EU RISK MANAGEMENT PLAN
FOR
ROMVIMZA
(VIMSELTINIB)

RMP Version to be Assessed as Part of this Application	
RMP Version Number	0.7
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Rationale for Submitting an Updated RMP	Not applicable for initial marketing authorisation application submission
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Details of the Currently Approved RMP	Not applicable

QPPV name: Wendy Huisman

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
AME	Absorption, metabolism, excretion
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
$AUC_{0\text{-}inf}$	Area under the concentration-time curve from time-zero extrapolated to infinity
$AUC_{0\text{-}t}$	Area under the concentration-time curve from time-zero to the time of the last quantifiable concentration
BCRP	Breast cancer resistance protein
BIW	Twice weekly
BSEP	Bile salt export pump
CCI	Charlson comorbidity index
CFR	Code of Federal Regulations
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
C_{max}	Maximum concentration observed
CNS	Central nervous system
CPK	Creatine phosphokinase
CPN	Chronic progressive nephropathy
CSF1	Colony-stimulating factor 1
CSF1R	Colony-stimulating factor 1 receptor
CSR	Clinical study report
CV	Cardiovascular
CYP	Cytochrome P450 enzyme
DCO	Data cut-off
DILI	Drug-Induced Liver Injury
DNA	Deoxyribonucleic acid
DP-7005	Metabolite of vimseltinib

Abbreviation	Explanation
D-TGCT	Diffuse-type tenosynovial giant cell tumour
ECG	Electrocardiogram
EFD	Embryofoetal development
eGFR	Estimated glomerular filtration rate
EU	European Union
FDA	Food and Drug Administration
FLT3	FMS-like tyrosine kinase 3
GCT-TS	Giant cell tumour of the tendon sheath
GD	Gestational day
GLP	Good Laboratory Practice
hAME	Human absorption, metabolism, and excretion
HCP	Healthcare professional
HI	Hepatic impairment
HIV	Human immunodeficiency virus
HLGT	High level group term
HNSTD	Highest non-severely toxic dose
ICH	International Conference on Harmonization
ICSR	Individual case safety report
INN	International nonproprietary name
IR	Incidence rate
KIT	Cellular homolog of the feline sarcoma viral oncogene v-kit
L-TGCT	Localised-type tenosynovial giant cell tumour
MDR1	Multidrug resistance protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MN	Micronuclei
MNU	Methyl nitrosurea
MRI	Magnetic resonance imaging
MST	Malignant solid tumour
MTD	Maximum tolerated dose
M-TGCT	Malignant tenosynovial giant cell tumour

Abbreviation	Explanation
NA	Not applicable
NASH	Non-alcoholic steatohepatitis
NHF	Normal hepatic function
NOAEL	No observed adverse effect level
N-TGCT	Nodular-type tenosynovial giant cell tumour
OAT	Organic anion transporter
OATP	Organic anion transporter polypeptide
OCT	Organic cation transporter
PASS	Post-authorisation safety study
PBPK	Physiologically based pharmacokinetic
PCE	Polychromatic erythrocytes
PD	Pharmacodynamics
P-gp	P-glycoprotein
PK	Pharmacokinetics
PSUR	Periodic safety update report
PVNS	Pigmented villonodular synovitis
QD	Once daily
QPPV	Qualified Person Responsible for Pharmacovigilance
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected by Fridericia's formula
QWBA	Quantitative whole body autoradiography
RECIST	Response Evaluation Criteria in Solid Tumors
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk management plan
SD	Sprague-Dawley
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SOC	System Organ Class
STD_{10}	Severely toxic dose for 10% of animals
TBD	To be determined

Abbreviation	Explanation
TEAE	Treatment emergent adverse event
TGCT	Tenosynovial giant cell tumour
ULN	Upper limit of normal
US	United States
UV-VIS	Ultraviolet-visible

PART I PRODUCT OVERVIEW

Table 1: Product Overview

Active substance (INN or common name)	Vimseltinib
Pharmacotherapeutic group (ATC Code)	Antineoplastic agents, protein kinase inhibitors (ATC code: L01EX29)
Marketing Authorisation Applicant	Deciphera Pharmaceuticals (Netherlands) BV
Medicinal products to which this RMP refers	1
Invented name in the European Economic Area (EEA)	ROMVIMZA
Marketing authorisation procedure	Centralised
Brief description of the product	**Chemical class:** Selective colony-stimulating factor 1 receptor (CSF1R) inhibitor
	Summary of mode of action: Vimseltinib is a selective small molecule tyrosine kinase inhibitor that targets colony stimulating factor 1 receptor (CSF1R). The CSF1/CSF1R signalling axis has a critical role in the development of tenosynovial giant cell tumour (TGCT). 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 exerts its anti-tumour effects via depletion of CSF1R-dependent macrophages and inflammatory cells.
	Important information about its composition: ROMVIMZA contains excipients with known effects including lactose, tartrazine (E 102) and sunset yellow FCF (E 110).
Hyperlink to the Product Information	Summary of Product Characteristics (SmPC)
Indication in the EEA	*Current*: 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.
	Proposed: Not applicable – This is an initial marketing authorisation application

Dosage in the EEA	*Current*: The recommended dose of vimseltinib is 30 mg taken twice weekly at least 72 hours apart as long as benefit is observed or until unacceptable toxicity.
	Proposed: Not applicable – This is an initial marketing authorisation application
Pharmaceutical form and strengths	*Current*: Hard Capsule *ROMVIMZA 14 mg hard capsules* The capsule is an orange opaque cap/white opaque body hard capsule of size 4 (approximate length 14 mm), imprinted with "DCV14" in black ink. *ROMVIMZA 20 mg hard capsules* The capsule is a yellow opaque cap/white opaque body hard capsule of size 2 (approximate length 18 mm), imprinted with "DCV20" in black ink. *ROMVIMZA 30 mg hard capsules* The capsule is a light blue opaque cap/white opaque body hard capsule of size 1 (approximate length 19 mm), imprinted with "DCV30" in black ink.
	Proposed: Not applicable – This is an initial marketing authorisation application
Will the product be subject to additional monitoring in the EU?	Yes

PART II SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION AND TARGET POPULATION

Indication:

Vimseltinib 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.

Incidence:

TGCT is a rare tumour arising from the synovium of joints, bursae, and tendon sheaths (de Saint 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). These tumours fall into two subtypes — localised-type TGCT (L-TGCT), also called nodular-type TGCT (N-TGCT), and diffuse-type TGCT (D-TGCT) according to their growth pattern (localised and diffuse) and location (intra- and extra-articular) with varying clinical courses and symptoms (Kager et al, 2022; Stacchiotti et al, 2023).

The incidence rate (IR) depends on the type of TGCT, with L-TGCT occurring at a higher incidence than D-TGCT. A registry-based cohort study in Denmark that identified 2,087 patients with L-TGCT and 574 patients with D-TGCT between 1997 and 2012 calculated the IR per million person-years for L-TGCT and D-TGCT as 30.3 and 8.4, respectively (Ehrenstein et al, 2017).

