to RECIST v1.1, which remains still methodologically the gold standard.

Thus, in order to demonstrate the translation of the observed ORR into the clinically relevant outcomes, the pivotal study included change key secondary endpoints such as in ROM and ORR according TVS as well as PRO Instruments (as PROMIS-PF, Worst Stiffness BPI-30 Worst Pain) and explorative QoL-endpoints like EQ-5D-5L and others.

With respect to the time of endpoint evaluation, primary endpoint assessment at week 25 appears rather early. Taken into account the large range of different tumour sizes included; it should have been recognised during the planning that for larger tumours as well as for the symptomatic secondary endpoints this time-point of endpoint assessment was challenging to evaluate a meaningful treatment effect even for complete responses. This issue was specifically addressed in the Protocol Assistance but not followed by the applicant. The same consideration applies to the assessment of the main secondary endpoints where long term outcomes are important to reliably assess the stability of the claimed symptomatic effects. Thus, the short period of 25 weeks to assess the difference in QoL to placebo is also considered as a limitation of the study design.

As seen in the last updated dataset (DCO date 22 Feb 2025) the assessment of efficacy endpoints at week 24 was significantly too early as shown by the more mature outcome at week 97, which now became available for assessment (median time to CR was 50.1 weeks).

Supportive data regarding efficacy and safety after longer treatment duration is available from some subjects included in the phase I/II trial DCC-3014-01-001, the ongoing multicentre Phase 1 /2 uncontrolled, open-label trial, investigating the safety, efficacy, pharmacokinetics and pharmacodynamics in patients with advanced tumours and TGCTs.

The study comprised 2 distinct parts: Dose Escalation (enrolled both malignant solid tumour (MST) and TGCT participants [Phase 1]) and Expansion (enrolled TGCT participants only [Phase 2] at RP2D).

The main relevance of this Phase 1/ 2 trial in the pivotal context is to provide some additional evidence for efficacy and safety after longer exposure than the 6 to 12 months available from MOTION trial.

From a statistical point of view, the final version of the SAP is aligned to the final version of the protocol. The analysis of the primary endpoint as well as the analyses of the type-I-error controlled key-secondary endpoints are statistically pre-specified in the SAP and statistical analyses have been conducted accordingly. Multiplicity related to the key-secondary endpoints is controlled by pre-specification of a hierarchy for testing. An interim analysis was neither planned nor conducted.

For all continuous type-I-error controlled key secondary endpoints, the MMRM analysis model used by the applicant and in particular the handling of missing data after treatment discontinuation is likely to overestimate the treatment effect of interest. It makes the implausible assumption that patients discontinuing from treatment with missing data would have similar outcomes as patients that continue treatment.

The Applicant provided an overview of the relevant intercurrent events, of frequency and time-pattern of missing data and the occurrence of treatment discontinuation. Sensitivity analyses for key-secondary endpoints using placebo-based imputation have been presented as well and are considered more appropriate for addressing the regulatory estimand of interest. Additional sensitivity methods were used and results provided upon request: jump-to-reference, copy increment from reference, tipping point analysis. The outcomes of these sensitivity analyses were supportive (data not shown).

In addition, subgroups had been pre-specified in the protocol, the analyses were conducted accordingly. The results thereof are also supportive, in that the estimate of central tendency was in all cases in favour of the verum medication (Figure 19, data not shown for secondary endpoints). This is considered to be a consistent outcome.

Efficacy data and additional analyses

The MOTION trial achieved statistical significance with regards to its primary endpoint and demonstrated an effect on tumour shrinkage in TGCT.

Outcome of ORR (according RECIST v1.1 as primary and TVS as key secondary)

The ORR per RECIST v1.1 at Week 25 by blinded IRR in the ITT was 39.8% (95% CI: 29.2%, 51.1%), including 4 patients with complete response for the vimseltinib arm and 0% (95% CI: 0%, 8.8%) for the placebo arm. The stratified difference in ORR was 39.0% based on IRT, and unstratified differences were 39.8%. The difference was statistically significant ($p<0.0001$) based on CMH, Chi-square, and Fisher's exact tests.

However, the majority of the treated subjects (n=42, 50.6%) had no or only minor effects listed as "stable disease". The issue that also 33 (82.5%) subjects in the placebo arm had such stable disease indicate the difficulties in efficacy assessment in the target population with a highly variable clinical course. Although the outcomes in terms of RR appear to increase after a long treatment period, the response remains limited in a significant number of patients, even after longer vimseltinib treatment.

The outcome for the ORR by TVS at Week 25 was also statistically significant showing even higher rate in the vimseltinib arm compared with the placebo arm (67.5% versus 0%; $p<0.0001$) compared with the ORR per RECIST v1.1.

Overall, 56 participants instead of 35 in the primary endpoint assessment were classified as responder in the vimseltinib arm. The difference is caused by a higher rate of subjects classified as PR by ORR per TVS [52 (62.7%)]. Insofar, the response for ORR by TVS can be seen as the best case scenario for the tumour size reduction in this trial.

The ORR in different joints in responders and non-responders and the impact of initial tumour size on the observed ORR-results at Week 25 for the primary and key secondary ORR endpoints was provided by the applicant upon request from the CHMP (data not shown). The results were indicating that ORR per RECIST v1.1 is observed across all tumour size and appeared higher for small tumours compared to the 2nd and 3rd tertiles (tumour size cutoffs: 45.2 mm and 77 mm), while ORR according to TVS response is relatively consistent across tumour size.

In general, a tumour size reduction of about 30% was observed according to RECISTv1.1 in responders across a range of tumour sizes with both measures, while the difference in response rate (vimseltinib vs placebo) was more pronounced in smaller tumours (< 3cm). This difference was not shown in ORR with TVS, in which response was higher and most pronounced in larger tumours, which could be expected from the principle of the methods.

Moreover, the time between diagnosis of the target tumour lesion, start of treatment and observation of best response plateau according to the different joints to assess treatment duration needed for efficacy was very heterogenous (between 1 month up to 22 years, median for the total population: 4.28 years) Considering the high heterogeneity in the joint subgroups no further interpretation appears meaningful.

The time to Best Response Plateau Based on Independent Radiological Review per RECIST v1.1 and TVS was reported in after a median of 13.1 weeks for RECISTv1.1 and 12.3 for ORR TVS.

Translation of the observed endpoint results regarding ORR in a clinically relevant meaningful benefit, is most likely possible in patients who had complete response. While at the time of the primary endpoint assessment at week 25, only 4 subjects (~5 %) reached CR, the latest available data at week 97 show a significant

increase of CRs up to 23 % (19/83 for TVS) in the vimseltinib treated population which can be seen as clinically relevant.

Upon final analysis of the Independent radiological review data, the Kaplan Meier estimated median DOR for responders to vimseltinib per RECIST v1.1 was not reached with the maximum DOR of approximately 134 weeks with response ongoing (Table 40). A slightly more favourable outcome was observed for the related DOR per TVS in MOTION.

It remains currently unknown whether the remaining subjects showing only PR also reach CR at the end. It cannot be excluded that considering slow response dynamic observed with vimseltinib treatment and shorter follow up of treatment (cross-over subjects) the CR rate may even further increase.

Since treatment resistance was already reported after week 25 and stable disease probably indicates primary resistance, it is uncertain whether the observed complete responses will be durable and to which dimension joint function can be restored from the treatment over longer follow-up.

It this context it remains critical that the maximal duration of treatment is not specified in section 4.2 of the SmPC, which applies in particular for patients not reaching CR. In the case that CR is reached, additional treatment options (radiation, radiosynoviorthesis) may be needed to avoid recurrence.

Considering the small number of patients and the intrinsic large heterogeneity in this orphan disease trial subgroup analysis are not considered very informative and as in the sensitivity analyses, chance findings alone may be an explanation for difference occurred.

Outcome for the Key and other secondary endpoints

Considering the substantial increase in CR rate observed upon provision of efficacy data with longer follow-up, the need to rely on other secondary endpoints to conclude on clinical relevance was decreased. They are nevertheless of interest to understand the impact of the treatment on joint function and patient's QoL.

Since ORR per RECIST v1.1 or by TVS per se in TGCT has not the same clinical relevance as in the cancer setting, the Applicant has used several PROs and QoL and other key secondary endpoints in the pivotal study with the aim to translate the primary endpoint results into a clinically meaningful benefit.

These are change in active and passive Range of motion (ROM) and several PRO measures aiming to further characterise patient's range of motion in the limb and to show improvement of QoL due to relief in symptoms after treatment (PROMIS-PF, worst stiffness, EQ-5D-%L-VAS and worst pain).

The outcome for all these key secondary endpoints assessed at Week 25 was reported consistently as statistically significant in favour for vimseltinib over placebo: Active ROM (LS mean difference 14.6% [95% CI: 4.0, 25.3]; p=0.0077), physical function (LS mean difference 3.3 [95% CI: 1.4, 5.2]; p=0.0007), worst stiffness (LS mean difference -1.8 [95% CI: -2.5, -1.1]; p<0.0001), EQ-5D-5L VAS to assess health status (LS mean difference 7.4 [95% CI: 1.4, 13.4]; p=0.0155), and worst pain (48.2% versus 22.5%; p=0.0056).

The applicant claims that this outcome for the secondary endpoints proves that vimseltinib provided clinically meaningful improvement in function and clinically meaningful improvement in symptoms in patients with TGCT. This view is not shared at present.

The visible, easy to recognise, frequently occurring adverse events of the skins (Rush, periorbital oedema and others) are well known from phase 1/2 trial by the investigators and patients and can negatively affect the blinding and is probable to have bias the evaluation of PRO and QoL symptomatic endpoints.

In addition, the MCID threshold of an improvement chosen by then applicant for interpreting to proportion of patient deriving a clinical benefit based on PROs was not endorsed by the CHMP. Franceschini et al (2023) have recently demonstrated clearly for the knee joint that different MCID calculation methods lead to highly heterogeneous values with different calculation methods, which significantly affect the percentages of patients achieving the MCID. This analysis challenge significantly the current perception in musculoskeletal studies of MCID being able to reflect the treatment success based on the patient perception and on predefined thresholds, as these are highly dependent and variable based on the calculation method chose.

Moreover, for the assessment of PROMIS-PF scores, considering that the endpoint results again are summarised all together for the different joints, the clinical impact of the claimed improvement cannot be contextualized. Similarly, it remains critical that the baseline evaluation was performed as a single assessment shortly before start of treatment, which is contrary to the recommended multiple assessment during a longer run in phase for comparable clinical trials in other joint disorders to be reliable.

Although this information provided on (key) secondary endpoints has significant limitations as already discussed above and several uncontrolled and not further evaluable sources of bias can be presumed, the totality of data show improvement in the QoL of the vimseltinib treated patients.

Primary Resistance against treatment

In order to better understand how the drug acts in the benign tumour entity with mixed cellularity, it was recommended in the scientific advice that the applicant provides more histological data during the course of treatment. It may be that in tumours with a lack of response, treatment resistance is caused by different histology or due to primary resistance against vimseltinib. However, since histology is not available from the studied population, it is not possible to identify a difference between responders and non-responders based on histology, e.g. due to a lower or even absent inflammatory component. Similarly, primary resistance against the applied product as explanation for the 50% non-responders needs to be considered.

Neo-adjuvant treatment to enable tumour resection

Apart from complete response, a successful tumour reduction due to vimseltinib allowing tumour resection in a neo-adjuvant setting is a clinically relevant benefit. It is noted that the study protocol foresees that patients initially not amenable to surgery should be offered the surgery option after successful treatment in MOTION. It appears that this option may have also existed in the Phase 1/2 trial. However, although this was recommended in CHMP's advice, this aspect is not further addressed and subjects who selected the surgery option were excluded and not further followed regarding the outcome.

Wording of the indication

The initially sought indication was "*ROMVIMZA is indicated for treatment of adult patients with tenosynovial giant cell tumour (TGCT) who are not amenable to surgery*."

During the procedure, it was agreed to restrict the indication to patients in whom the benefit-risk balance is positive (excluding patients with asymptomatic or milder disease or for whom systemic therapy is not indicated) as follows:

"ROMVIMZA is indicated for treatment of adult patients with symptomatic tenosynovial giant cell tumour (TGCT) associated with clinically relevant physical function deterioration and in whom surgical options have been exhausted or would induce unacceptable morbidity or disability."

2.6.7. Conclusions on the clinical efficacy

The MOTION trial successfully met its primary endpoint, demonstrating a statistically significant difference in tumour response rate (ORR per RECIST v1.1) at Week 25. After 97 weeks of follow up, the number of subjects with CR and PR increase significantly up to 19/83 subjects which could indicate that the timepoint of assessment was too early to show the full efficacy of the treatment. Nevertheless, it appears that half of the target population had no response on the treatment.

For patients who were able to continue receiving the treatment, the chance to reach a complete response is about 23%, which appears to be a clear benefit for the target population.

With respect to the reported outcome for the (key) secondary endpoints, the data show a positive outcome. However, clinical robustness is limited due to methodological issues and potential functional unblinding for a relevant subset of the study population.

The higher rate of CR at the week 97 analysis and the apparent stability of response allows to translate the pharmacological activity observed at the primary analysis into sufficient evidence of clinical benefit. Treatment interruptions and temporarily discontinuation due to safety reasons did not significantly affect the chance to reach CR; however, treatment interruptions may prolong the time needed to reach CR.

2.6.8. Clinical safety

For this application, safety data from 6 clinical studies were submitted. Main evidence regarding the safety profile in the target population is derived from the two studies in adult participants with solid tumours, including TGCT.

- **MOTION**: A pivotal Phase 3, multicentre, randomised, placebo-controlled study to assess the efficacy and safety of vimseltinib in participants with TGCT, consisting of 2 parts. Part 1 is double-blind, and Part 2 is open-label (participants randomised to placebo in Part 1 had the option to cross over and receive open-label vimseltinib). Symptomatic participants with histologically confirmed TGCT for whom surgical resection may potentially cause worsening functional limitation or severe morbidity were eligible.
- **Phase 1/2 study**: An open-label, multicentre, first-in-human, dose escalation and expansion study. The Dose Escalation Phase of this study seeks to determine preliminary safety and tolerability, the MTD, the RP2D, preliminary efficacy, and PK and pharmacodynamic effects of vimseltinib in participants with MST or TGCT. The Expansion Phase seeks to further evaluate the preliminary efficacy, safety, PK, and pharmacodynamics of vimseltinib in participants with TGCT.