In a nationwide registry study conducted in The Netherlands that identified 2,815 patients with TGCT in digits, 933 patients with TGCT in localised-extremity and 390 patients with D-TGCT, the Dutch IRs are estimated as 34 per million person-years for TGCT in fingers and toes, 11 in localised-extremity and 5 in D-TGCT (Mastboom et al, 2017). Using these data, the worldwide estimated IRs in digits, localised-extremity, and D-TGCT are 29, 10, and 4 per million person-years, respectively (Mastboom et al, 2017).

The annual incidence in the United States (US) is approximately 11 per million (9.2 localised and 1.8 diffuse) (Giustini et al, 2018).

Prevalence:

TGCT has an estimated prevalence of 20 per 100,000 persons based on European data according to the Orphanet Report Series (Orphanet Report Series, 2022).

The Danish registry-based cohort study described above also presented prevalence data for the 2,087 patients with L-TGCT and 574 patients with D-TGCT; at the end of 2012, prevalence per 100,000 persons was 44.3 for L-TGCT and 11.5 for D-TGCT in Denmark (Ehrenstein et al, 2017).

Global prevalence data are not available for TGCT.

Demographics of the population in the proposed indication – age, sex, racial and/or ethnic origin and risk factors for the disease:

The mean age of TGCT at diagnosis is 35–50 years, with modest gender and subtype differences (Stacchiotti et al, 2023). L-TGCT normally occurs in the 4th and 5th decades of life whereas D-TGCT occurs a little earlier (<40 years) (Gouin and Noailles, 2017). Although rare, children are also diagnosed with TGCT (Kager et al, 2022; Shahriari et al, 2020).

Both L-TGCT and D-TGCT are more common in females than males (Stacchiotti et al, 2023). In the Dutch registry-based cohort study, women made up 61% of the patients with L-TGCT and 51% of the patients with D-TGCT (Ehrenstein et al, 2017). Similarly, females had a higher IR than males in the nationwide Netherlands registry study with a male:female ratio of about 1:1.5 for any type of TGCT (Mastboom et al, 2017).

A cross-sectional, web-based survey collecting data on patients with TGCT via the US Food and Drug administration (FDA) Risk Evaluation and Mitigation Strategy (REMS) programme for pexidartinib (TURALIO®, Daiichi Sankyo) in May 2021 found that of the 83 patients who completed the survey, the median age at REMS enrollment was 45.0 years (range: 34.5 to 55.5 years), and the cohort was predominantly female (62.7%) and White (65.1%) (Lin et al, 2024). The other racial groups in this study were Black or African American (8.4%), Asian (7.2%), Other (18.1%), and missing (1.2%) (Lin et al, 2024).

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

Clinical presentation of TGCT is relatively nonspecific as a result of variations in site and progression. TGCT may be intra- or extra-articular and is classified by clinical presentation and biological behaviour as localised or diffuse (Gouin and Noailles, 2017). L-TGCT arises in soft tissue, near tendons or interphalangeal joints. While any location is possible, localised forms mainly involve the digits and wrist (85% of cases); foot and ankle, knee, hip or other joint locations are rarer. L-TGCT usually presents as a single lesion, often evolving over years, and is systematically benign.

D-TGCT mainly involves the larger joints: knee, hip, ankle and elbow. Diffuse forms show extensive and infiltrative involvement of the synovium of the joint and/or tendon sheath and extend into extra-articular structures. D-TGCT can cause hemarthrosis, destruction of bone and cartilage with severe disability, as well as frequent local relapse (Stacchiotti et al, 2023). As such, diffuse forms are more aggressive and destructive and may exceptionally include a malignant component.

TGCT can cause substantial morbidity, but it is not fatal. An exception is malignant TGCT (M-TGCT), an exceedingly rare form of TGCT that can arise de novo or following multiple recurrences of conventional TGCT (Stacchiotti et al, 2023).

The main existing treatment options:

Surgery is the recommended treatment for all forms of TGCT, when feasible. L-TGCT can generally be surgically removed, but removal of D-TGCT may be challenging because the diffuse nature of the lesions may make full excision difficult (van der Heijden et al, 2023). Retrospective analysis of patients with newly diagnosed or first relapse TGCT was conducted to understand surgical outcomes and shows most patients (85%) with L-TGCT have a complete resection, while only 37% of patients with D-TGCT have a complete resection (Palmerini et al, 2015).

Recurrence is observed in both forms of the disease following surgery. In L-TGCT, reported recurrence rate is approximately 10% after surgery (Gouin and Noailles, 2017; Staals et al, 2016; van der Heijden et al, 2023). Recurrence of L-TGCT is strongly associated with a negative outcome. Approximately 43% of patients who experience a relapse, even after a complete surgical resection, have a subsequent relapse within 5 years (Palmerini et al, 2015). Recurrence rates are considerably higher for D-TGCT, up to 55% (Ehrenstein et al, 2017; Gouin and Noailles, 2017; Staals et al, 2016) and a relapse-free survival rate of approximately 40% in 10 years (van der Heijden et al, 2023). Patients with recurring TGCT may require repetitive surgical treatment that can lead to substantial damage to the affected joint and impaired quality of life (Gouin and Noailles, 2017; Staals et al, 2016; Mastboom et al, 2018). Eventually, some patients may require limb amputation for severe complications (Gouin and Noailles, 2017; Staals et al, 2016). Multiple surgeries owing to recurrence may not be possible for patients who have significant risks associated with open surgery (eg, older patients, patients with comorbidities), or present with inoperable disease. Surgery for such patients could cause significant functional limitation or severe morbidity.

Systemic therapies have been tested in patients with locally advanced or relapsed diffuse TGCT (Brahmi et al, 2016), including kinase inhibitors that non-selectively target the CSF1/CSF1R axis (eg, imatinib and nilotinib), and monoclonal antibodies targeting CSF1R expression (eg, emactuzumab, and cabiralizumab) (Stacchiotti et al, 2023; Gronchi et al, 2021). These kinase inhibitors have not been developed for the treatment of TGCT and have been accessed outside of approved labeling for the treatment of TGCT, and monoclonal antibodies are not yet approved. Best clinical practices have justified the use of systemic therapies in symptomatic TGCT based on the location and extent of the disease, particularly if disease progression or surgical intervention may result in joint damage and affect QoL (Stacchiotti et al, 2023).

Pexidartinib (TURALIO®), a selective kinase inhibitor of CSF1R, KIT, and FLT3, was first approved by the US FDA in 2019 for the treatment of adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery. In the US, pexidartinib's prescribing information includes a black box warning of hepatotoxicity and is only available to patients through a REMS program (TURALIO USPI, 2022). Pexidartinib's Marketing Authorisation Application was reviewed through the centralised procedure but was not approved in the European Union (EU). The Committee for Medicinal Products for Human Use (CHMP) raised concerns that although tumour shrinkage was observed in patients treated with pexidartinib, there was only a small improvement in symptoms such as pain and the ability to use the joint, and it was not clear how long this effect lasts. They also raised a serious concern about unpredictable, potentially life-threatening effects of pexidartinib on the liver, and thus concluded that the benefits of pexidartinib did not outweigh its risks (Turalio EPAR).

Important co-morbidities:

Comorbidities in patients with TGCT have been evaluated in a US retrospective cohort study that identified 4,664 TGCT patients including 284 patients with L-TGCT and 4,380 patients with D-TGCT (in the study named giant cell tumour of the tendon sheath [GCT-TS] and pigmented villonodular synovitis [PVNS], respectively) (Burton et al, 2018). Hypertension was present among approximately a third of patients (Total TGCT 38.4%; L-TGCT 31.3%; D-TGCT 38.8%), and Type 2 diabetes was present among 13.4% of all TGCT patients, 8.5% L-TGCT patients, and 13.8% D-TGCT patients. Obesity (Total TGCT 8.3%; L-TGCT 7.8%;

D-TGCT 8.3%) and gout (Total TGCT 4.4%; L-TGCT 0.4%; D-TGCT 4.6%) were also observed.

In this study, the most prevalent Agency for Healthcare Research and Quality (AHRQ)-classified comorbidities occurred more frequently in patients with D-TGCT compared with those with L-TGCT. These included non-traumatic joint disorders (Total TGCT 75.4%; L-TGCT 47.9%; D-TGCT 77.2%) and other connective tissue disease (Total TGCT 64.0%; L-TGCT 64.4%; D-TGCT 64.0%), followed by disorders of lipid metabolism (Total TGCT 41.7%; L-TGCT 35.9%; D-TGCT 42.1%), and respiratory infections (Total TGCT 36.7%; L-TGCT 30.3%; TGCT 37.1%) (Burton et al, 2018).

Similarly, a retrospective analysis conducted using the US OptumHealth Care Solutions, Inc. database from January 1999 to March 2017 identified hypertension as a common comorbidity in patients with TGCT (Lin et al, 2021). In this study, a total of 1,395 eligible patients with TGCT were matched with 13,950 TGCT-free controls. Despite similar demographics (36% women, mean age 45 to 47 years), the TGCT cohort had a slightly higher comorbidity burden than the TGCT-free cohort (mean Charlson Comorbidity Index [CCI]: 0.3 vs 0.2, $P<0.001$), with the top three most common comorbidities (hypertension, depression, and hypothyroidism) being more prevalent in the TGCT cohort than the TGCT-free cohort (24.1%, 8.5%, and 8.2% versus 16.8%, 6.9%, and 5.5%, respectively).

PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Vimseltinib is an oral, small molecule, selective CSF1R inhibitor. CSF1R is a tyrosine kinase receptor expressed predominantly on monocytes and macrophages. Vimseltinib binds to the pocket controlling the conformation of the CSF1R kinase domain and locks the kinase domain in the inactive form.

The non-clinical testing strategy encompassed a series of *in vitro* and *in vivo* experiments for evaluation of the pharmacology, pharmacokinetics (PK) and toxicology of vimseltinib.

The non-clinical safety and toxicology evaluation included a cardiovascular safety pharmacology study in dogs, a central nervous system safety pharmacology study in rats, and a respiratory safety pharmacology study in rats. Repeat-dose toxicity studies were conducted, including pivotal 28-day toxicology/toxicokinetic studies in rats and dogs, pivotal 13-week toxicology/toxicokinetic studies in rats and dogs, a 26-week toxicology/toxicokinetic study in rats, and a 39-week toxicology/toxicokinetic study in dogs. Additional evaluations included in vitro and in vivo studies evaluating the genotoxic potential of vimseltinib, non-pivotal embryofoetal development (EFD) studies in rats and rabbits, a pivotal EFD study in rats, a pivotal fertility and early embryonic development toxicity study in rats, a pivotal pre- and post-natal development toxicity study in rats, and assessment of the in vitro phototoxic and cytotoxic potential by reduction in neutral red uptake in cultures of normal BALB/c 3T3 mouse fibroblasts. CNS penetration of vimseltinib was demonstrated in two in vivo distribution studies (a rat blood brain barrier PK study and a rat mass balance study).

To assess genotoxic potential, a bacterial reverse mutation assay, an in vitro human lymphocyte micronucleus assay, and an in vivo rat micronucleus plus alkaline comet assay were also completed. The carcinogenic potential was evaluated in a 6-month RasH2 transgenic mouse study and in a 2-year rat study.

Rat and dog were chosen as appropriate species for the toxicity studies based on the homology of the kinase domains between species and in vitro studies of metabolic stability and metabolite identification comparing mouse, rat, dog, monkey, and human, where rat and/or dog were demonstrated to form the same metabolites as humans. These species have been used previously in safety testing of this class of compounds, are commonly accepted by regulatory authorities, and there was substantial background data available to assess any findings.

Pivotal repeated-dose and genotoxicity safety studies were conducted in compliance with current International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines and generally accepted procedures for the testing of pharmaceutical compounds and in full concordance with the US FDA Good Laboratory Practice (GLP) regulations, 21 Code of Federal Regulations (CFR) Part 58. Non-pivotal repeated-dose studies were conducted in accordance with test-site SOPs and study protocols.

The key safety findings from non-clinical studies and relevance to human usage are presented in Table 2 below. As discussed further in Part II: Module SIII, the clinical data are presented for the double-blind period of the pivotal Phase 3 placebo-controlled study DCC-3014-03-001 (hereafter referred to as MOTION) and for Pool 1, which includes all TGCT participants who received the recommended dose of 30 mg twice weekly (BIW) in MOTION and Study DCC–3014-01-001, an open-label, first-in-human, dose escalation/dose expansion study.

There is also reference to Pool 3 which includes all participants who received at least one dose of vimseltinib in MOTION and Study DCC-3014-01-001 regardless of tumour type or dose of vimseltinib.

Table 2: Key Safety Findings from Non-clinical Studies and Relevance to Human Usage

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
Toxicity	

Acute or repeat-dose toxicity studies
No single-dose toxicity studies were conducted with vimseltinib.
In repeat-dose toxicity studies, the safety of vimseltinib was evaluated following daily oral administration for 28 days, 91 days (13 weeks), and 26 weeks in Sprague-Dawley (SD) rats (Pivotal Studies DCC-3014-04-0003, DCC-3014-04-0008, and DCC-3014-04-0012) and 28 days, 13 weeks, and 39 weeks in Beagle dogs (Pivotal Studies DCC-3014-04-0004, DCC-3014-04-0007, and DCC-04-0013).
Overall, the low dose of vimseltinib was well tolerated at 5 mg/kg/day in rats for 28 days and at 1.876 mg/kg/day for 91 days. In dogs, vimseltinib at doses of ≤7.5 mg/kg/day was well tolerated for 28 days and 2, 4, or 8 mg/kg/day vimseltinib was well tolerated for 91 days.
In the pivotal repeat-dose 4-week study in rats (DCC-3014-04-0003), the low dose of 5 mg/kg/day was clinically well tolerated without adverse in-life findings and identified as the no observed adverse effect level (NOAEL). Hypertrophy of the physis and primary spongiosa was present in the femur of animals administered ≥5 mg/kg/day.
The 15 mg/kg/day dose was determined to be the STD_{10} and resulted in the unscheduled euthanasia/deaths, significant compound-related clinical observations, and pathology changes consistent with inflammation and bone marrow suppression/toxicity (also noted microscopically). Dosing at 30 mg/kg/day was not tolerated and animals were euthanized between Days 10 and 14.
While the 15 mg/kg/day dose in the pivotal rat study showed pathology changes consistent with inflammation and bone marrow suppression/toxicity, in vivo comet and micronucleus assays in rats (discussed below)
	• Decreased neutrophils and neutropenia have been observed in the clinical development programme. Overall, vimseltinib was not shown to cause significant hematologic toxicity. Neutrophil count decreased is listed as an adverse reaction in the Undesirable effects section (Section 4.8) of the Summary of Product Characteristics (SmPC) and is discussed in Module SVII.1.1. No other notable hematologic laboratory abnormalities were observed.
	• The alteration in bone characteristics observed in rats is unlikely to be a significant factor for adult humans that are not undergoing active bone growth. No significant microscopic changes were seen in dogs.
	  • In the double-blind period of MOTION, 2 (2.4%) participants in the vimseltinib arm experienced treatment emergent adverse events (TEAEs) of Bone pain (MOTION CSR Table 14.3.1.2.1.1), both of which were non-serious and Grade 1 or 2 in severity (MOTION CSR Table 14.3.2.1.1.1; MOTION CSR Table 14.3.1.3.1.1). In the placebo arm, there were no TEAEs related to alterations in bone characteristics.
	  • In Pool 1, 2 (1.1%) participants experienced TEAEs of Bone pain, 2 (1.1%) participants experienced TEAEs of Ankle fracture and 1 (0.5%) participant experienced a TEAE of Foot deformity (ISS Table 12.1.1). Serious TEAEs included Ankle fracture and Foot deformity, which were reported in 1 (0.5%) participant each (ISS Table 12.3.1); both serious TEAEs were assessed as unrelated to vimseltinib (ISS Table 12.6.1). The TEAEs of Bone pain and Foot deformity were all Grade 1