Table 44. Exposure to vimseltinib in participants across clinical studies supporting safety

Clinical Study	Any Exposure to Vimseltinib	Participants With TGCT Exposed to Vimseltinib 30 mg Twice Weekly
Pivotal Study		
MOTION	118	83 (randomised to vimseltinib during double-blind period) 35 (crossed over from placebo to vimseltinib during open-label period)
Supportive Study		
Phase 1/2	135	46 (Cohort A)

(Dose Escalation/Dose Expansion[a])		20 (Cohort B)
Clinical Pharmacology Studies		
Study 002 (Phase 1, PK, Food Effect, QTc)	98	0
Study 003 (Phase 1 hAME)	8	0
Study 004 (Hepatic Impairment)	16 (of 48 planned)	0
Study 006 (DDI, P-gp)	89	0
Total Exposure	464	184

Abbreviations: BCRP=breast cancer resistance protein; CSF1=colony-stimulating factor 1; CSF1R=colony- stimulating factor 1 receptor; CSR=clinical study report; DDI=drug-drug interaction; hAME=human absorption, metabolism, and excretion; P-gp=P-glycoprotein; PK=pharmacokinetic(s); PPL=periplakin; QTc=QT interval corrected for heart rate; TGCT=tenosynovial giant cell tumour.
a In the Expansion Phase, Cohort A was comprised of participants with TGCT who were not amenable to surgery and who did not receive prior CSF1 or CSF1R therapy; Cohort B enrolled participants with TGCT who were not amenable to surgery and who received prior CSF1 or CSF1R therapy.

2.6.8.1. Patient exposure

The safety profile of vimseltinib was based on pooled analyses of 253 participants who were exposed to at least 1 dose of vimseltinib from MOTION (DCO 22 Feb 2024) and the Phase 1/2 study (DCO 27 Dec 2023). Of these, 184 participants were included in Pool 1 (Table 45) and is most relevant for the safety assessment in this procedure.

Table 45. Drug exposure to vimseltinib – Pool 1 (all participants with TGCT at 30 mg twice weekly)

Category	Phase 1/2 Study Expansion		MOTION (N=118)	Cohort A + MOTION (N=164)	Overall (N=184)
	Cohort A (N=46)	Cohort B (N=20)			
Treatment duration (months)[a]					
Mean (SD)	19.6 (12.50)	15.4 (12.09)	12.4 (6.04)	14.4 (8.92)	14.5 (9.28)
Median	22.2	9.9	12.9	13.1	13.0
Min, max	0, 36	1, 36	1, 25	0, 36	0, 36
Treatment duration (months) by category, n (%)[a]					
<1 month	1 (2.2)	1 (5.0)	2 (1.7)	3 (1.8)	4 (2.2)
1 - <3 months	3 (6.5)	1 (5.0)	7 (5.9)	10 (6.1)	11 (6.0)
3 - <6 months	6 (13.0)	3 (15.0)	13 (11.0)	19 (11.6)	22 (12.0)
6 - <9 months	6 (13.0)	4 (20.0)	15 (12.7)	21 (12.8)	25 (13.6)
9 - <12 months	2 (4.3)	2 (10.0)	17 (14.4)	19 (11.6)	21 (11.4)
12 - <15 months	2 (4.3)	1 (5.0)	23 (19.5)	25 (15.2)	26 (14.1)
15 - <18 months	1 (2.2)	0	15 (12.7)	16 (9.8)	16 (8.7)
18 - <21 months	1 (2.2)	1 (5.0)	16 (13.6)	17 (10.4)	18 (9.8)
21 - <24 months	2 (4.3)	2 (10.0)	8 (6.8)	10 (6.1)	12 (6.5)
≥24 months	22 (47.8)	5 (25.0)	2 (1.7)	24 (14.6)	29 (15.8)
Number of cycles initiated					
Mean (SD)	21.7 (13.63)	17.3 (13.25)	14.0 (6.58)	16.2 (9.72)	16.3 (10.12)
Median	24.5	11.5	14.5	15.0	15.0
Min, max	1, 40	1, 40	1, 28	1, 40	1, 40
Total number of doses received					
Mean (SD)	155.2 (100.84)	122.8 (103.91)	99.5 (51.66)	115.2 (73.16)	116.0
Median	176.0	74.5	100.0	106.0	102.5
Min, max	2, 311	7, 308	8, 214	2, 311	2, 311

Category	Phase 1/2 Study Expansion		MOTION (N=118)	Cohort A + MOTION (N=164)	Overall (N=184)
	Cohort A (N=46)	Cohort B (N=20)			
Total planned dose (mg)[c]					
Mean (SD)	5212.2	4140.0	3360.0	3879.5	3907.8
Median	5880.0	2760.0	3480.0	3600.0	3600.0
Min, max	240, 9600	240, 9600	240, 6720	240, 9600	240, 9600
Total administered dose (mg)[d]					
Mean (SD)	3737.2	3228.6	2618.7	2932.4	2964.6
Median	3653.0	2006.0	2526.0	2580.0	2525.0
Min, max	60, 9330	210, 9240	240, 6420	60, 9330	60, 9330
Relative dose intensity (%)[e]					
Mean (SD)	71.32 (20.128)	78.52 (16.020)	77.27 (18.672)	75.60	75.92
Median	70.65	80.14	78.60	77.50	77.69
Min, max	25.0, 100.0	47.9, 106.3	25.0, 100.0	25.0, 100.0	25.0, 106.3
Participants with dose reduction or dose interruption, n (%)	36 (78.3)	15 (75.0)	86 (72.9)	122 (74.4)	137 (74.5)
Any dose reduction	28 (60.9)	10 (50.0)	60 (50.8)	88 (53.7)	98 (53.3)
Any dose interruption	33 (71.7)	13 (65.0)	74 (62.7)	107 (65.2)	120 (65.2)

Abbreviations: ISS=Integrated Summary of Safety; max=maximum; min=minimum; n=number of participants in a category; N=sample size; SD=standard deviation; TGCT=tenosynovial giant cell tumour.

[a] Treatment duration (months): (date of last vimseltinib dose – date of first vimseltinib dose +1)/30.4375.

[b] Number of cycles initiated: taking treatment duration (days)/28, round up to integer to get number of cycles.

[c] Total planned dose (mg) was defined as the sum of the prescribed doses (mg).

[d] Total administered dose (mg) was defined as the sum of the actual doses (mg) administered.

[e] Relative dose intensity (%) was defined as total administered dose (mg)/total planned dose (mg) × 100.

Note: Pool 1 included all participants with TGCT in Phase 1/2 and MOTION who received at least 1 dose of vimseltinib at the recommended dose of 30 mg twice weekly.

2.6.8.2. Adverse events

Table 46. Overall summary of treatment-emergent adverse events in MOTION double-blind period, safety set

Category, n (%)	Vimseltinib N=83	Placebo N=39
Any TEAE	83 (100.0)	37 (94.9)
Any TEAE with maximum Grade 3/4	31 (37.3)	4 (10.3)
Any SAE	6 (7.2)	1 (2.6)
Any drug-related TEAE	79 (95.2)	29 (74.4)
Any drug-related TEAE with maximum Grade 3/4	25 (30.1)	1 (2.6)
Any drug-related SAE	1 (1.2)	0
Any TEAE leading to dose modification	52 (62.7)	4 (10.3)
Drug interruption	44 (53.0)	4 (10.3)
Dose reduction	35 (42.2)	0
Any drug-related TEAE leading to dose modification	47 (56.6)	2 (5.1)
Drug interruption	37 (44.6)	2 (5.1)
Dose reduction	35 (42.2)	0
Any drug-related TEAE leading to treatment discontinuation	3 (3.6)	0
Any TEAE leading to death	0	0

Abbreviations: AE=adverse event; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants in a category; N=sample size; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; SAE=serious adverse event; TEAE=treatment-emergent adverse event.

Note 1: TEAEs were coded per MedDRA v26.0. The severity of AE was documented using the NCI-CTCAE v5.0. Note 2: Drug-related AEs included AEs reported by the Investigator as possibly related and related to study drug. Note 3: Data cutoff date was 22 Aug 2023.

Table 47. Treatment-emergent adverse events with ≥10% of total by preferred term in MOTION double-blind period, safety set

Preferred Term, n (%)	Vimseltinib N=83	Placebo N=39	Total N=122
Any TEAE	**83 (100.0)**	**37 (94.9)**	**120 (98.4)**
Periorbital oedema	37 (44.6)	5 (12.8)	42 (34.4)
Fatigue	27 (32.5)	6 (15.4)	33 (27.0)
Headache	23 (27.7)	10 (25.6)	33 (27.0)
Asthenia	22 (26.5)	9 (23.1)	31 (25.4)
Face oedema	26 (31.3)	3 (7.7)	29 (23.8)
Nausea	21 (25.3)	8 (20.5)	29 (23.8)
Pruritus	24 (28.9)	3 (7.7)	27 (22.1)
Arthralgia	16 (19.3)	6 (15.4)	22 (18.0)
Blood CPK increased	20 (24.1)	0	20 (16.4)
AST increased	19 (22.9)	1 (2.6)	20 (16.4)
Rash	16 (19.3)	2 (5.1)	18 (14.8)
Oedema peripheral	15 (18.1)	3 (7.7)	18 (14.8)
Hypertension	14 (16.9)	4 (10.3)	18 (14.8)
Diarrhoea	10 (12.0)	8 (20.5)	18 (14.8)
Rash maculo-papular	16 (19.3)	0	16 (13.1)
Eyelid oedema	11 (13.3)	2 (5.1)	13 (10.7)

Abbreviations: AST=aspartate aminotransferase; CPK=creatine phosphokinase; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants in a category; N=sample size; TEAE=treatment-emergent adverse event.
Note 1: TEAEs were coded per MedDRA v26.0. If a preferred term was reported more than once for a participant, the participant would be counted only once.
Note 2: Table cut off was based on ≥10% of total participants by preferred term in double-blind period. Note 3: Data cutoff date was 22 Aug 2023.

Drug related Adverse events

Table 48. Drug-related treatment-emergent adverse events occurring in ≥10% of participants by system organ class and preferred term – Pool 1 (all participants with TGCT at 30 mg twice weekly)

System Organ Class Preferred Term	Phase 1/2 Study Expansion		MOTION (N=118) n (%)	Cohort A + MOTION (N=164) n (%)	Overall (N=183)[a] n (%)
	Cohort A (N=46) n (%)	Cohort B (N=20) n (%)			
Any drug-related TEAE	45 (97.8)	20 (100.0)	114 (96.6)	159 (97.0)	178 (97.3)
General disorders and administration site conditions	35 (76.1)	15 (75.0)	89 (75.4)	124 (75.6)	138 (75.4)
Fatigue	9 (19.6)	10 (50.0)	33 (28.0)	42 (25.6)	52 (28.4)
Asthenia	15 (32.6)	3 (15.0)	33 (28.0)	48 (29.3)	51 (27.9)
Face oedema	10 (21.7)	2 (10.0)	34 (28.8)	44 (26.8)	46 (25.1)
Oedema peripheral	8 (17.4)	3 (15.0)	22 (18.6)	30 (18.3)	33 (18.0)

System Organ Class Preferred Term	Phase 1/2 Study Expansion		MOTION (N=118) n (%)	Cohort A + MOTION (N=164) n (%)	Overall (N=183)[a] n (%)
	Cohort A (N=46) n (%)	Cohort B (N=20) n (%)			
Generalised oedema	7 (15.2)	2 (10.0)	18 (15.3)	25 (15.2)	26 (14.2)
Eye disorders	30 (65.2)	13 (65.0)	88 (74.6)	118 (72.0)	131 (71.6)
Periorbital oedema	18 (39.1)	9 (45.0)	55 (46.6)	73 (44.5)	82 (44.8)
Eyelid oedema	8 (17.4)	2 (10.0)	13 (11.0)	21 (12.8)	23 (12.6)
Lacrimation increased	5 (10.9)	2 (10.0)	12 (10.2)	17 (10.4)	19 (10.4)
Skin and subcutaneous tissue disorders	30 (65.2)	14 (70.0)	77 (65.3)	107 (65.2)	120 (65.6)
Pruritus	8 (17.4)	3 (15.0)	37 (31.4)	45 (27.4)	48 (26.2)
Rash maculo-papular	11 (23.9)	6 (30.0)	25 (21.2)	36 (22.0)	42 (23.0)
Rash	8 (17.4)	4 (20.0)	27 (22.9)	35 (21.3)	39 (21.3)
Investigations	34 (73.9)	14 (70.0)	57 (48.3)	91 (55.5)	105 (57.4)
Blood CPK increased	32 (69.6)	12 (60.0)	33 (28.0)	65 (39.6)	77 (42.1)
AST increased	9 (19.6)	7 (35.0)	32 (27.1)	41 (25.0)	48 (26.2)
ALT increased	4 (8.7)	4 (20.0)	21 (17.8)	25 (15.2)	29 (15.8)
Gastrointestinal disorders	27 (58.7)	11 (55.0)	42 (35.6)	69 (42.1)	80 (43.7)
Nausea	15 (32.6)	5 (25.0)	22 (18.6)	37 (22.6)	42 (23.0)
Diarrhoea	5 (10.9)	5 (25.0)	16 (13.6)	21 (12.8)	26 (14.2)
Nervous system disorders	24 (52.2)	10 (50.0)	46 (39.0)	70 (42.7)	80 (43.7)
Headache	17 (37.0)	9 (45.0)	24 (20.3)	41 (25.0)	50 (27.3)
Musculoskeletal and connective tissue disorders	22 (47.8)	7 (35.0)	26 (22.0)	48 (29.3)	55 (30.1)
Myalgia	12 (26.1)	4 (20.0)	8 (6.8)	20 (12.2)	24 (13.1)
Arthralgia	5 (10.9)	2 (10.0)	13 (11.0)	18 (11.0)	20 (10.9)
Vascular disorders	7 (15.2)	3 (15.0)	24 (20.3)	31 (18.9)	34 (18.6)
Hypertension	5 (10.9)	3 (15.0)	20 (16.9)	25 (15.2)	28 (15.3)

Abbreviations: AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants in a category; N=sample size; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event; TGCT=tenosynovial giant cell tumour.

a One participant from the Expansion Phase (Cohort A) re-enrolled into Cohort B. This participant was counted as 1 participant for the total column.