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
demonstrated no evidence of bone marrow toxicity.	or 2 in severity, while Ankle fracture was Grade 3 in severity (ISS Table 13.1.1).
In the repeat-dose 13-week study in rats (DCC-3014-04-0008), daily administration of 1.876, 3.75, or 7.5 mg/kg/day vimseltinib resulted in clinical observations of swollen legs/limbs and/or limited use of limbs (7.5 mg/kg/day only); periorbital porphyrin staining, corneal haze, discoloured skin, swelling, and scabs for animals administered ≥3.75 mg/kg/day. Five animals administered 7.5 mg/kg/day were euthanized at an unscheduled interval due to limited use of limbs, swollen feet/limb, or periorbital skin ulceration. The NOAEL for vimseltinib was 1.876 mg/kg/day, while the highest non-severely toxic dose (HNSTD) was 3.75 mg/kg/day and the STD_{10} was 7.5 mg/kg/day.	• Oedema has been observed in the clinical development programme and is an identified risk of vimseltinib. Periorbital oedema, peripheral oedema, face oedema, and generalised oedema are listed in Section 4.8 of the SmPC and discussed in Module SVII.1.1. These adverse drug reactions can be managed in clinical practice. • Dermatologic effects have been observed in the clinical development programme and are an identified risk of vimseltinib. Rash, Pruritus, and Dry skin are listed in Section 4.8 of the SmPC. Pruritus is also listed as a warning in Section 4.4 of the SmPC. Dermatologic effects are discussed in Module SVII.1.1. These adverse drug reactions can be managed in clinical practice.
In the pivotal 4-week study in dogs (DCC-3014-04-0004), vimseltinib was given by oral gavage at 0, 2.5, 7.5, 15, and 25 mg/kg/day. Vimseltinib at doses of ≤7.5 mg/kg/day was well tolerated, without adverse in-life findings or effects on health. Animals administered 15 or 25 mg/kg/day were euthanized early due to adverse vimseltinib-related clinical observations, and these dose levels exceeded the maximum tolerated dose (MTD). Vimseltinib-related effects on pathology results at all dose levels were consistent with inflammation, pancreatic injury, and suggestive of hepatocellular and/or skeletal muscle injury. Pathology findings were not as prominent or adverse at ≤7.5 mg/kg/day compared with those at higher doses and were reversible during the recovery phase. Correlating microscopic findings involved several tissues, including the pancreas, intestine, liver (neutrophil infiltration at 25 mg/kg/day), heart, eye, sternum bone marrow, and lymphoid tissues; these were adverse in animals administered >15 mg/kg/day. All microscopic findings were fully or partially reversible during the recovery phase at doses ≤7.5 mg/kg/day. Based on these results, 7.5 mg/kg/day is the NOAEL.	• In the MOTION study and Pool 1, the most frequently reported TEAEs in the Musculoskeletal and connective tissue disorders System Organ Class (SOC) were Arthralgia, Myalgia and Pain in extremity. • In the MOTION double-blind period, 16 (19.3%) participants in the vimseltinib arm experienced TEAEs of Arthralgia, 7 (8.4%) participants experienced TEAEs of Myalgia and 5 (6%) participants experienced TEAEs of Pain in extremity (MOTION CSR Table 14.3.1.2.1.1). All were non-serious (MOTION CSR Table 14.3.2.1.1.1) and Grade 1 or 2 in severity (MOTION CSR Table 14.3.1.3.1.1). In the placebo arm, similar frequencies were observed; 6 (15.4%) participants experienced TEAEs of Arthralgia, 2 (5.1%) participants experienced TEAEs of Myalgia and 3 (7.7%) participants experienced TEAEs of Pain in extremity (MOTION CSR Table 14.3.1.2.1.1). All were non-serious (MOTION CSR Table 14.3.2.1.1.1) and Grade 1 or 2 in severity, with the exception of 1 (2.6%) participant who experienced a Grade 3 TEAE of Arthralgia (MOTION CSR Table 14.3.1.3.1.1). None of the TEAEs led to discontinuation of treatment (MOTION CSR Table 14.3.1.2.7.1).

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
	• In Pool 1, 50 (27.3%) participants experienced TEAEs of Arthralgia, 31 (16.9) participants experienced TEAEs of Myalgia and 18 (9.8%) participants experienced TEAEs of Pain in extremity (ISS Table 12.1.1). The majority were Grade 1 or 2 in severity (ISS Table 13.1.1) and none led to discontinuation of treatment (ISS Table 12.7.2.1). One (0.5%) participant experienced a serious TEAE of Myalgia (ISS Table 12.3.1), and no evidence of muscle injury was observed. • There was no evidence of drug-induced liver injury in the clinical development programme, although mild to moderate elevations in hepatic enzymes were observed. Drug-Induced Liver Injury (DILI) is an important potential risk and is discussed in Modules SVII.1.2 and SVII.3.1. Serum enzyme elevations including aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) are listed as a warning in Section 4.4 of the SmPC and as adverse reactions in Section 4.8 of the SmPC.
In the repeat-dose 13-week study in dogs (DCC-3014-04-0007), daily administration of 2, 4, or 8 mg/kg/day vimseltinib by oral gavage to beagles for 13 weeks was well tolerated at all dose levels. Vimseltinib-related observations of eye discharge (in animals administered 8 mg/kg only), without ophthalmic changes, or increased body weight gain during the dosing phase were the only test article-related changes. Pathology findings included mildly decreased red blood cell mass; minimally increased fibrinogen concentration; minimally increased aspartate aminotransferase, glutamate dehydrogenase, and creatine phosphokinase (CPK) activities; and mildly decreased inorganic phosphorus. These pathology changes did not have any microscopic correlates or reflect negative effects on the overall health of the animal; therefore, the NOAEL for vimseltinib was 8 mg/kg/day and the HNSTD was >8 mg/kg/day.	• Ophthalmologic effects including Lacrimation increased, Dry eye and Vision blurred were observed in MOTION and Pool 1. These events are listed as adverse reactions in Section 4.8 of the SmPC and are discussed in Module SVII.1.1. Ophthalmologic effects are an identified risk of vimseltinib that can be managed in clinical practice. • There was no evidence of DILI in the clinical development programme, although mild to moderate elevations in hepatic enzymes were observed. DILI is an important potential risk and is discussed in Modules SVII.1.2 and SVII.3.1. Serum enzyme elevations including AST, ALT, and ALP, are listed as a warning in Section 4.4 of the SmPC and as adverse reactions in Section 4.8 of the SmPC. • Muscle injury/Rhabdomyolysis is an important potential risk and is discussed in Modules SVII.1.2 and SVII.3.1. There was no evidence of rhabdomyolysis in the clinical development programme, although elevations in CPK were observed. Serum enzyme elevations including CPK are listed as a