Note 1: MedDRA v26.0 was used. TEAE was defined as any AE that occurred or worsened after the administration of the first dose of vimseltinib and through 30 days after the last dose of vimseltinib or the day before the start of new anti-tumour therapy.

Note 2: Drug-related AEs reported after 30 days following the last dose of vimseltinib were considered treatment-emergent.

Note 3: If an SOC or PT was reported more than once for a participant, the participant was counted only once in the incidence for that SOC or PT.

Note 4: Pool 1 included all participants with TGCT in Phase 1/2 and MOTION who received at least 1 dose of vimseltinib at the recommended dose of 30 mg twice weekly.

Table 49. Drug-related treatment-emergent adverse events with ≥10% of total by preferred term in MOTION double-blind period, safety set

Preferred Term, n (%)	Vimseltinib N=83	Placebo N=39	Total N=122
Any drug-related TEAE	**79 (95.2)**	**29 (74.4)**	**108 (88.5)**
Periorbital oedema	36 (43.4)	5 (12.8)	41 (33.6)
Fatigue	27 (32.5)	6 (15.4)	33 (27.0)
Face oedema	25 (30.1)	2 (5.1)	27 (22.1)
Asthenia	21 (25.3)	5 (12.8)	26 (21.3)
Pruritus	22 (26.5)	3 (7.7)	25 (20.5)
Headache	17 (20.5)	8 (20.5)	25 (20.5)
Nausea	16 (19.3)	6 (15.4)	22 (18.0)
Blood CPK increased	19 (22.9)	0	19 (15.6)
AST increased	17 (20.5)	1 (2.6)	18 (14.8)
Rash	16 (19.3)	2 (5.1)	18 (14.8)
Rash maculo-papular	15 (18.1)	0	15 (12.3)
Oedema peripheral	14 (16.9)	1 (2.6)	15 (12.3)
Hypertension	11 (13.3)	3 (7.7)	14 (11.5)
Eyelid oedema	11 (13.3)	2 (5.1)	13 (10.7)
Diarrhoea	7 (8.4)	6 (15.4)	13 (10.7)

Abbreviations: AE=adverse event; AST=aspartate aminotransferase; CPK=creatine phosphokinase; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants in a category; N=sample size; TEAE=treatment-emergent adverse event.
Note 1: TEAEs were coded per MedDRA v26.0. If a preferred term was reported more than once for a participant, the participant would be counted only once.
Note 2: Drug-related AEs included AEs reported by the Investigator as possibly related and related to study drug. Note 3: Table cut off was based on ≥10% of total participants by preferred term in double-blind period.
Note 4: Data cutoff date was 22 Aug 2023.

Table 50. Treatment-emergent adverse events with maximum grade 3/4 in >1 participant total by preferred term in MOTION double-blind period, safety set

Preferred Term, n (%)	Vimseltinib	Placebo	Total
Any TEAE with maximum Grade 3/4	**31 (37.3)**	**4 (10.3)**	**35 (28.7)**
Blood CPK increased	8 (9.6)	0	8 (6.6)
Hypertension	4 (4.8)	1 (2.6)	5 (4.1)
Periorbital oedema	3 (3.6)	0	3 (2.5)
Pruritus	2 (2.4)	0	2 (1.6)
Asthenia	1 (1.2)	1 (2.6)	2 (1.6)

Abbreviations: AE=adverse event; CPK=creatine phosphokinase; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants in a category; N=sample size; NCI-CTCAE=National Cancer Institute- Common Terminology Criteria for Adverse Events; TEAE=treatment-emergent adverse event.
Note 1: TEAEs were coded per MedDRA v26.0. The severity of AE was documented using the NCI-CTCAE v5.0. Note 2: If a preferred term was reported more than once for a participant, the participant would be counted only once.
Note 3: Table cutoff was based on >1 participant in the total column by preferred term in double-blind period. Note 4: Data cutoff date was 22 Aug 2023.

Table 51. Maximum severity grade 3/4 treatment-emergent adverse events occurring in >1 participant by system organ class and preferred term – Pool 1 (all participants with TGCT at 30 mg twice weekly)

System Organ Class Preferred Term	Phase 1/2 Study Expansion		MOTION (N=118) n (%)	Cohort A + MOTION (N=164) n (%)	Overall (N=183)[a] n (%)
	Cohort A (N=46) n (%)	Cohort B (N=20) n (%)			
Any maximum severity Grade 3/4 TEAE	29 (63.0)	12 (60.0)	57 (48.3)	86 (52.4)	97 (53.0)
Investigations	23 (50.0)	8 (40.0)	16 (13.6)	39 (23.8)	47 (25.7)
Blood CPK increased	22 (47.8)	7 (35.0)	14 (11.9)	36 (22.0)	43 (23.5)
Lipase increased	1 (2.2)	1 (5.0)	0	1 (0.6)	2 (1.1)
Vascular disorders	4 (8.7)	3 (15.0)	10 (8.5)	14 (8.5)	16 (8.7)
Hypertension	4 (8.7)	3 (15.0)	10 (8.5)	14 (8.5)	16 (8.7)
Skin and subcutaneous tissue disorders	2 (4.3)	2 (10.0)	10 (8.5)	12 (7.3)	14 (7.7)
Pruritus	0	0	5 (4.2)	5 (3.0)	5 (2.7)
Eczema	0	2 (10.0)	1 (0.8)	1 (0.6)	3 (1.6)
Rash maculo-papular	1 (2.2)	0	2 (1.7)	3 (1.8)	3 (1.6)
Urticaria	0	0	2 (1.7)	2 (1.2)	2 (1.1)
General disorders and administration site conditions	4 (8.7)	1 (5.0)	7 (5.9)	11 (6.7)	12 (6.6)
Fatigue	2 (4.3)	1 (5.0)	1 (0.8)	3 (1.8)	4 (2.2)
Asthenia	1 (2.2)	0	2 (1.7)	3 (1.8)	3 (1.6)
Musculoskeletal and connective tissue disorders	4 (8.7)	4 (20.0)	4 (3.4)	8 (4.9)	12 (6.6)
Pain in extremity	1 (2.2)	1 (5.0)	1 (0.8)	2 (1.2)	3 (1.6)
Arthralgia	1 (2.2)	1 (5.0)	0	1 (0.6)	2 (1.1)
Myalgia	1 (2.2)	1 (5.0)	0	1 (0.6)	2 (1.1)
Infections and infestations	2 (4.3)	0	9 (7.6)	11 (6.7)	11 (6.0)
Cellulitis	0	0	4 (3.4)	4 (2.4)	4 (2.2)
Eye disorders	0	0	6 (5.1)	6 (3.7)	6 (3.3)
Periorbital oedema	0	0	4 (3.4)	4 (2.4)	4 (2.2)
Nervous system disorders	1 (2.2)	0	4 (3.4)	5 (3.0)	5 (2.7)
Headache	0	0	2 (1.7)	2 (1.2)	2 (1.1)
Injury, poisoning and procedural complications	0	0	3 (2.5)	3 (1.8)	3 (1.6)
Ankle fracture	0	0	2 (1.7)	2 (1.2)	2 (1.1)

Abbreviations: AE=adverse event; CPK=creatine phosphokinase; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants in a category; N=sample size; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event; TGCT=tenosynovial giant cell tumour.

[a] One participant from the Expansion Phase (Cohort A) re-enrolled into Cohort B. This participant was counted as 1 participant for the total column.

Note 1: MedDRA v26.0 was used. The severity grade of the AEs for Phase 1/2 was assessed by NCI-CTCAE v4.03 and for MOTION was assessed by NCI-CTCAE v5.0. TEAE was defined as any AE that occurred or worsened after the administration of the first dose of vimseltinib and through 30 days after the last dose of vimseltinib or the day before the start of new anti-tumour therapy.

Note 2: Drug-related AEs reported after 30 days following the last dose of vimseltinib were considered treatment-emergent.

Note 3: If an SOC or PT was reported more than once for a participant, the participant was counted only once in the incidence for that SOC or PT.

Note 4: Pool 1 included all participants with TGCT in Phase 1/2 and MOTION who received at least 1 dose of vimseltinib at the recommended dose of 30 mg twice weekly.

Incidence of Frequently Occurring Treatment-emergent Adverse Events Over Time

Table 52. Most frequent treatment-emergent adverse events by preferred term over time – Pool 1 (all participants with TGCT at 30 mg twice weekly)

Preferred Term, n (%)	Pool 1[a]			
	First Year (N=183)	Second Year (N=112)	Third Year (N=31)	Fourth Year (N=4)
Periorbital oedema	78 (42.6)	11 (9.8)	1 (3.2)	0
Blood CPK increased	77 (42.1)	10 (8.9)	1 (3.2)	0
Headache	61 (33.3)	4 (3.6)	1 (3.2)	0
Fatigue	53 (29.0)	5 (4.5)	1 (3.2)	0
Asthenia	50 (27.3)	9 (8.0)	1 (3.2)	0
AST increased	48 (26.2)	5 (4.5)	2 (6.5)	0
Nausea	47 (25.7)	2 (1.8)	1 (3.2)	0
Pruritus	47 (25.7)	2 (1.8)	4 (12.9)	0
Face oedema	45 (24.6)	2 (1.8)	3 (9.7)	0
Arthralgia	43 (23.5)	6 (5.4)	2 (6.5)	0

Abbreviations: AE=adverse event; AST=aspartate aminotransferase; CPK=creatine phosphokinase; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; TGCT=tenosynovial giant cell tumour.
a One participant from the Expansion Phase (Cohort A) re-enrolled into Cohort B. This participant was counted as 1 participant for each column.
Note 1: MedDRA version 26.0 was used.
Note 2: N corresponds to number of participants at risk per year.
Note 3: If a PT was reported more than once for a participant, the participant was counted only once in the incidence for that PT.
Note 4: Pool 1 included all participants with TGCT in Phase 1/2 and MOTION who received at least 1 dose of vimseltinib at the recommended dose of 30 mg twice weekly.
Note 5: AEs were attributed to a year based on AE start date. An ongoing AE across time intervals was considered a new AE in the subsequent time interval if it increased in severity.

2.6.8.3. Serious adverse event/deaths/other significant events

Table 53. Treatment-emergent serious adverse events in MOTION double-blind period by preferred term, safety set

Preferred Term, n (%)	Vimseltinib N=83	Placebo N=39	Total N=122
Any SAE	6 (7.2)	1 (2.6)	7 (5.7)
Cellulitis	1 (1.2)	0	1 (0.8)
Fall	**1 (1.2)**	**0**	**1 (0.8)**
Papillary thyroid cancer	1 (1.2)	0	1 (0.8)
Plasma cell myeloma	1 (1.2)	0	1 (0.8)
Subcutaneous abscess	1 (1.2)	0	1 (0.8)
Uveitis	1 (1.2)	0	1 (0.8)
Diarrhoea	0	1 (2.6)	1 (0.8)
Vomiting	0	1 (2.6)	1 (0.8)

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants in a category; N=sample size; SAE=serious adverse event.
Note 1: SAEs were coded per MedDRA v26.0.
Note 2: If a preferred term was reported more than once for a participant, the participant would be counted only once.
Note 3: Data cutoff date was 22 Aug 2023.

Adverse drug reactions (ADRs)

All reported TEAEs and laboratory abnormalities from both MOTION and the Phase 1/2 study were evaluated to identify those that were reasonably associated with the use of vimseltinib. ADRs were identified based on event incidence, difference between the vimseltinib and placebo arms in MOTION, temporal relationship, seriousness, severity, consistency across studies, nonclinical findings and plausible mechanism of action.

Placebo-controlled data from the double-blind period of MOTION (DCO date 22 Aug 2023) were selected as the best available data for the presentation of ADRs. Participants were counted once for each ADR term, and incidence rates were based on the number of participants who initially received placebo or vimseltinib.

Table 54. Adverse reactions observed in MOTION through week 25

System organ class	Frequency category	Adverse reaction	Incidence and CTCAE Grades[a]			
			Vimseltinib N=83		Placebo N=39	
			All Grades (%)	Grade 3 or 4 (%)	All Grades (%)	Grade 3 or 4 (%)
Eye disorders	Very common	Periorbital edema[b]	60%	4%	21%	0%
	Very common	Lacrimation increased	12%	0%	0%	0%
	Common	Dry eye[c]	10%	0%	0%	0%
	Common	Vision blurred	6%	0%	0%	0%
Skin and subcutaneous tissue disorders	Very common	Rash[d]	43%	2%	5%	0%
	Very common	Pruritus	29%	2%	8%	0%
	Common	Dry skin	8%	0%	0%	0%
General disorders and administration site conditions	Very common	Fatigue	33%	0%	15%	0%
	Very common	Face edema	31%	1%	8%	0%
	Very common	Peripheral edema[e]	18%	0%	8%	0%
	Very Common	Generalized edema	13%	1%	0%	0%
Vascular disorders	Very Common	Hypertension	17%	5%	10%	3%
Nervous system disorders	Very common	Neuropathy[f]	12%	1%	3%	0%

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; N=sample size.
a The severity of adverse drug reactions was assessed using CTCAE v5.0.
b Periorbital edema comprises eye oedema, eyelid oedema, periorbital oedema.
c Dry eye comprises dry eye, xerophthalmia.
d Rash comprises rash, rash erythematous, rash macular, rash maculo-papular, rash pruritic, dermatitis acneiform, erythema.

Table 55. Laboratory abnormalities observed in MOTION through week 25

Frequency Category	Laboratory Abnormality	Incidence and CTCAE Grade			
		Vimseltinib N=83		Placebo N=39	
		Any Grade (%)	Grade 3 or 4 (%)	Any Grade (%)	Grade 3 or 4 (%)
Very common	Increased AST	92%	0%	10%	0%
Very common	Increased cholesterol	43%	0%	15%	0%
Very common	Decreased neutrophils	31%	1%	3%	0%
Very common	Increased ALT	24%	0%	15%	0%
Very common	Increased creatinine	17%	0%	3%	0%
Very common	Increased ALP	14%	0%	8%	0%

Abbreviations: AST=aspartate aminotransferase; ALT=alanine transaminase; ALP=alkaline phosphatase; CTCAE=Common Terminology Criteria for Adverse Events.
Note: The severity was assessed using CTCAE v5.0.

ADRs of special interest causally related to the medicinal product

Oedema and rash are very common TEAEs affecting most vimseltinib-treated participants. Both conditions are recognized AEs associated with CSF1R inhibition. Most of these events were typically non-serious and low grade in severity. However, long lasting.

Transient elevations in serum enzymes are also frequently observed in patients treated with CSF1R inhibitors. Changes in chemistry laboratory parameters are further discussed below in this section.

Events of Oedema

Oedema events were reported by 80.9% (148/183) of participants in Pool 1, the most frequently reported oedema PTs were periorbital oedema (45.4% [83/183]), face oedema (25.7% [47/183]), and oedema peripheral (21.3% [39/183]). Periorbital oedema was the only PT with Grade 3 events reported in ≥2 participants. There were no Grade 4 events reported. A total of 79.2% (145/183) of oedema events were considered related to study drug. The only SAE reported was oedema peripheral in 1 participant. In Pool 1, the mean (SD) time from the start of treatment to the first oedema event (onset) was 48.9 days (88.68); 52.4% of first oedema events resolved whereas 47.6% of the events were reported as ongoing, and the median duration of the first event was 226.0 days (range: 1-1019 days).

Events of Rash

Rash events were reported by 55.7% (102/183) of participants in Pool 1, the most frequently reported PTs were rash maculo-papular (23.5% [43/183]), rash (21.3% [39/183]), and dermatitis acneiform (8.7% [16/183]). Grade 3 rash events reported by ≥2 participants were rash maculo-papular (1.6% [3/183]), eczema (1.6% [3/183]), and urticaria (1.1% [2/183]). There were no Grade 4 events reported. Almost all rash events (54.1%, 99/183) considered related to study drug. The only SAE of rash reported was eczema in 1 participant. The mean (SD) time from the treatment start to the first rash event (onset) was 100.5 days

(93.33); 55.4% of first rash events resolved whereas 44.6% of the events were reported as ongoing, and the median duration of the first event was 159.0 days (range: 1-938 days).

Creatine Phosphokinase

In Pool 1, 42.6% (78/183) of participants reported a TEAE of blood CPK increased, with 23.5% (43/183) of participants reporting a Grade 3/4 TEAE. Most TEAEs of blood CPK increased were considered related to study drug (42.1% of participants [77/183]). More details are provided in Table 57.

One participant in Phase 1/2 Cohort B experienced a drug-related SAE of blood CPK increased.

> *"Approximately 16 days after receiving last dose of study drug, the participant experienced two SAEs of blood creatine phosphokinase increased (verbatim term: creatine phosphokinase increased) and myalgia (verbatim term: myalgia) which resulted in hospitalization. The event of blood creatine phosphokinase increased was considered by the Investigator as life-threatening in severity and probably related to the study drug. The event of myalgia was considered by the Investigator as severe in severity and probably related to the study drug. The Sponsor assessed both events as possibly related to study drug. According to CIOMS, the participant "complained of a 2-week history of significant muscle aches, pain and severely limited mobility. Pain was pronounced on bilateral upper and lower extremities, worsened with any physical activity. She was unable to move left upper extremity due to pain. She had trouble walking and experienced falls in the past. She did not have a cane or walker to help with ambulation."*

2.6.8.4. Laboratory findings

Haematology

Table 56. Shift table of haematology parameters from baseline to the worst postbaseline grade per CTCAE criteria – Pool 1 (all participants with TGCT at 30 mg twice weekly)

Parameter Change	Phase 1/2 Study Expansion		MOTION (N=118) n (%)	Cohort A + MOTION (N=164) n (%)	Overall (N=184) n (%)
	Cohort A (N=46) n (%)	Cohort B (N=20) n (%)			
Anaemia					
No change from baseline	36 (78.3)	14 (70.0)	93 (78.8)	129 (78.7)	143 (77.7)
Any worsening	10 (21.7)	6 (30.0)	25 (21.2)	35 (21.3)	41 (22.3)
Worsening to less than Grade 3	10 (21.7)	6 (30.0)	25 (21.2)	35 (21.3)	41 (22.3)
Haemoglobin increased					
No change from baseline	42 (91.3)	20 (100.0)	118 (100.0)	160 (97.6)	180 (97.8)
Any worsening	3 (6.5)	0	0	3 (1.8)	3 (1.6)
Worsening to Grade 3/4	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Worsening to Grade 3	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Worsening to less than Grade 3	2 (4.3)	0	0	2 (1.2)	2 (1.1)
Improve from baseline	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Lymphocyte count decreased					
No change from baseline	23 (50.0)	10 (50.0)	105 (89.0)	128 (78.0)	138 (75.0)
Any worsening	22 (47.8)	10 (50.0)	11 (9.3)	33 (20.1)	43 (23.4)
Worsening to Grade 3/4	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Worsening to Grade 4	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Worsening to less than Grade 3	21 (45.7)	10 (50.0)	11 (9.3)	32 (19.5)	42 (22.8)
Improve from baseline	1 (2.2)	0	2 (1.7)	3 (1.8)	3 (1.6)
Lymphocyte count increased					

Parameter Change	Phase 1/2 Study Expansion		MOTION (N=118) n (%)	Cohort A + MOTION (N=164) n (%)	Overall (N=184) n (%)
	Cohort A (N=46) n (%)	Cohort B (N=20) n (%)			
No change from baseline	45 (97.8)	20 (100.0)	117 (99.2)	162 (98.8)	182 (98.9)
Any worsening	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Worsening to less than Grade 3	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Improve from baseline	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Neutrophil count decreased					
No change from baseline	28 (60.9)	12 (60.0)	72 (61.0)	100 (61.0)	112 (60.9)
Any worsening	16 (34.8)	7 (35.0)	44 (37.3)	60 (36.6)	67 (36.4)
Worsening to Grade 3/4	1 (2.2)	0	4 (3.4)	5 (3.0)	5 (2.7)
Worsening to Grade 3	1 (2.2)	0	4 (3.4)	5 (3.0)	5 (2.7)
Worsening to less than Grade 3	15 (32.6)	7 (35.0)	40 (33.9)	55 (33.5)	62 (33.7)
Improve from baseline	2 (4.3)	1 (5.0)	2 (1.7)	4 (2.4)	5 (2.7)
Platelet count decreased					
No change from baseline	40 (87.0)	19 (95.0)	111 (94.1)	151 (92.1)	170 (92.4)
Any worsening	6 (13.0)	1 (5.0)	6 (5.1)	12 (7.3)	13 (7.1)
Worsening to less than Grade 3	6 (13.0)	1 (5.0)	6 (5.1)	12 (7.3)	13 (7.1)
Improve from baseline	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Leukocytosis					
No change from baseline	46 (100.0)	20 (100.0)	118 (100.0)	164 (100.0)	184 (100.0)
White blood cell decreased					
No change from baseline	28 (60.9)	16 (80.0)	78 (66.1)	106 (64.6)	122 (66.3)
Any worsening	18 (39.1)	4 (20.0)	39 (33.1)	57 (34.8)	61 (33.2)
Worsening to Grade 3/4	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Worsening to Grade 3	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Worsening to less than Grade 3	17 (37.0)	4 (20.0)	39 (33.1)	56 (34.1)	60 (32.6)
Improve from baseline	0	0	1 (0.8)	1 (0.6)	1 (0.5)

Abbreviations: CTCAE=Common Terminology Criteria for Adverse Events; ISS=Integrated Summary of Safety; n=number of participants in a category; N=sample size; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; TGCT=tenosynovial giant cell tumour.
Note 1: Baseline was defined as the most recent non-missing measurement prior to the first administration of vimseltinib.
Note 2; Clinical laboratory values for Phase 1/2 and MOTION were graded programmatically according to the NCI-CTCAE v4.03 and v5.0, respectively.
Note 3: Pool 1 included all participants with TGCT in Phase 1/2 and MOTION who received at least 1 dose of vimseltinib at the recommended dose of 30 mg twice weekly.

Chemistry

Across all pools, the most frequently reported shifts in chemistry laboratory parameters (worsening from baseline in ≥20% of participants) were ALT increased, AST increased, cholesterol high, creatinine increased, hypertriglyceridemia, and hypoglycaemia.

Table 57. Shift table of serum chemistry parameters from baseline to the worst postbaseline grade per CTCAE criteria – Pool 1 (all participants with TGCT at 30 mg twice weekly)

Parameter Change	Phase 1/2 Study Expansion		MOTION (N=118) n (%)	Cohort A + MOTION (N=164) n (%)	Overall (N=184) n (%)
	Cohort A (N=46) n (%)	Cohort B (N=20) n (%)			
Hypoalbuminemia					
No change from baseline	45 (97.8)	20 (100.0)	118 (100.0)	163 (99.4)	183 (99.5)
Improve from baseline	1 (2.2)	0	0	1 (0.6)	1 (0.5)
ALP increased					
No change from baseline	45 (97.8)	19 (95.0)	100 (84.7)	145 (88.4)	164 (89.1)
Any worsening	1 (2.2)	1 (5.0)	18 (15.3)	19 (11.6)	20 (10.9)
Worsening to less than Grade 3	1 (2.2)	1 (5.0)	18 (15.3)	19 (11.6)	20 (10.9)
ALT increased					
No change from baseline	34 (73.9)	14 (70.0)	86 (72.9)	120 (73.2)	134 (72.8)
Any worsening	12 (26.1)	6 (30.0)	32 (27.1)	44 (26.8)	50 (27.2)
Worsening to less than Grade 3	12 (26.1)	6 (30.0)	32 (27.1)	44 (26.8)	50 (27.2)
AST increased					
No change from baseline	1 (2.2)	0	13 (11.0)	14 (8.5)	14 (7.6)
Any worsening	45 (97.8)	20 (100.0)	105 (89.0)	150 (91.5)	170 (92.4)
Worsening to Grade 3/4	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Worsening to Grade 3	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Worsening to less than Grade 3	45 (97.8)	20 (100.0)	104 (88.1)	149 (90.9)	169 (91.8)
Blood bilirubin increased					
No change from baseline	45 (97.8)	19 (95.0)	116 (98.3)	161 (98.2)	180 (97.8)
Any worsening	1 (2.2)	1 (5.0)	2 (1.7)	3 (1.8)	4 (2.2)
Worsening to less than Grade 3	1 (2.2)	1 (5.0)	2 (1.7)	3 (1.8)	4 (2.2)
Cholesterol high					
No change from baseline	16 (34.8)	7 (35.0)	64 (54.2)	80 (48.8)	87 (47.3)
Any worsening	30 (65.2)	13 (65.0)	54 (45.8)	84 (51.2)	97 (52.7)
Worsening to Grade 3/4	1 (2.2)	1 (5.0)	0	1 (0.6)	2 (1.1)
Worsening to Grade 3	1 (2.2)	1 (5.0)	0	1 (0.6)	2 (1.1)
Worsening to less than Grade 3	29 (63.0)	12 (60.0)	54 (45.8)	83 (50.6)	95 (51.6)
Creatinine increased					
No change from baseline	6 (13.0)	2 (10.0)	96 (81.4)	102 (62.2)	104 (56.5)
Any worsening	40 (87.0)	18 (90.0)	21 (17.8)	61 (37.2)	79 (42.9)
Worsening to less than Grade 3	40 (87.0)	18 (90.0)	21 (17.8)	61 (37.2)	79 (42.9)
Improve from baseline	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Chronic kidney disease					
No change from baseline	0	0	83 (70.3)	83 (50.6)	83 (45.1)
Any worsening	0	0	31 (26.3)	31 (18.9)	31 (16.8)
Worsening to less than Grade 3	0	0	31 (26.3)	31 (18.9)	31 (16.8)
Improve from baseline	0	0	2 (1.7)	2 (1.2)	2 (1.1)
Unable to evaluate	46 (100.0)	20 (100.0)	2 (1.7)	48 (29.3)	68 (37.0)
GGT increased					
No change from baseline	1 (2.2)	9 (45.0)	103 (87.3)	104 (63.4)	113 (61.4)
Any worsening	0	3 (15.0)	15 (12.7)	15 (9.1)	18 (9.8)
Worsening to less than Grade 3	0	3 (15.0)	15 (12.7)	15 (9.1)	18 (9.8)
Improve from baseline	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Unable to evaluate	44 (95.7)	8 (40.0)	0	44 (26.8)	52 (28.3)
Hyperkalaemia					