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
	warning in Section 4.4 of the SmPC and as adverse reactions in Section 4.8 of the SmPC.
In the pivotal 26-week study in rats (DCC-3014-04-0012), daily administration of 0, 1.0, 2.5, or 5.0 mg/kg/day vimseltinib by oral gavage for 26 weeks, followed by a 4-week recovery phase, resulted in observations of swollen head and/or limbs and abnormal teeth (discoloured, broken, or thickened) either clinically or at necropsy at all dose levels. The broken and discoloured teeth in males administered 5.0 mg/kg/day were associated with decreased body weight gain and lower food consumption. Vimseltinib-related microscopic findings of degeneration/necrosis of vessels in multiple tissues and increased physis thickness were observed in animals administered 5.0 mg/kg/day, while chronic progressive nephropathy (CPN) occurred in animals administered (≥2.5 mg/kg/day, and degeneration/necrosis and dental dysplasia of molar teeth occurred in animals administered ≥1.0 mg/kg/day. These microscopic findings were considered adverse. Due to the severity and persistence of the microscopic findings, all dose levels were considered adverse, and a NOAEL could not be determined.	• Teeth abnormalities observed in vimseltinib treated rats are unlikely to represent a significant safety concern for adult patients since both bone and incisors in the rodent continue growing into adulthood, unlike humans. In the clinical development programme, there were no TEAEs of broken or discoloured teeth. In the vimseltinib arm, no TEAEs involving the teeth were reported in the MOTION double-blind period. In Pool 1, 1 (0.5%) participant experienced a Grade 2 TEAE of Toothache (ISS Table 12.1.1; ISS Table 13.1.1) and 2 (1.1%) participants experienced TEAEs of Tooth infection (ISS Table 12.1.1), both of which were Grade 1 or Grade 2 in severity (ISS Table 13.1.1). All were non-serious (ISS Table 12.3.1). • There was no evidence of nephrotoxicity in the clinical development programme, although elevations in creatinine were observed. Nephrotoxicity is an important potential risk and is discussed in Modules SVII.1.2 and SVII.3.1. Increases in creatinine are described as a warning in Section 4.4 of the SmPC and listed as an adverse reaction in Section 4.8 of the SmPC.
In the repeat-dose 39-week study in dogs (DCC-3014-04-0013), daily administrations of 0, 2, 4, or 8 mg/kg/day vimseltinib via oral gavage to beagles for 39 weeks, followed by a 4-week recovery phase, were well tolerated. Vimseltinib-related clinical observations of periocular swelling, epiphora (excessive tear production), excessive lacrimation and discoloured and depigmented skin on the head and legs (which were swollen and wrinkled [head only]) were observed for animals administered ≥4 mg/kg/day. All observations showed complete or partial recovery by the recovery phase for animals administered 4 mg/kg/day, while observations of wrinkled skin, excessive lacrimation, and skin de-pigmentation (females only) persisted throughout the recovery phase for animals administered 8 mg/kg/day. Vimseltinib related increased body weight and body weight gain were noted during the dosing phase for animals administered 8	• Oedema is an identified risk of vimseltinib. Periorbital oedema, peripheral oedema, face oedema, and generalised oedema are listed as adverse reactions in Section 4.8 of the SmPC and discussed in Module SVII.1.1. Oedema can be managed in clinical practice. • Ophthalmologic effects are an identified risk of vimseltinib and are listed as adverse reactions in Section 4.8 of the SmPC. These events are discussed in Module SVII.1.1 and can be managed in clinical practice. • There were no TEAEs of discoloured or depigmented skin in the MOTION study. In Pool 1, 3 (1.6%) participants experienced TEAEs of Pigmentation disorder and 1 (0.5%) participant experienced each experienced TEAEs of Skin hyperpigmentation and Skin hypopigmentation (ISS Table 12.1.1). All

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
mg/kg/day; however, during the recovery phase, animals administered 8 mg/kg/day were observed with body weight loss and clinical observations of decreased activity, thin appearance, fever, and hunched posture (which necessitated veterinary examination and/or treatment). Pathology findings included mildly increased aspartate aminotransferase and CPK activities, which may have resulted from CSF1R inhibition of macrophage function (the mechanism of action for vimseltinib). Microscopic findings included slight to moderate oedema in the skin collected from the head of animals administered 8 mg/kg/day, which correlated with macroscopic observations of swollen head and subcutaneous tissue having a gelatinous appearance. Based on the veterinary intervention and body weight loss noted during the recovery phase for animals administered 8 mg/kg/day, this dose level was considered adverse.	were non-serious (ISS Table 12.3.1) and Grade 1 or 2 in severity (ISS Table 13.1.1). • DILI is an important potential risk and is discussed in Modules SVII.1.2 and SVII.3.1. Serum enzyme elevations including AST, ALT, and ALP are listed as a warning in Section 4.4 of the SmPC and as adverse reactions in Section 4.8 of the SmPC. Serum enzyme elevations are discussed in Module SVII.3.1. • Muscle injury/Rhabdomyolysis is an important potential risk and is discussed in Modules SVII.1.2 and SVII.3.1. Serum enzyme elevations including CPK are listed as a warning in Section 4.4 of the SmPC and as adverse reactions in Section 4.8 of the SmPC.

Reproductive/developmental toxicity
In the pivotal EFD study (DCC-3014-04-0011) vimseltinib was administered to pregnant SD rats once daily by oral gavage on gestational day (GD) 6 through 17 at doses of 0, 2.5, 5, and 15 mg/kg/day. No adverse maternal effects were attributed to vimseltinib administration, and therefore, the maternal NOAEL for vimseltinib was 15 mg/kg/day, the highest dose tested.
Vimseltinib administered at a dose of 15 mg/kg/day was a selective developmental toxicant (teratogenic) in rats, producing malformations of the cardiovascular and skeletal systems. Additional indications of developmental toxicity, including structural anatomic variations and indications of developmental delay, also occurred at this dose. Based on these data, the developmental NOAEL for vimseltinib was 5 mg/kg/day.
Based on findings in the pivotal fertility and early embryonic development (FEED) study (DCC-3014-04-0020), the NOAEL of vimseltinib for general toxicity was 1 mg/kg/day in males and 2.5 mg/kg/day in females. The NOAELs for mating and fertility were 5 and 10 mg/kg/day in males and females, respectively, and the NOAEL for early embryonic development was 5 mg/kg/day in males and females.
	• While there are no data on the effect of vimseltinib on human fertility, vimseltinib may impair fertility in males based on findings from animal studies, as described in Section 4.6 of the SmPC.
	• Non-clinical findings of embryo-foetal toxicity may be relevant for humans and in the absence of clinical data suggest a potential safety concern. Embryo-foetal toxicity is considered as an important potential risk of vimseltinib (Modules SVII.1.2 and SVII.3.1).
	  • There has been one pregnancy reported in the clinical development programme in Pool 3. The patient was enrolled in DCC-3014-01-001, took an unspecified "morning after pill" and experienced a spontaneous abortion 26 days later (assessed as unrelated to study treatment). There has also been one partner pregnancy reported in the open-label period of MOTION. The pregnancy resulted in a term live birth with no congenital abnormalities reported.
	  • Section 4.4 and 4.6 of the SmPC advise that based on data from animal studies, vimseltinib may cause foetal harm when administered to pregnant women. Women should be advised to avoid pregnancy while taking vimseltinib. Pregnant women