Parameter Change	Phase 1/2 Study Expansion		MOTION (N=118) n (%)	Cohort A + MOTION (N=164) n (%)	Overall (N=184) n (%)
	Cohort A (N=46) n (%)	Cohort B (N=20) n (%)			
No change from baseline	43 (93.5)	19 (95.0)	116 (98.3)	159 (97.0)	178 (96.7)
Any worsening	3 (6.5)	0	1 (0.8)	4 (2.4)	4 (2.2)
Worsening to Grade 3/4	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Worsening to Grade 4	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Worsening to less than Grade 3	2 (4.3)	0	1 (0.8)	3 (1.8)	3 (1.6)
Improve from baseline	0	1 (5.0)	1 (0.8)	1 (0.6)	2 (1.1)
Hypokalaemia					
No change from baseline	42 (91.3)	19 (95.0)	116 (98.3)	158 (96.3)	177 (96.2)
Any worsening	4 (8.7)	1 (5.0)	2 (1.7)	6 (3.7)	7 (3.8)
Worsening to less than Grade 3	4 (8.7)	1 (5.0)	2 (1.7)	6 (3.7)	7 (3.8)
Hypermagnesemia					
No change from baseline	45 (97.8)	18 (90.0)	102 (86.4)	147 (89.6)	165 (89.7)
Any worsening	1 (2.2)	2 (10.0)	16 (13.6)	17 (10.4)	19 (10.3)
Worsening to Grade 3/4	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Worsening to Grade 3	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Worsening to less than Grade 3	1 (2.2)	2 (10.0)	15 (12.7)	16 (9.8)	18 (9.8)
Hypomagnesemia					
No change from baseline	45 (97.8)	20 (100.0)	118 (100.0)	163 (99.4)	183 (99.5)
Any worsening	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Worsening to less than Grade 3	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Hypernatremia					
No change from baseline	44 (95.7)	20 (100.0)	115 (97.5)	159 (97.0)	179 (97.3)
Any worsening	2 (4.3)	0	3 (2.5)	5 (3.0)	5 (2.7)
Worsening to less than Grade 3	2 (4.3)	0	3 (2.5)	5 (3.0)	5 (2.7)
Hyponatremia					
No change from baseline	42 (91.3)	19 (95.0)	118 (100.0)	160 (97.6)	179 (97.3)
Any worsening	4 (8.7)	1 (5.0)	0	4 (2.4)	5 (2.7)
Worsening to less than Grade 3	4 (8.7)	1 (5.0)	0	4 (2.4)	5 (2.7)
Hypertriglyceridemia					
No change from baseline	29 (63.0)	12 (60.0)	88 (74.6)	117 (71.3)	129 (70.1)
Any worsening	16 (34.8)	7 (35.0)	27 (22.9)	43 (26.2)	50 (27.2)
Worsening to Grade 3/4	1 (2.2)	0	1 (0.8)	2 (1.2)	2 (1.1)
Worsening to Grade 3	1 (2.2)	0	1 (0.8)	2 (1.2)	2 (1.1)
Worsening to less than Grade 3	15 (32.6)	7 (35.0)	26 (22.0)	41 (25.0)	48 (26.1)
Improve from baseline	1 (2.2)	1 (5.0)	3 (2.5)	4 (2.4)	5 (2.7)
Hypoglycaemia					
No change from baseline	32 (69.6)	11 (55.0)	97 (82.2)	129 (78.7)	140 (76.1)
Any worsening	14 (30.4)	8 (40.0)	20 (16.9)	34 (20.7)	42 (22.8)
Worsening to less than Grade 3	14 (30.4)	8 (40.0)	20 (16.9)	34 (20.7)	42 (22.8)
Improve from baseline	0	1 (5.0)	1 (0.8)	1 (0.6)	2 (1.1)

Abbreviations: ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; GGT=gamma-glutamyl transferase; ISS=Integrated Summary of Safety; n=number of participants in a category; N=sample size; NCI-CTCAE=National Cancer Institute-Common Terminology Criteria for Adverse Events; TGCT=tenosynovial giant cell tumour.
Note 1: Baseline was defined as the most recent non-missing measurement prior to the first administration of vimseltinib.
Note 2: Clinical laboratory values for Phase 1/2 and MOTION were graded programmatically according to the NCI-CTCAE v4.03 and v5.0, respectively.
Note 3: Pool 1 included all participants with TGCT in Phase 1/2 and MOTION who received at least 1 dose of vimseltinib at the recommended dose of 30 mg twice weekly.

Hepatotoxicity

In non-clinical studies, hepatotoxicity was identified as a potentially relevant safety risk also for the human population, probably associated with the mechanism of action. Across all pools, the most frequently reported shifts in chemistry laboratory parameters (worsening from baseline in ≥20% of participants) were ALT increased, and AST increased.

In Pool 1, ALT was increased in 27.2% (50/184) of the subjects and AST was increased in almost all (92.4% [170/184]). However, only one subject showed an event of worsening to Grade 3/4 for AST increased (0.5% [1/184]). Although ALT an particular AST increases were frequently observed in participants who received vimseltinib, a small proportion of elevations were ≥3×ULN (16 participants total). None of these elevations were accompanied by >1×ULN of total bilirubin. No potential Hy's Law cases were identified.

Electrocardiogram

From the ECG data as submitted in the integrated analysis of the MOTION and Phase 1/2 studies no effect of vimseltinib on cardiac function was identified. It appears that that vimseltinib did not appear to have an effect on the QTcF interval, which is in line with preclinical assumptions (no impact on hERG). No signal was detected for any increase in cardiotoxicity in humans from the reported AEs in contrast to toxicological trials.

Blood pressure

A total of 89.7% (165/184) of participants in Pool 1 had a systolic BP within the normal range (<140 mmHg) at baseline, and 96.7% (178/184) of participants had a diastolic BP within normal range (<90 mmHg) at baseline. The mean (SD) baseline systolic and diastolic BPs for all participants in Pool 1 were 123.9 (13.01) and 75.3 (9.38) mmHg, respectively. A total of 38.6% (71/184) of participants experienced no shift in postbaseline systolic BP during treatment, and 10.9% (20/184) of participants experienced a maximum shift in systolic BP from baseline from <140 to ≥160 mmHg. A total of 46.2% (85/184) of participants experienced no shift in postbaseline diastolic BP, and 6.5% (12/184) of participants experienced a maximum shift in diastolic BP from baseline from <90 to ≥100 mmHg.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable.

2.6.8.6. Safety in special populations

Subgroup analyses of TEAEs and SAEs by age, sex, and race were performed for each analysis pool in the integrated analysis of the MOTION and Phase 1/2 studies. Overall, the results observed for subgroup analysis were similar to the overall safety results observed for each analysis pool. No major differences were observed by age, sex, or race. (With respect to effects if renal and hepatic impairment please refer to the PK section of this AR.

2.6.8.7. Immunological events

No information regarding immunological events was provided. It remains uncertain whether antibody formation against vimseltinib at least in patients who lost response or developed resistance was actually investigated during the clinical development.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Vimseltinib is an inhibitor of BCRP and P-gp. Concomitant use of vimseltinib with BCRP or P-gp substrates may increase the concentrations of BCRP substrates or Ppg substrate and increase the risk of adverse reactions related to these substrates.

The impact of food interaction is also low, thus, vimseltinib is taken twice weekly at least 3 days apart with or without food.

2.6.8.9. Discontinuation due to adverse events

Treatment-emergent AEs leading to discontinuation occurred in 9.3% (17/183) of participants in Pool 1. The most frequently reported TEAEs leading to treatment discontinuation were rash and periorbital oedema (each reported in 1.6% of participants [3/183]). Details are provided in the Table below:

Table 58. Treatment-emergent adverse events leading to treatment discontinuation by system organ class and preferred term – Pool 1 (all participants with TGCT at 30 mg twice weekly)

System Organ Class Preferred Term	Phase 1/2 Study Expansion		MOTION (N=118) n (%)	Cohort A + MOTION (N=164) n (%)	Overall (N=183)[a] n (%)
	Cohort A (N=46) n (%)	Cohort B (N=20) n (%)			
Any TEAE leading to treatment discontinuation	6 (13.0)	2 (10.0)	9 (7.6)	15 (9.1)	17 (9.3)
Skin and subcutaneous tissue disorders	3 (6.5)	2 (10.0)	3 (2.5)	6 (3.7)	8 (4.4)
Rash	0	1 (5.0)	2 (1.7)	2 (1.2)	3 (1.6)
Pruritus	0	0	2 (1.7)	2 (1.2)	2 (1.1)
Rash maculo-papular	1 (2.2)	1 (5.0)	0	1 (0.6)	2 (1.1)
Dermatitis acneiform	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Eczema	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Eye disorders	2 (4.3)	0	2 (1.7)	4 (2.4)	4 (2.2)
Periorbital oedema	1 (2.2)	0	2 (1.7)	3 (1.8)	3 (1.6)
Eyelid oedema	1 (2.2)	0	0	1 (0.6)	1 (0.5)
General disorders and administration site conditions	1 (2.2)	0	1 (0.8)	2 (1.2)	2 (1.1)
Asthenia	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Face oedema	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Generalised oedema	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (2.2)	0	1 (0.8)	2 (1.2)	2 (1.1)
Breast cancer	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Plasma cell myeloma	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Nervous system disorders	0	0	2 (1.7)	2 (1.2)	2 (1.1)
Paraesthesia	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Peripheral sensory neuropathy	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Cardiac disorders	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Palpitations	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Musculoskeletal and connective tissue disorders	1 (2.2)	0	0	1 (0.6)	1 (0.5)

System Organ Class Preferred Term	Phase 1/2 Study Expansion		MOTION (N=118) n (%)	Cohort A + MOTION (N=164) n (%)	Overall (N=183)[a] n (%)
	Cohort A (N=46) n (%)	Cohort B (N=20) n (%)			
Mixed connective tissue disease	1 (2.2)	0	0	1 (0.6)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Pneumonitis	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Vascular disorders	0	0	1 (0.8)	1 (0.6)	1 (0.5)
Hypertension	0	0	1 (0.8)	1 (0.6)	1 (0.5)

Abbreviations: AE=adverse event; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants in a category; N=sample size; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event; TGCT=tenosynovial giant cell tumour.

[a] One participant from the Expansion Phase (Cohort A) re-enrolled into Cohort B. This participant was counted as 1 participant for the total column.

Note 1: MedDRA v26.0 was used. TEAE was defined as any AE that occurred or worsened after the administration of the first dose of vimseltinib and through 30 days after the last dose of vimseltinib or the day before the start of new anti-tumour therapy.

Note 2: Drug-related AEs reported after 30 days following the last dose of vimseltinib were considered treatment-emergent.

Note 3: If an SOC or PT was reported more than once for a participant, the participant was counted only once in the incidence for that SOC or PT.

Note 4: Pool 1 included all participants with TGCT in Phase 1/2 and MOTION who received at least 1 dose of vimseltinib at the recommended dose of 30 mg twice weekly.

2.6.8.10. Adverse events leading to dose modification

Treatment-emergent AEs leading to dose modification (reduction or interruption) occurred in 74.3% (136/183) of participants in Pool 1. The most frequently PT reported TEAEs were blood CPK increased (16.9% [31/183]), periorbital oedema (13.7% [25/183]), asthenia (12.0% [22/183]), pruritus (9.8% [18/183]), rash maculo-papular (9.3% [17/183]), and COVID-19 (8.2% [15/183]).

2.6.8.11. Post marketing experience

During this MAA procedure vimseltinib was approved in the US on 14.02.2025, however, as far as known no post marketing data is available from this source.

2.6.9. Discussion on clinical safety

When assessing the safety of vimseltinib in adult patients with TGCT, it is important to consider that TGCT is a non-malignant condition. While it can cause significant symptoms and impair joint mobility, it does not impact overall life expectancy. Most patients can be cured with surgery and radiation alone.

Safety data collection in the pivotal MOTION trial and the supportive Phase 1/ 2 trial is overall acceptable and fulfils the appropriate standards to characterised safety. Frequency of safety assessment was triggered by the efficacy evaluation, which raise no specific concern.

Exposure

In total, 464 study participants have been exposed to at least 1 dose of vimseltinib. However, only 184 participants with TGCT (Pool 1) received the proposed dose of vimseltinib 30 mg twice weekly. While the

majority were included in MOTION trial (N=118, including cross-over from 35 placebo arm subjects in Part 2), the other were treated in Cohort A (N=46) and Cohort B (N=20) of the Phase 1/ 2 trial. Pool 1 data is most relevant for the applied posology and no relevant additional information was raised from the assessment of the other pools (2+3) (data not shown).

Median duration of exposure is reported with 13.0 months (range: 0 to 36 months), the median age was 44 years (range from 20 to 78 years) and the population was 60% female and 72% White for the 184 TGCT patients in the pooled safety population. 138 (75.0%) subjects were still on treatment at cut-off date for submission. With respect to the duration of treatment, 101 subjects (54.95 %) were treated for more than 12 months, which appears insufficient for the assessment of potential long-term consequences for the intended long-term treatment with a new product and a new mechanism of action for which experience is very limited.

In the pivotal MOTION population, median duration of exposure was similar between placebo and vimseltinib arm (5.5 months) (data not shown). The median relative dose intensity was 87.5% for vimseltinib and 95.8% for placebo and overall significant more subjects in the vimseltinib arm (V: 59.0% vs Plc:12.8%) had a dose modification caused by adverse events. 6.0% of the vimseltinib treated participants experienced treatment discontinuation due to TEAE during double-blind period. Together these data indicate that vimseltinib' s toxicity during the first 25 weeks is clinically relevant and not trivial. This is confirmed by the data in the larger pool 1, which includes all TGCT subjects who had received 30 mg vimseltinib with the applied posology.

Comparing the demographic characteristics of the included study population with literature data (e.g. Ehrenstein et al, 2017) it is confirmed that the trial population adequately reflects the applied target population. Males were slightly underrepresented in the trial population and Caucasians dominate the cohort. A majority of participants (67.9% [125/184]) were enrolled in sites in Europe.

Adverse events, serious adverse events and deaths

Overall, 95.2% of patients experienced at least one treatment-related adverse event in comparison to 74.4% in the placebo-arm. The 20.8 % difference to placebo during the first 25 weeks characterises that treatment is associated with a higher number of AEs in the target population.

Comparing the differences observed for other relevant safety key parameters, e.g. related grade ≥3 TEAEs events (30.1% in vimseltinib patients compared with 2.6% in the placebo arm) or the rates for TE-SAEs and related TE-SAEs (TE-SAEs: V: 7.2% versus PLB: 2.6%/ related TE-SAEs: V:1.2% vs. PLB:0%), indicate an increase of safety risks due to vimseltinib which appears clinically relevant.

In Pool 1, the drug-related TEAEs reported in ≥25% of participants were periorbital oedema (44.8% [82/183]), blood CPK increased (42.1% [77/183]), fatigue (28.4% [52/183]), asthenia (27.9% [51/183]), headache (27.3% [50/183]), AST increased (26.2% [48/183]), pruritus (26.2% [48/183]), and face oedema (25.1% [46/183]).