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
In the FEED study in rats, vimseltinib was administered to male Sprague-Dawley rats once daily beginning 10 weeks prior to cohabitation, during cohabitation/mating and continuing through the day before euthanasia at dose levels of 0, 1, 2.5, and 5 mg/kg/day and to females beginning 2 weeks prior to cohabitation, during cohabitation/mating, and continuing until GD 7 at dose levels of 0, 2.5, 5, and 10 mg/kg/day. Vimseltinib-related effects on reproductive systems included 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 oestrous cycling in females or mating and fertility in males and females at any dose level.	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. The pregnancy status of females of childbearing potential must be verified prior to initiating vimseltinib and during treatment. Effects of vimseltinib on hormonal contraceptives have not been studied. A barrier method should be added if systemic contraceptives are used.
Genotoxicity Vimseltinib was devoid of mutagenic activity when assessed in an In Vitro Ames Mutagenicity Test (DCC-3014-04-0015). The potential for vimseltinib to induce chromosomal damage (micronuclei) in vitro was evaluated in human lymphocyte cultures in the absence and presence of S9 from Aroclor 1254-induced rats. Vimseltinib was negative for induction of micronuclei in the 3-hour incubations without and with S9 but was positive when incubated with human lymphocytes in the absence of S9 for 24 hours. Vimseltinib was tested for its potential to induce micronuclei (MN) in polychromatic erythrocytes (PCE; reticulocytes) of the bone marrow of treated rats and/or to induce unrepaired DNA strand breaks in the liver of the same animals using the alkaline Comet assay. Under the conditions of this study, vimseltinib was not genotoxic in vivo. The totality of the data indicates a low genotoxic liability for vimseltinib.	• Vimseltinib is unlikely to be genotoxic in humans based on non-clinical studies.
Carcinogenicity A 26-week with 4-week recovery period carcinogenicity study (DCC-3014-04-0018) with vimseltinib in transgenic mice was completed. Male and female mice were administered vehicle control article, 1.0, 4.0, or 12.5 mg/kg/day vimseltinib via oral gavage once daily for up to 26 weeks; a positive control group received methyl nitrosurea (MNU) once on Day 1.	• Vimseltinib is unlikely to be carcinogenic in humans based on completed non-clinical studies. While the relevance of the findings from the 2-year rat carcinogenicity to humans is unknown, considering all available clinical and non-clinical data, the carcinogenic risk after vimseltinib administration is considered low. Malignancies are considered as an

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
Vimseltinib was well tolerated, and there was no evidence of carcinogenic potential noted in the study. In a 2-year oral rat carcinogenicity study (DCC-3014-04-0025), male rats were orally administered 0.1, 0.3 or 1.0 mg/kg/day. In the male rats receiving 1.0 mg/kg/day (approximately 1.4 times the total vimseltinib exposure at the recommended dose and less than the unbound [free] vimseltinib exposure for patients with TGCT based on AUC), two out of sixty (3%) were identified as having histomorphologically different sarcomas in the synovium of the femorotibial joint. Both were classified as sarcoma, not otherwise specified. No other neoplasms related to vimseltinib were noted at any dose in this study. There were no neoplastic findings in this study when vimseltinib was orally administered to female rats at any dose level (0.15, 0.45, or 1.5 mg/kg/day).	important potential risk of vimseltinib (Modules SVII.1.2 and SVII.3.1). • Section 5.3 of the SmPC states that vimseltinib was shown to be non-carcinogenic in a 6-month transgenic mouse carcinogenicity study at systemic exposures that were equivalent to 7.6-times the vimseltinib exposure at the recommended human dose based on AUC. • Section 5.3 of the SmPC states that the relevance of the findings from the 2-year oral rat carcinogenicity study is unknown but considering all available clinical and non-clinical data the carcinogenic risk after vimseltinib administration is considered low.
Safety pharmacology	
Cardiovascular system, including potential effect on the QT interval and nervous system A stand-alone GLP cardiovascular safety pharmacology study (DCC-3014-02-0028) in telemeterised dogs was performed with vimseltinib. No treatment-related abnormal electrocardiogram (ECG) waveforms or arrhythmias were noted, and vimseltinib had no physiologically significant (adverse) effects on PR interval, QRS duration, QT interval, or QTc interval up to 25 hours post-dose. Administration of vimseltinib had no physiologically significant effect on heart rate, systolic, diastolic, mean arterial, or arterial pulse pressure up to 25 hours post-dose. In safety pharmacology studies, vimseltinib had no effect on central nervous system (CNS) parameters (DCC-3014-02-0026). There were no treatment-related adverse effects on any of the respiratory parameters evaluated (DCC-3014-02-0027). Mildly higher, reversible tidal volume (up to +17%) was noted at the high dose and was not considered of physiological concern because of its small magnitude and transient nature and the unaffected minute volume.	• Vimseltinib is unlikely to have significant cardiovascular (CV), CNS or respiratory safety pharmacology liabilities in humans. • Based on results from a concentration QTc modeling analysis, vimseltinib has no clinically relevant effect on heart rate or cardiac conduction (PR and QRS intervals). This is further discussed in Module SIV.1. • In the double-blind period of the MOTION study, 3 (3.6%) participants experienced TEAEs of Palpitations and 1 (1.2%) participant experienced a TEAE of Bradycardia (MOTION CSR Table 14.3.1.2.1.1) in the Cardiac disorders SOC. All were non-serious (MOTION CSR Table 14.3.2.1.1.1) and Grade 1 in severity (MOTION CSR Table 14.3.1.3.1.1). None led to discontinuation of treatment (MOTION CSR Table 14.3.1.2.7.1). In the placebo arm, there were no TEAEs in the Cardiac disorders SOC. • In Pool 1, 4 (2.2%) participants experienced TEAEs of Palpitations, 3 (1.6%) participants experienced TEAEs of Bradycardia, 2 (1.1%) participants experienced TEAEs of Tachycardia, 1 (0.5%) participant experienced a TEAE of Angina pectoris, 1 (0.5%)