Comparing the differences of TEAE frequencies regarding the preferred term of vimseltinib and placebo treated TGCT patients in the clinical trials, the following adverse events were clearly related to vimseltinib (difference ≥ 10% not in favour for vimseltinib): Periorbital oedema (+31.8%), Blood CPK increased (+24.1%), Pruritus (+21.2%), AST (+20.3), Rash, maculo-papular (19.3%), Fatigue (+17.1%), Rash (+14.2%) and Oedema peripheral (10.4%).

The same TEAEs led to dose modification (reduction or interruption) in 74.3% (136/183) of participants in Pool 1 (see *Discontinuation, dose reduction and treatment interruptions due to AEs* below).

The majority of the most frequently reported TEAEs (≥25% of participants) in Pool 1, were experienced during the first year of vimseltinib exposure, and the incidence did not increase over time. According to the information provided in the limited population treated from longer than one year, it appears that all TEAEs occurring in Years 2 through 4 did not reveal an increased incidence of events typically occurring with long latency. No new signals for worsening of cardiovascular toxicities, secondary malignancies, renal or hepatic toxicities, or other clinically significant AEs were reported from the limited and pre-selected subjects with long-term vimseltinib-exposure. Overall, these data are not very informative but illustrate that exposure for periods beyond the second year is limited.

Adverse drug reactions

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Long-term safety

Long-term safety data remain largely missing, with only a few subjects treated over longer periods of time. As a results, it is currently not possible to assess the long-term effects of CSF1R (and other kinases) inhibition. Given that this is a novel, continuously dosed treatment for a non-life-threatening condition, robust long-term safety data are of utmost importance. Safety data from healthy volunteers offer limited value, as these subjects have a limited exposure and might receive only a single or few doses. In contrast, data from TGCT patients are more relevant, as patients with advanced malignancies may have additional risks from their disease and prior treatments. Ultimately, sufficient long-term safety data are needed to identify potential adverse events that appear more infrequently. As a results, 'long-term safety' was classified as missing information in the RMP. To address this safety concern, the applicant has committed to conducting a PASS study (Category 3 PASS, required additional pharmacovigilance activities, MEA). Study design and timelines will be defined after submitting the feasibility assessment to PRAC in November 2025. In addition, a warning has been included in section 4.4 of the SmPC to indicate that the long-term safety of Romvimza has not been established.

Malignancies

Two SAE of malignancy were observed during the placebo phase of MOTION. In Pool 1, 6 (3.3%) participants experienced TEAEs within the SMQ Malignancies (broad). With the exception of 1 participant with prior medical history of squamous cell carcinoma who experienced multiple events (basal cell carcinoma and squamous cell carcinoma of skin), all events were assessed as unrelated to vimseltinib. While all of the events observed in clinical trials were either assessed as unrelated or confounded by prior medical history, malignancies are considered an important potential risk as the relevance of the non-clinical findings from the 2-year rat carcinogenicity study are unknown, and this has been reflected in the RMP. 'Malignancies 'will be further characterised as part of the Category 3 PASS.

Renal impairment due to Rhabdomyolysis/Myositis

One of the most frequently observed TEAE was Blood CPK increased and most grade 3/ 4 events in MOTION were also reported for this adverse event. Since the observed AST increases were significantly higher than the ALT increases, it was presumed that rhabdomyolysis or drug-induced myositis may be the reason behind the discrepant AST increases.

Chronic rhabdomyolysis/myositis can affect the renal function, which may cause arterial hypertension. Thus, a high increase of post-baseline creatinine levels was observed in 17.8% of the vimseltinib subjects during the first 25 weeks in MOTION trial and in up to 42.9% in the total population, which includes more subjects with longer treatment. This may indicate a risk for renal impairment associated with vimseltinib treatment and would be in line with the observation that overall, 43.1% of the participants developed an increase in systolic and diastolic BP over baseline upper limit of <140 mmHg systolic and ≥90 mmHg after baseline. Moreover, one life-threatening SAE case of CPK increase occurred in the Phase 1/ 2 trial and focused intention.

Taking all together, it was presumed that the high rate of CPK increases could reflect clinically relevant low-grade rhabdomyolysis or myositis, which during longer treatment may impair renal function as reflected by the concomitant increase of creatinine and hypertension rate.

However, since the applicant clarified that no myoglobinuria or discoloured urine was detected in this subject, it appears not plausible that rhabdomyolysis explains the very frequent CPK elevations in the MOTION population alone. Similarly, it was clarified that CPK elevation are unlikely to be related to brain damage.

Nevertheless, although no cases of rhabdomyolysis with organ involvement have been reported, observed treatment interruptions and hospitalisations indicate a potential clinical impact of this adverse event. The Applicant attributes these elevations to reduced hepatic clearance of muscle enzymes due to hepatic macrophage depletion; however, this hypothesis does not entirely rule out underlying muscle toxicity.

Considering the non-clinical signals for chronic progressive nephropathy in animals and the observed related increase in creatinine and blood pressure, an impact of vimseltinib on renal function and blood pressure appears probable and are included in the RMP. 'Muscle injury/Rhabdomyolysis' and 'Nephrotoxicity' were classified as important potential risks in the RMP. These safety concerns will be further characterised as part of the Category 3 PASS study.

Skin adverse events

Cutaneous adverse events (rash, erythema and oedema) may be seen as class effects due to the mechanism of action, but are difficult to interpret. Oedema events (broad term search) were reported in up by 80.9% (148/183) of participants in Pool 1 and 74.5% (187/251) of participants in Pool 3. Rash, periorbital oedema and pruritus were the most frequently reported TEAEs leading to treatment discontinuation. These have been reflected as ADR in section 4.8 of the SmPC.

It was clarified that the association between increased CPK and the occurrence of rash seems not indicating dermatomyositis. Similarly, there appears to be no evidence that these rash and erythema are caused by vasculitis, a frequently toxic non-clinical finding. However, no further confirmative histology or specific diagnostics appears to be available.

Pruritus, facial oedema/periorbital oedema, and xerosis (dry skin) are a class-effect safety event and are presumed to be caused because of depleting or functionally disrupting macrophages in the skin. Events are described as overall manageable with concomitant administration of antihistaminics. Whether an increase of cutaneous adverse events over the time occurs remains unknown. A statement has been included in section 4.2 of the SmPC to indicate that dose interruptions or dose reductions may be required for patients experiencing pruritus based on individual safety and tolerability.

Hepatotoxicity

In non-clinical studies, hepatotoxicity was identified as a potentially relevant safety risk also for the human population, probably associated with the mechanism of action. Across all pools, the most frequently reported shifts in chemistry laboratory parameters (worsening from baseline in ≥20% of participants) were ALT increased, and AST increased.

In Pool 1, ALT was increased in 27.2% (50/184) of the subjects and AST was increased in almost all (92.4% [170/184]). However, only one subject showed an event of worsening to Grade 3/4 for AST increased (0.5% [1/184]). For the pool 3 population, including all participants in both trials with TGCT, 29 (11.5%) participants experienced ALT or AST elevations ≥3×ULN, none of which were associated with bilirubin >1×ULN (data not shown). Of the 4 participants with TGCT with bilirubin >1×ULN, 1 initiated vimseltinib treatment with elevated bilirubin at baseline; the remaining 3 participants experienced Grade 1 bilirubin elevations <1.5×ULN lasting 1 to 3 cycles that returned to normal range without any subsequent elevations. No participants modified or discontinued treatment with vimseltinib due to TEAEs of blood bilirubin increased. No potential Hy's Law case was identified until cut-off-date.

The mechanism behind the liver toxicity indicated by animal and human data remains unclear. Despite structural and metabolic differences with pexidartinib -known for its hepatic toxicity-, long-term hepatic toxicity cannot be ruled out due to the absence of histological data in patients treated with vimseltinib. The proportion of patients with AST elevations ≥3xULN (7.6% to 10.7%) was not negligible and structural changes as consequence of the regression of Kupffer cells in the liver may occur.

As a consequence 'Drug-induced liver injury (DILI)' has been classified as important potential risk in the RMP. This safety concern will be further characterised as part of the Category 3 PASS study.

Vimseltinib should be avoided in patients with pre-existing serum transaminase elevations, total bilirubin or direct bilirubin elevations, or active liver or biliary tract disease. Patients should be monitored for liver function prior to the start of Romvimza, once a month for the first two months and once every 3 months for the first year of therapy and as clinically indicated thereafter (see section 4.4 of the SmPC).

Cognitive Disorders

Vimseltinib was highly brain penetrant, but the toxic effects of the brain penetration and the clinical relevance of the effects on microglia observed in the non-clinical animals are currently not known. In some clinical trials with other products of the same class, occurrence of cognitive disorders and memory disturbance as part of potential neurotoxicity was frequent and led to treatment discontinuation in several subjects. This raised concerns regarding a class effect toxicity for CSF1R inhibiting products like vimseltinib.

In vimseltinib treated subjects only 9/251 subjects of pool 4 developed low grade and non-serious TEAEs regarding cognitive disorders (data not shown), which appears to be not concerning. However, it is not addressed whether these events were assessed as drug-related and reversible after discontinuation. Since cognitive disorders are multifactorial, a valid assessment needs an adequate specifically testing to be reliable. The applicant reported that there was an embedded exit interview study with 96 patients out of the 123 randomised participants as a part of the MOTION study with the objective of the exit interview study to cognitively debrief on the PROMIS -PF, PGIS, PGIC, and Worst Stiffness NRS to evaluate the relevance and comprehension for each measure as well as the understanding of the response scales for each measure. Interviews were conducted within 28 days prior to the End of Part 1 visit (Week 25), and prior to unblinding. Beside the discussion whether the selected approach is validated, it appears challenging to accept this approach alone to rule out any impact of vimseltinib on cognitive disorders. As a result, 'Cognitive

disorders/CNS adverse events' has been classified as important potential risk in the RMP and will be further characterised as part of the Category 3 PASS.

Cardiac Disorders

Vimseltinib did not demonstrate a clinically relevant hERG inhibition and based on the integrated analysis, vimseltinib did not appear to have any effect on the QTcF interval neither in non-clinical nor in clinical trials. In Pool 1, 15.4% (28/184) of participants experienced a QTcF increase from baseline >30 ms and 1.1% (2/184) of participants experienced a QTcF increase from baseline >60 ms.

Since only one case of palpitations is reported as cardiac TEAEs in the vimseltinib population (from MOTION trial), cardiac toxicity is currently not an identified safety risk according to the data.

Vimseltinib treatment is associated with an increased risk to develop arterial hypertension. Overall, 43.1% participants with systolic BP at baseline <140 mmHg experienced a shift in postbaseline BP to ≥140 mmHg and 41.5% of participants with diastolic BP at baseline <90 mmHg experienced a shift in diastolic BP to ≥90 mmHg. Considering the observed increase of creatinine post baseline, a causal relationship with vimseltinib probably indicating induction of renal impairment may be presumed. In total, 19 vimseltinib-treated participants experienced TEAEs of hypertension during the MOTION study who did not have previous medical history of hypertension, 11 (57.9%) of whom reported a concomitant antihypertensive medication.

'Arterial hypertension' has been classified as important identified risk in the RMP and will be further characterised as part of the Category 3 PASS. A warning has been included in section 4.4 of the SmPC to indicate that the treatment with vimseltinib in clinical studies was frequently associated with an increase in blood pressure and de-novo diagnosis of arterial hypertension.

Myelosuppression

Due to its mode of action vimseltinib causes myelosuppression, which in clinical trials was mainly of low grade. TEAEs like anaemia, neutropenia and decreases in other leukocytes as well as thrombocytopenia, occurred more frequent in the vimseltinib treated TGCT population than in the placebo arm.

In Pool 1, neutrophil count decreased in 36.4% of the patients [67/184]) and white blood cell decreased was reported slightly higher with 33.2% [61/184]). However, only few participants showed worsening to Grade 3/4 (2.7% [5/184] of participants with neutrophil count decreased and 0.5% [1/184] of participants with white blood cell decreased). However, this reflects only the short-term safety up to ~12 months. The impact of long-term treatment on bone marrow function and bone marrow microenvironment as well as spleen function seems important considering the drug's mode of action.

Vimseltinib might have from the mechanism of action an impact on the bone-marrow microenvironment and the macrophage/monocytic system, which may induce potentially dangerous irreversible changes in bone marrow function during longer treatment periods not assessable at present.

Currently, infection rates are not concerning in the small population investigated. However, it remains uncertain whether long-term depletion of macrophages in the liver, skins and other organs may lead to increase of infection rates. Particularly to the reduced clearance capacity from intestinal derived bacteria in the liver and skin infections (considering the high rate of cellulitis events) concerns are not resolved and clarification is expected from the PASS and post-marketing data.

Laboratory abnormalities

Besides the already discussed abnormal hematologic, increased CPK and liver laboratory results, information regarding other potential laboratory abnormalities was not further discussed. As mentioned already above, the impact of vimseltinib on renal and liver function during long term treatment remains uncertain, and will be further explored as part of the PASS and post-marketing data.

Immunological events

No information regarding immunological events was provided.

Safety in special populations

It is acknowledged that subgroup analyses in small orphan-disease target populations like TGCT are difficult to interpret and the reliability of this data is often questionable. Additionally, disease immanent limitations in the population (e.g. few patients elder that 65 years with TGCT are available and included) have an additional impact on the outcome of such analyses. Overall, the results observed for subgroup analysis were rather like the overall safety results observed for each analysis pool. No major differences were observed by geographic region or prior systemic therapy.

Due to the age structure in an orphan disease population, safety in elderly remains not sufficiently established from the MOTION trial. It remains uncertain whether differences need to be considered.

Discontinuation, dose reduction and treatment interruption due to AEs

Treatment-emergent AEs leading to discontinuation occurred in 9.3% (17/183) of participants in Pool 1. However, after long treatment follow-up at week 97 it appears that only 19/83 of the studied population was still on treatment while 77% discontinued. The most frequently reported TEAEs leading to treatment discontinuation occurred in the SOC "Skin and subcutaneous tissue disorders "(rash, periorbital oedema and pruritus), while non-response was probably the most frequent reason for discontinuation.