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
	participant experienced a TEAE of Myocardial ischaemia, 1 (0.5%) participant experienced a TEAE of Sinus bradycardia and 1 (0.5%) participant experienced a TEAE of Sinus tachycardia in the Cardiac disorders SOC (ISS Table 12.1.1). All were non-serious and Grade 1 in severity, with the exception of Myocardial ischemia, which was serious, Grade 3 in severity, and assessed as unrelated to vimseltinib (ISS Table 13.1.1; ISS Table 12.3.1; ISS Table 12.6.1). One (0.5%) participant experienced a TEAE of Palpitations that led to discontinuation of treatment (ISS Table 12.7.2.1). • In the clinical development programme, 15 (18.1%) participants in the vimseltinib arm of MOTION (compared with 4 [10.3%] in the placebo arm) and 39 (21.3%) participants treated with vimseltinib in Pool 1 experienced TEAEs within the Standardised MedDRA Query (SMQ) Hypertension (narrow). Arterial hypertension is considered as an important identified risk of vimseltinib (Modules SVII.1.2 and SVII.3.1). Arterial hypertension is described as a warning in Section 4.4 of the SmPC, and hypertension is listed as an adverse reaction in Section 4.8 of the SmPC. • In the MOTION study, the most frequently reported TEAE in the Nervous system disorders SOC was the PT of Headache. In the double-blind period, 23 (27.7%) participants in the vimseltinib arm experienced TEAEs of Headache (MOTION CSR Table 14.3.1.2.1.1). All were non-serious (MOTION CSR Table 14.3.2.1.1.1); 16 (19.3%) participants experienced Grade 1 TEAEs, 6 (7.2%) participants experienced Grade 2 TEAEs and 1 (1.2%) participant experienced a Grade 3 TEAE (MOTION CSR Table 14.3.1.3.1.1). In the placebo arm, the proportion was similar (10 [25.6%] of 39 participants experienced TEAEs of Headache) (MOTION CSR Table 14.3.1.2.1.1). All were non-serious (MOTION CSR Table 14.3.2.1.1.1) and Grade 1 or 2 (MOTION CSR Table 14.3.1.3.1.1). No TEAEs of Headache in either group led to discontinuation of

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
	treatment (MOTION CSR Table 14.3.1.2.7.1). • In Pool 1, the most frequently reported TEAE in the Nervous system disorders SOC was also the PT of Headache; 62 (33.9%) participants experienced TEAEs of Headache (ISS Table 12.1.1). All were non-serious (ISS Table 12.3.1); 44 (24%) participants experienced Grade 1 TEAEs, 16 (8.7%) participants experienced Grade 2 TEAEs and 2 (1.1%) participants experienced Grade 3 TEAEs (ISS Table 13.1.1). None led to discontinuation of treatment (ISS Table 12.7.2.1).
Mechanism for drug interactions	
In vitro, both vimseltinib and its active metabolite DP-7005 exhibited IC_{50} values >40 µM for all cytochrome P450 enzyme (CYP) isoforms studied. Additionally, vimseltinib and DP-7005 did not exhibit time-dependent or metabolism dependent inhibition of any CYP isoform. Vimseltinib and DP-7005 exhibit a low/minimal liability for a drug-drug interaction mediated by CYP inhibition. Vimseltinib demonstrated low to minimal risk for drug-drug interactions involving induction of CYP1A2 or CYP3A4, and slight risk for drug-drug interactions involving CYP2B6 induction. Vimseltinib and its human metabolite DP-7005 are moderate to weak inhibitors of various human efflux and uptake transporters. Two transporters, breast cancer resistance protein (BCRP) and organic cation transporter 2 (OCT2), were inhibited with IC_{50} values of less than 1 µM (0.556 and 0.456 µM, respectively) by vimseltinib. P-glycoprotein (P-gp) (multidrug resistance protein 1; MDR1) was inhibited with IC_{50}=4.4 µM, while bile salt export pump (BSEP), organic anion transporter polypeptide (OATP)1B1, OATP1B3, organic anion transporter (OAT)1, and OAT3 had IC_{50} >10 µM. DP-7005 inhibited all tested transporters by <35% when evaluated at 10 µM. Vimseltinib may alter the PK of concurrent medications that are substrates for BCRP, by inhibition of BCRP at the systemic and intestinal level. Vimseltinib and DP-7005 exhibit low potential to be a victim of a drug-drug	• Vimseltinib caused concentration-dependent increases (>2-fold) in CYP2B6 *in vitro* in clinically relevant concentrations. Based on physiologically based PK (PBPK) modelling, no interaction was predicted following co-administration of bupropion, a CYP2B6 substrate with vimseltinib 30 mg twice weekly. • Vimseltinib inhibited P-gp, BCRP and OCT2 in vitro in clinically relevant concentrations. Section 4.5 of the SmPC advises that concomitant use of BCRP, OCT2, and P-gp substrates should be avoided.

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
interactions mediated by inhibition of other transporters. Vimseltinib was a moderately weak substrate of P-gp (MDR1). 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 (ie, BCRP, BSEP, OATP1B1, OATP1B3 OAT1, OAT3, and OCT2) as evidenced by the efflux or uptake ratios of <2. These results suggest that vimseltinib exhibits low potential to be a victim of a drug-drug interaction mediated by inhibition of drug transporters. Due to its pH-dependent solubility, vimseltinib exhibits the potential to be subject to a drug interaction with acid-reducing agents.	
Other toxicity-related information or data	
Vimseltinib has a potential for photo irritation/phototoxicity based on absorption in the ultraviolet-visible (UV-VIS) range (above 290 nm). However, vimseltinib did not demonstrate phototoxic potential in the Neutral Red Uptake Phototoxicity Assay in BALB/c 3T3 Mouse Fibroblasts (DCC-3014-04-0023).	• In the double-blind period of the MOTION study, 1 (1.2%) participant in the vimseltinib arm experienced a TEAE of Sunburn (MOTION CSR Table 14.3.1.2.1.1). This event was non-serious (MOTION CSR Table 14.3.2.1.1.1) and Grade 1 severity (MOTION CSR Table 14.3.1.3.1.1). In the placebo arm, no TEAEs relevant to photo irritation/phototoxicity were reported. • In Pool 1, 1 (0.5%) participant experienced a TEAE of Photophobia and 3 (1.6%) participants experienced TEAEs of Photosensitivity reaction (ISS Table 12.1.1). All of the reported TEAEs were non-serious, Grade 1 or 2 in severity (ISS Table 12.3.1; ISS Table 13.1.1) and reported in patients taking concomitant medications with labelled phototoxicity or similar adverse drug reactions. • Following comprehensive data review, photosensitivity reactions are not considered a risk of vimseltinib.
In vivo distribution studies demonstrated CNS penetration of vimseltinib. In the rat blood brain barrier PK study (DCC-3014-03-0015), the brain:plasma ratio was 0.73 after a 1 mg/kg intravenous dose. CNS penetration was determined to be lower in the rat mass balance study (DCC-3014-03-0022). After a single oral	• In the double-blind period of the MOTION study, 4 (4.8%) participants in the vimseltinib arm of MOTION (compared to 0 participants in the placebo arm) experienced TEAEs within the High Level Group Term (HLGT) Deliria (incl confusion) and HLGT Mental impairment disorders. In Pool 1, 9 (4.9%)

Key Safety Findings (from Non-clinical Studies)	Relevance to Human Usage
dose of 10 mg/kg (100 μCi/kg) [^{14}C]-vimseltinib, brain accumulation was considered low from 0.5-672 hours, as determined by quantitative whole body autoradiography (QWBA). No neurobehavioral observations were attributable to vimseltinib administration in safety pharmacology or repeated-dose toxicity studies.	participants experienced TEAEs within the HLGT Deliria (incl confusion) and HLGT Mental impairment disorders. Cognitive disorders/CNS adverse events are considered as an important potential risk of vimseltinib (Modules SVII.1.2 and SVII.3.1). Uncertainty surrounding the long-term implications of macrophage depletion in several organs are described in Section 4.4 of the SmPC, including the CNS.