9 to 10% of the TGCT population from Pool 1 to 4 discontinued due to TEAEs. Mostly due TEAEs regarding the SOCs Skin and subcutaneous tissue disorders (rash, pruritus) and Eye disorders (periorbital oedema). It is noted that withdrawal of subject's consent was reported in 16.5 % of the vimseltinib treated population in the phase 1/ 2 trial and about 5% in MOTION. In the provided week 97 analysis, it appears that only 19 subjects (probably those with CR) were treated in the trial while all others have discontinued. (22 Feb 2025). Considering that ~50 % of the 83 subjects were non-responders, it seems that also many subjects who reached ORR discontinued the trial probably due to adverse events after 97 weeks of treatment.

2.6.10. Conclusions on the clinical safety

Vimseltinib's safety profile in the treatment of a non-malignant tumour with normal life expectancy remains incompletely characterised. Relevant safety data is only available from 184 patients (Pool 1) with a median treatment duration of approximately 14 months, which limits the ability to fully assess long-term risks in this orphan disease population.

Despite this limited exposure, several safety concerns have emerged. Clinically relevant risks include hepatic and hypertension as well as renal adverse events, as well as persistent skin toxicities.

The CHMP considers the following measures necessary to address issues related to safety:

A PASS (Category 3 PASS, MEA) will be conducted to assess the long-term safety and tolerability of vimseltinib and further characterise the safety concerns of arterial hypertension, DILI, muscle injury/rhabdomyolysis, nephrotoxicity, cognitive disorders/CNS adverse events and malignancies.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	Arterial hypertension
Important potential risk	Embryo-foetal toxicity Drug-Induced Liver Injury (DILI) Muscle injury/Rhabdomyolysis Nephrotoxicity Cognitive disorders/CNS Adverse Events Malignancies
Missing information	Long-term safety

2.7.2. Pharmacovigilance plan

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None				
Category 3 - Required additional pharmacovigilance activities				
DCC-3014-04-002 Planned	• The study design and objectives will be determined following a comprehensive feasibility assessment currently in progress	Arterial hypertension Drug-Induced Liver Injury (DILI) Muscle injury/ Rhabdomyolysis Nephrotoxicity	Study start date	To be determined (TBD)
			Study end date	TBD

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
		Cognitive disorders/CNS adverse events Malignancies Long-term safety	Final study report	TBD

2.7.3. Risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Arterial hypertension (Important Identified risk)	Routine risk minimisation measures: • *SmPC sections 4.4 and 4.8* • *Package leaflet section 2* Other routine risk minimisation measures beyond SmPC/Product information: • *Prescription medicine* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *PASS (DCC-3014-04-002)*
Embryo-foetal toxicity (Important potential risk)	Routine risk minimisation measures: • *SmPC sections 4.3, 4.4, 4.5, 4.6 and 5.3* • *Package leaflet section 2* Other routine risk minimisation measures beyond SmPC/Product information: • *Prescription medicine* Additional risk minimisation measures: • *Patient card* • *HCP guide*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *None*
Drug-induced liver injury (DILI) (Important potential risk)	Routine risk minimisation measures: • *SmPC sections 4.4 and 5.1* • *Package leaflet section 2* Other routine risk minimisation measures beyond SmPC/Product information:	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities:

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	• *Prescription medicine* Additional risk minimisation measures: • *None*	• *PASS (DCC-3014-04-002)*
Muscle injury/Rhabdomyolysis (Important potential risk)	Routine risk minimisation measures: • *SmPC sections 4.4 and 5.1* Other routine risk minimisation measures beyond SmPC/Product information: • *Prescription medicine* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: • *PASS (DCC-3014-04-002)*
Nephrotoxicity (Important potential risk)	Routine risk minimisation measures: • *SmPC section 4.4* • *Package leaflet section 2* Other routine risk minimisation measures beyond SmPC/Product information: • *Prescription medicine* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *Specific adverse reaction follow-up questionnaire* Additional pharmacovigilance activities: • *PASS (DCC-3014-04-002)*
Cognitive disorders/CNS adverse events (Important potential risk)	Routine risk minimisation measures: • *SmPC section 4.4* • *Package leaflet section 2* Other routine risk minimisation measures beyond SmPC/Product information: • *Prescription medicine* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *PASS (DCC-3014-04-002)*
Malignancies (Important potential risk)	Routine risk minimisation measures: • *SmPC section 5.3* Other routine risk minimisation measures beyond SmPC/Product information: • *Prescription medicine*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *PASS (DCC-3014-04-002)*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	Additional risk minimisation measures: • *None*	
Long-term safety (Missing information)	Routine risk minimisation measures: • *SmPC section 4.4* • *Package leaflet section 2* Other routine risk minimisation measures beyond SmPC/Product information: • *None* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *PASS (DCC-3014-04-002)*

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.7 is acceptable.

2.8. Pharmacovigilance

2.8.1. 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.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 14.02.2025. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. 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.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Romvimza (vimseltinib) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

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

The finally agreed indication is:

> *"ROMVIMZA is indicated for treatment of adult patients with symptomatic tenosynovial giant cell tumour (TGCT) associated with clinically relevant physical function deterioration and in whom surgical options have been exhausted or would induce unacceptable morbidity or disability."*

3.1.1. Disease or condition

Tenosynovial giant cell tumour (TGCT) is a rare, non-malignant proliferative neoplasm involving the synovium and tendon sheaths that typically presents in young and middle-aged adults. TGCT almost always involves a single joint; the knee and ankle synovial structures are most commonly affected, while involvement of the shoulder, elbow, wrist/hand, and hip is less common. Symptoms often include pain, stiffness, swelling, and reduced range of motion (ROM) of the affected joint, which may result in marked functional limitation.

For disease management please refer to section 2.1.5 above.

3.1.2. Available therapies and unmet medical need

Despite a lack of hard evidence, once TGCT has been diagnosed, different situations can be distinguished for this non-malignant proliferative neoplasm:

- symptoms are absent or mild (primary disease or recurrence): as there is no systemic risk, and given present-day means of imaging surveillance progression can be monitored on radiological and clinical surveillance;
- symptomatic localized forms: maximal surgical resection is recommended; in case of total resection clinical results are mostly good and show little recurrence (van der Heijden et al, 2023).
- symptomatic diffuse articular forms:
    - first-line resection should be as complete as possible (combined arthroscopic and open surgery in the knee; arthroscopic or open surgery in the hip, according to extension and location). Isotopic synoviorthesis or external RT may be considered as adjuvants, especially when synovectomy was incomplete and in joints other than the knee.

- in recurrence or rapid progression, when total resection is not feasible or would induce severe morbidity, options comprise subtotal resection with adjuvant therapy, or exclusive therapy. This includes systemic treatment by targeted therapy (off-label use of imatinib recommended by NCCN guidelines, or nilotinib) or radiation therapy (Gronchi et al, 2021; Stacchiotti et al, 2023).

In conclusion, diffuse forms of the disease can be challenging to manage surgically, and local control is uncertain with a risk of multiple recurrences, and affected patients often have more extensive involvement and a poorer likelihood of success with surgery (van der Heijden et al, 2023). Surgical resection may involve removal of major tendons, neurovascular structures, or limbs, leading to significant postsurgical morbidity.

Considering the severe morbidity that a patient can experience with in particular diffuse TGCT in recurrence, (or rapid progression), when surgery is not appropriate (or unresectable disease) and when radiotherapy is not an option, a systemic therapy that provides a meaningful clinical benefit in these situations is highly needed. The aim of systemic therapy in the context of a non-lethal tumour which is not amenable to surgery could also be to reduce the tumour in a dimension which allows successful resection (neo-adjuvant setting) and to preserve joint function and improve patient quality of life.

With respect to a systemic treatment option pexidartinib, a product with a similar mechanism of action, was approved in the US in 2019 for "*adult patients with symptomatic tenosynovial giant cell tumor (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery*". However, due to uncertainties concerning the translation of clinical activity into clinically relevant benefit in conjunction with significant toxicity (in particular severe hepatotoxicity) in a non-malignant proliferative disease, it was not authorised in the EU (application refused in 2020).

3.1.3. Main clinical studies

The main evidence regarding efficacy and safety of vimseltinib in the applied broad TGCT indication is provided from one pivotal Phase III trial (DCC-3014-03-001; MOTION).

MOTION was a multicentre, 2:1 randomised, placebo-controlled study investigating vimseltinib monotherapy in patients with histological TGCT (V: n=83 vs PLc: n=40) located in a single joint for which surgical resection will potentially cause worsening functional limitation or severe morbidity. The study evaluated efficacy, safety, clinical outcome assessments, pharmacokinetics (PK), and pharmacodynamics of vimseltinib. Randomisation was stratified by tumour location (lower limb/all other) and region (U.S./non-U.S.).

MOTION trial includes 2 parts: Part 1 consists of a 24-week double blinded placebo-controlled treatment comparison, while Part 2 was an open label extension and offers placebo-treated Phase 1 participants the option for cross-over to vimseltinib treatment.

The primary efficacy endpoint was ORR (CR+PR) according to centrally read MRI and RECIST 1.1 criteria at the end of the double-blind Part 1 (at week 25). Secondary endpoints were ROM, OOR by TVS, and PROs (PROMIS physical function, stiffness, pain and others).

Vimseltinib 30 mg or matching placebo twice weekly was administered as oral capsules on an empty stomach, at least 1 hour before and no sooner than 2 hours after ingestion of food.

Treatment was continued until radiological confirmation of disease progression as defined in the protocol, unacceptable toxicity, withdrawal by participant, physician's decision, or commercial availability of vimseltinib, and for as long as vimseltinib was being developed to support the indication, and continuation of treatment did not conflict with the Sponsor's right to terminate the study.

The trial design has large similarity with the ENLIVEN trial of pexidartinib, a similar CSF1R targeting product not approved in the EU due to a negative Benefit-Risk Balance (see above).

3.2. Favourable effects

During the double-blind period, the ORR per RECIST v1.1 at Week 25 by blinded IRR in the ITT was 39.8% (95% CI: 29.2%, 51.1%), including 4/83 patients (4.4%) with complete response and 31/83 (34.9%) with partial response for the vimseltinib arm, and 0% (95% CI: 0%, 8.8%) for the placebo arm. The stratified difference in ORR was 39.0% based on IRT, and unstratified differences were 39.8%. The difference was statistically significant ($p<0.0001$) based on CMH, Chi-square, and Fisher's exact tests.

Among objective responders in the vimseltinib arm at Week 25, the median DOR was not reached at either the primary or updated analysis with additional 6 months of follow-up, with responses lasting up to 84.4+ weeks and with all but 1 response ongoing at the time of the updated analysis. Subgroup analyses for ORR showed a consistent effect over most subgroups. Thus, vimseltinib was in principle effective in TGCT tumour size reduction.

A significantly higher ORR per TVS (key secondary endpoint 1) was noted at Week 25 in the vimseltinib arm compared with the placebo arm (67.5% versus 0%; $p<0.0001$).

At Week 97 IRR tumour analysis, the ORR on study per RECIST v1.1 further increased to 48.2% and the ORR on study per TVS was 80.7% for the participants randomised to vimseltinib. The rate of CR increased up to 19/83 (~23%) in the vimseltinib arm, which is seen as a clinically relevant benefit. The median DOR was not reached for responders on study using RECIST v1.1 (maximum DOR of 134 weeks with response ongoing) and for responders on study using TVS (maximum DOR of 144 weeks with response ongoing).

Nominally significant higher response rates were observed with vimseltinib at Week 25 for the other key secondary endpoint parameters in terms of active ROM (LS mean difference 14.6% [95% CI: 4.0, 25.3]; $p=0.0077$), physical function (LS mean difference 3.3 [95% CI: 1.4, 5.2]; $p=0.0007$), worst stiffness (LS mean difference -1.8 [95% CI: -2.5, -1.1]; $p<0.0001$), EQ-5D-5L VAS to assess health status (LS mean difference 7.4 [95% CI: 1.4, 13.4]; $p=0.0155$), and worst pain (48.2% versus 22.5%; $p=0.0056$).

The increase in ORR and particularly in subjects who reached CR at Week 97 was mostly associated with a trend for further improvement in the PRO key secondary endpoints. The Mean Change from Baseline regarding these PRO endpoints remained stable on the same level (shortly above the MCID) as observed at week 25.

3.3. Uncertainties and limitations about favourable effects

Between the week 25 analysis and the updated analysis at week 97, three patients who initially showed PR to vimseltinib were no longer responding, likely due to the development of treatment resistance or other unknown factors. The majority of patients treated with vimseltinib had 'stable disease' indicating that primary resistance to vimseltinib may be prevalent in this patient population. These findings suggest that patients achieving only stable disease by week 25 are unlikely to become responders with prolonged treatment.

The very frequent and visible adverse events of the skins (rash, periorbital oedema and others) have likely resulted in functional unblinding and may have negatively impacted the evaluation of PRO and QoL symptomatic endpoints, which are relevant for the translation of tumour shrinking into a meaningful clinical benefit. This type of bias is a challenge in clinical trials involving agents with distinctive side effect profiles,

and it is often an inherent limitation that must be acknowledged and carefully considered in the interpretation of results.

3.4. Unfavourable effects

During the 25 weeks in Phase 1 of the MOTION trial, the comparison against placebo showed that 95.2% of patients experienced at least one treatment-related adverse event (TEAE) in comparison to 74.4% in the placebo-arm. The 20.8 % difference to placebo in TEAE during the first 25 weeks characterise that vimseltinib treatment is associated with a higher number of AEs in the target population. A comparison of drug related grade ≥3 TEAEs events (V: 30.1% vs PLc: 2.6% and the rates for TE-SAEs (V: 7.2% vs PLB: 2.6%) and drug related TE-SAEs (V:1.2% vs. PLB:0%), indicate in general an increase of safety risks due to vimseltinib already after short term treatment for 25 weeks during the placebo controlled part of MOTION. After long treatment duration as reflected by the pool 1, the rate significantly increases up to 53.0% of participants and SAEs rate increase to 18.0% of the participants. The most frequently reported SAEs were cellulitis (2.7%) and fall (1.1%). The latter event of fall leads to the only death in the studies at data cut-off data, and was assessed as not related.

The most frequently reported Grade 3/4 TEAEs were blood CPK increased (23.5%), hypertension (8.7%), and pruritus (2.7%). All have to be seen as drug related.

The most drug related TEAEs reported in ≥25% of participants in Pool 1 were: periorbital oedema (44.8% [82/183]), blood CPK increased (42.1% [77/183]), fatigue (28.4% [52/183]), asthenia (27.9% [51/183]), headache (27.3% [50/183]), AST increased (26.2% [48/183]), pruritus (26.2% [48/183]), and face oedema (25.1% [46/183]).

Comparing the differences of TEAE frequencies regarding the preferred term of vimseltinib and placebo treated TGCT patients in the clinical trials, the following adverse events were clearly related to vimseltinib (difference ≥ 10% not in favour for vimseltinib): Periorbital oedema (+31.8%), Blood CPK increased (+24.1%), Pruritus (+21.2%), AST (+20.3), Rash, maculo-papular (19.3%), Fatigue (+17.1%), Rash (+14.2%) and Oedema peripheral (10.4%).

The significant clinical relevance of these drug related TEAEs is illustrated by the finding that dose modifications (reduction or interruption) were needed in 74.3% (136/183) of participants in Pool 1 to make treatment safe and tolerable. Nevertheless, 9.3% (17/183) of participants in Pool 1 discontinued treatment due to adverse events (pool 1). The most frequently reported TEAEs leading to treatment discontinuation occurred in the SOC "Skin and subcutaneous tissue disorders" (rash, periorbital oedema and pruritus) and demonstrate the overall low tolerability of these events.

Given the cardiovascular and skeletal malformations identified in the rat EFD study and the literature data, a contraindication for the use in pregnancy is issued (see section 4.3 of the SmPC).

3.5. Uncertainties and limitations about unfavourable effects

The currently available long-term safety data are not sufficient to fully assess the potential risks of the treatment associated with extended use. To address this uncertainty, the applicant has committed to conducting a PASS study (Category 3 PASS, RMP).

Blood CPK increased was one of the most frequent and most severe adverse events reported in MOTION. One life-threatening SAE case with significant CPK increases and severe myalgia occurred in the Phase 1/2 trial.

The cause of the dramatic CPK event remains unclear. 'Muscle injury/Rhabdomyolysis' and 'Nephrotoxicity' have been included as important potential risks in the RMP. These safety concerns will be addressed as part of the PASS study to be conducted (Category 3 PASS, RMP).

Hepatotoxicity was identified in non-clinical trial as a potentially relevant safety risk also for the human population, probably associated with the mechanism of action. Considering the limitations of the safety database and the hepatotoxicity observed with similar acting products, 'Drug-induced liver injury (DILI)' has been included as an important potential risk in the RMP and will be further investigated in the context of the PASS study (Category 3 PASS, RMP).

Vimseltinib was highly brain penetrant in animal studies, but the toxic effects of the brain penetration and the clinical relevance of the suppressive effects on microglia in humans are currently unknown. Considering that the occurrence of cognitive disorders and memory disturbance as part of potential neurotoxicity was common and led to treatment discontinuation in patients treated with CSF1R inhibiting products, 'Cognitive disorders/CNS adverse events' have been classified as important potential risk in the RMP and will be further characterised as part of the PASS study (Category 3 PASS, RMP).

With respect to haematotoxicity it is recognised that vimseltinib affect bone marrow function and cause myelosuppression due to the mechanism of action. It remains uncertain whether long-term depletion of macrophages in the liver, skins and other organs may lead to increase of infection rates. Particularly to the reduced clearance capacity from intestinal derived bacteria in the liver and skin infections (considering the high rate of cellulitis events) concerns are not resolved and clarification is expected from the PASS and post-marketing data.

3.6. Effects Table

Table 59. Effects table for vimseltinib in the treatment of adult patients with tenosynovial giant cell tumour (TGCT) who are not amenable to surgery (MOTION trial; DCC-3014-03-001)

Effect	Short Description	Unit	Vimseltinib 30 mg twice weekly Part 1 N=83	Control arm Placebo, Part 1 N=40	Vimseltinib Safety Pool 1	Uncertainties/ Strength of evidence
Favourable effects						
ORR RECIST v1.1 at Week 25	Objective response rate (CR+PR) Prim EP	N (%) (95%CI)	33 (39.8%) (29.2, 51.1) P=<0,0001 CR:4/83(4.8) PR:29/83(34.9)	0%	NA	-Statistically significant -Uncertainties on the clinical relevance in PR.
At Week 97 (follow-up in extension phase)	CR		19/83 (22.8%)			-Open label phase of the study

Effect	Short Description	Unit	Vimseltinib 30 mg twice weekly Part 1 N=83	Control arm Placebo, Part 1 N=40	Vimseltinib Safety Pool 1	Uncertainties/ Strength of evidence
Active ROM	Active range of motion Change from baseline LS Median/Mean change (STD) from baseline in % normal reference at week 25	%	18.4 (5.6, 31.2)	3.8 (-10.5, 18.0)	NA	-statistically significant p=0.007 missing values at week 25 in both arms reported. -MMRM models for analysis.
PROMIS Physical function score	Change from Baseline LS Mean change from baseline score in PROMIS at week 25		4.6 (2.7, 6.5)	1.3 (-0.5, 3.0)	NA	- statistically significant P=0.0007 -results could be biased due to substantial proportion of missing values at week 25 (~30%? in both arms according waterfall plot -MMRM models for analysis.
Worst stiffness NRS (Numeric Rating Scale)	LS Mean change from baseline score in PROMIS at week 25		-2.1 (-2.5, -1.6)	-0.3 (-0.8;0.3)	NA	- statistically significant P=<0.0001 - results could be biased due to high proportion of missing data in both arms - The effect of ongoing use of anti-inflammatory/ anti-rheumatic and analgesic dosing on stiffness measurement is unclear. -MMRM models for analysis.
Median Duration of response at Week 25	Based on RECIST 1.1		NE	NE	NA	-Limitations as to the maturity of the data. -limitation as to the clinical interpretability in this very slow growing tumour. -Has not been reached, reporting currently not meaningful. -Some lost in response observed by unclear reasons
Unfavourable effects						
TEAEs		N (%)	83 (100)	37 (94.9)	NR	
Grade ≥3 AEs		N (%)	31 (37.3)	4 (10.3)	79 (53.0)	

Effect	Short Description	Unit	Vimseltinib 30 mg twice weekly Part 1 N=83	Control arm Placebo, Part 1 N=40	Vimseltinib Safety Pool 1	Uncertainties/ Strength of evidence
SAEs		N (%)	6 (7.2)	1 (2.6)	33 (18.0)	
AEs leading to discontinuation		N (%)	3 (3.6)	0	17 (9.3)	
Hepatic AEs (AST/ALT)		N (%)	21 (27.1) / 21 (17.8)	3 (5.1)	48 (26.2) 29 (15.8)	
Pruritus		N (%)	37 (31.4) 12 (19.7)	1 (1.7)	48 (26.1)	

Abbreviations: ORR: overall response rate; ROM: range of motion; TVS: tumour volume score; NRS: numeric rating scale; BPI: brief pain inventory; AE: adverse event; TEAE: treatment-emergent adverse event; SAE: Serious adverse event; AESI: adverse event of special interest

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The pivotal MOTION study included a (i) 24-week randomised, double-blind, placebo-controlled phase and (ii) an open-label extension phase. The placebo-to-vimseltinib crossover after week 24 limits median- and long-term comparative analyses, allowing for robust evaluation only of short-term efficacy and safety.

The study met its primary endpoint, demonstrating a statistically significant ORR at Week 25 (40% vs 0% placebo; $p<0.0001$). While in responders, complete responses were rarely observed at week 25 (5%), the majority of ORR responses were partial responses, the CR-rate increases up to 19 (23%) at week 97 of treatment in the updated dataset (22nd Feb 2025). About 50% of the population showed no response to treatment and remained in stable disease or progressed.

Updated data after longer follow-up demonstrate that treatment duration of at least 97 weeks appears necessary to reach full efficacy as reflected by CR. While the clinical relevance of partial responses of benign tumours is not intrinsically evident, occurrence of CR in one quarter of the vimseltinib treated patients appears clinically relevant and meaningful.

Efficacy appears to depend on maintaining treatment, with relapse observed upon discontinuation, reflecting the mechanism of action. Regarding the durability of response during long-term treatment, the latest dataset (22nd Feb 2025) reported that MOTION DoR according to ORR responses per RECIST at Week 25 were maintained for at least 6 months in 85% of responders, for at least 12 months in 70% of responders, and for at least 24 months in 40% of responders. Since currently only 19/83 subjects receive vimseltinib treatment in the trial, it appears possible that the other 64 subjects with PR and SD have terminated treatment at the recent cut-off.

To address the clinical significance of tumour shrinkage, key secondary endpoints included ROM and several PROs assessing physical function, stiffness, and pain. These showed statistically significant improvements over placebo at Week 25. Notably, improvements were also observed in patients with stable disease, suggesting benefits may extend beyond measurable tumour reduction. However, uncertainties regarding the reliability of the results and about the clinical meaningfulness of these findings remain. Potential biases include low thresholds for minimal clinically important differences (MCIDs), validation of these MCIDs with a

dataset of the pivotal MOTION study, joint-specific variation, or functional unblinding due to known side effects like skin reactions.

Vimseltinib's safety profile raises concerns, particularly regarding elevated CPK, liver enzymes (ALT/AST), and unresolved questions around renal toxicity and the long-term effects of these adverse events. A severe case of CPK elevation was not confirmed as rhabdomyolysis, but systematic data screening are lacking.

Hepatotoxicity is a known class risk; although Hy's law cases were not observed with vimseltinib, long-term liver effects remain uncertain. Similarly, skin toxicities – particularly periorbital oedema, rash, and pruritus – were frequent and led to many discontinuations. Moreover, vimseltinib treatment appears to increase the risk for development of arterial hypertension and possibly of renal function impairment. The applicant will conduct a post-authorisation safety study (Category 3 PASS, RMP) to address these uncertainties.

Approximately 75% of patients required dose adjustments, questioning long-term tolerability and dose optimisation. The broader impact of prolonged CSF1R inhibition, including macrophage depletion in key organs, remains unknown.

3.7.2. Balance of benefits and risks

The submission is based on data from an open-label Phase 1/2 proof-of-concept and dose-finding study, as well as a single pivotal confirmatory trial (MOTION).

Although TGCT is a non-malignant tumour with no direct impact on overall survival, the observed improvement in objective response rate of 40% (CR + PR) at week 25 suggests a meaningful potential for tumour shrinkage in a rare population with severe morbidity and no established systemic options. This effect is further supported by improvements in key secondary endpoints, including range of motion (ROM) and patient-reported outcomes (PROs), which collectively point to the potential for symptomatic benefit and improved quality of life in affected patients.

The available update of efficacy outcome at week 97 follow up demonstrates a clinically relevant and meaningful efficacy characterised by an increase in CR rate up to 23%. This confirms that longer treatment up to 97 weeks is needed in general to reach a clear benefit in the studied patients, while the initial assessment at week 25 was significantly too early. A CR in a quarter of the treated patients is considered a clinically relevant benefit for the target population.

Importantly, previously anticipated safety concerns, such as the risk of drug-induced liver injury (DILI), muscle injury/rhabdomyolysis and nephrotoxicity, have not emerged in the updated data. However, these safety signals still warrant further investigation. In addition, other adverse events such as oedema, rash, and pruritus have been reported, and although generally of low grade, they required dose modifications in approximately 75% of patients. This indicates the need for careful dose management and monitoring in clinical practice.

Despite these challenges, the safety profile of vimseltinib appears manageable, however, considering the new mechanism of action for the treatment of a rare disease the degree of uncertainties about the actual risks remains important. Considering the likely need for long-term – potentially life-long – treatment, a thorough understanding of the long-term safety and tolerability of vimseltinib is essential.

To resolve these uncertainties, a PASS trial will be conducted to further characterise long-term safety outcome (Category 3 PASS, RMP).

3.7.3. Additional considerations on the benefit-risk balance

N/A.

3.8. Conclusions

The overall benefit/risk balance of Romvimza is positive, subject to the conditions stated in section 'Recommendations'.

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 Romvimza is favourable in the following indication(s):

Romvimza is indicated for treatment of adult patients with symptomatic tenosynovial giant cell tumour (TGCT) associated with clinically relevant physical function deterioration and in whom surgical options have been exhausted or would induce unacceptable morbidity or disability.
The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (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.

- **Additional risk minimisation measures**

Patient card

The MAH shall ensure that a patient card is included in each Romvimza package to address the important potential risk of embryo-foetal toxicity.

- Warning not to take Romvimza if pregnant
- Instruction to use effective contraception methods for women of childbearing potential
- Instruction regarding pregnancy testing before and during treatment
- Information on the importance of reporting pregnancies to healthcare provider

Healthcare professional guide

The MAH shall ensure that, at the time of launch, a healthcare professional guide is distributed to prescribers who are expected to prescribe Romvimza to address the important potential risk of embryo-foetal toxicity.

- Details of the potential risk to the foetus and the importance of informing patients to avoid pregnancy while taking vimseltinib
- Instruction that the pregnancy status of females of childbearing potential must be verified prior to initiating vimseltinib and during treatment
- Instruction that women of childbearing potential must use effective contraception during treatment with vimseltinib and for 30 days after the final dose
- Recommendation for patients to add a barrier method if systemic contraceptives are used as the effects of vimseltinib on hormonal contraceptives have not been studied
- Information on the importance of reporting pregnancies with details of how to report
- Instruction to discontinue vimseltinib immediately if a pregnancy occurs in a female patient during treatment with vimseltinib or within 30 days after the final dose. The patient should be counselled adequately by the HCP and/or referred to a specialist in teratogenicity.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that vimseltinib is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.