Conclusions from the non-clinical development programme

The non-clinical studies support the clinical use of vimseltinib for the treatment of TGCT. Overall, the low dose of vimseltinib was well tolerated at 5 mg/kg/day in rats for 28 days and at 1.876 mg/kg/day for 91 days. In dogs, vimseltinib at doses of ≤7.5 mg/kg/day was clinically well tolerated for 28 days and 2, 4, or 8 mg/kg/day vimseltinib was well tolerated for 91 days.

Vimseltinib administered at a dose of 15 mg/kg/day was a selective developmental toxicant (teratogenic) in rats, producing malformations of the cardiovascular and skeletal systems. Additional indications of developmental toxicity, including structural anatomic variations and indications of developmental delay, also occurred at this dose.

In the dog cardiovascular safety pharmacology study, no vimseltinib-related qualitative ECG effects or quantitative changes in PR interval, QRS duration, QT interval, corrected QT (QTc) interval, heart rate, arterial pressure, or body temperature were seen at doses up to 15 mg/kg (300 mg/m^2). In the rat safety pharmacology study, there were no treatment-related adverse effects on any of the respiratory parameters evaluated.

In safety pharmacology studies, vimseltinib had no effect on CNS parameters. While CNS penetration of vimseltinib was demonstrated in vivo, there were no vimseltinib-related CNS observations or neurobehavioral changes noted in repeated-dose toxicity studies in rats and dogs up to 26- and 39-weeks, respectively.

In the neutral red uptake phototoxicity assay in BALB/c 3T3 mouse fibroblasts, vimseltinib did not demonstrate phototoxic potential.

While the relevance of the findings from the 2-year rat carcinogenicity to humans is unknown, based on the weight of evidence from all available clinical and non-clinical data, the carcinogenic risk after vimseltinib administration is considered low. The totality of the data indicates a low genotoxic liability.

Vimseltinib and its human metabolite DP-7005 did not exhibit time-dependent or metabolism dependent inhibition of any CYP isoform. Vimseltinib and DP-7005 exhibit a low/minimal liability for a drug-drug interaction mediated by CYP inhibition. Vimseltinib demonstrated low to minimal risk for drug-drug interactions involving induction of CYP1A2 or CYP3A4, and slight risk for drug-drug interactions involving CYP2B6 induction.

Vimseltinib and DP-7005 are moderate to weak inhibitors of various human efflux and uptake transporters and exhibit low potential to be a victim of drug-drug interactions mediated by inhibition of other transporters.

Safety concerns based on non-clinical findings that have relevance for human usage and have been confirmed by clinical data:

- None

Safety concerns based on non-clinical findings that have relevance for human usage and have not been adequately refuted by clinical data and/or are of unknown significance:

- Embryo-foetal toxicity is an important potential risk
- Cognitive disorders/CNS adverse events are an important potential risk
- Malignancies are an important potential risk

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

Detailed analyses that support the safety conclusions of vimseltinib were derived from safety data from 6 clinical studies.

Two of the 6 clinical studies of vimseltinib were conducted in adult participants with solid tumours, including TGCT. These studies are ongoing and form the basis of the primary evaluation of safety:

- DCC-3014-01-001 (Phase 1/2, data cut off (DCO): 27 Dec 2023): 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 maximum tolerated dose (MTD), the recommended Phase 2 dose, preliminary efficacy, and PK and pharmacodynamic (PD) effects of vimseltinib in participants with malignant solid tumour (MST) or tenosynovial giant cell tumour (TGCT). The expansion phase seeks to further evaluate the preliminary efficacy, safety, PK, and PD of vimseltinib in participants with TGCT. In total, 69 patients (37 MST and 32 TGCT) were enrolled in Part 1 (escalation) and 66 in Part 2 (expansion).
- DCC-3014-03-001 (MOTION; DCO: 22 Feb 2024): A pivotal phase 3, multicentre, randomized, placebo-controlled study to assess the efficacy and safety of vimseltinib in participants with TGCT, consisting of 2 parts. Overall, 123 patients were randomized at a ratio of 2:1 (vimseltinib to placebo). Part 1 is double-blind and is completed, and Part 2 is open-label (participants randomized to placebo in Part 1 had the option to cross over and receive open-label vimseltinib).

Three completed clinical pharmacology studies contributed to the safety evaluation of vimseltinib in healthy participants:

- DCC-3014-01-002 is a completed phase 1, open-label study of 114 healthy volunteers to characterise the PK of vimseltinib and its active metabolite DP-7005, along with food effects in healthy adult participants. Arms 1a-1c consisted of a single-dose PK, Arm 1d-1e was single-blind placebo-controlled, and Arm 2 assessed food effect. In total, 98 participants received vimseltinib and 16 participants received placebo.
- DCC-3014-01-003 is a completed phase 1, open-label study to characterise the absorption, metabolism, excretion (AME) of radiolabelled DCC-3014 (14^{C}-DCC-3014) in 8 healthy male participants.
- DCC-3014-01-006 is a completed phase 1, open-label, randomized, parallel design study to evaluate the effects of P-glycoprotein inhibition and gastric acid suppression on single-dose PK of vimseltinib in 89 healthy adult participants. Arm 1 consisted of single dose vimseltinib, Arm 2 consisted of itraconazole + single dose vimseltinib and Arm 3 consisted of rabeprazole + single dose vimseltinib.

One ongoing clinical pharmacology study contributed to the safety evaluation of vimseltinib in participants with normal hepatic function and those with hepatic impairment:

- DCC-3014-01-004 is an ongoing phase 1, open-label study of the PK, safety and tolerability of single dose vimseltinib in participants with hepatic impairment compared to healthy control participants. The safety of vimseltinib in patients with mild, moderate, and severe hepatic impairment is compared to healthy control participants; up to 8 participants will be enrolled in each group. The study is ongoing, with only results from the mild hepatic impairment cohort available.

Table 3 summarizes exposure to vimseltinib in participants across clinical studies supporting safety, including any exposure to vimseltinib, and exposure in the target indication at the proposed dose.

Table 3: 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 (randomized to vimseltinib during double-blind period) 35 (crossed over from placebo to vimseltinib)
Supportive Study		
DCC-3014-01-001 (Phase 1/2, Dose Escalation/Dose Expansion[a])	135	66
Clinical Pharmacology Studies		
DCC-3014-01-002 (Phase 1, PK, Food Effect, QTc)	98	0
DCC-3014-01-003 (Phase 1 hAME)	8	0
DCC-3014-01-004 (Hepatic Impairment)	16 (of 48 planned)	0
DCC-3014-01-006 (DDI, P-gp)	89	0
Total Exposure	464	184

Abbreviations: CSF1=colony-stimulating factor 1; CSF1R=colony-stimulating factor 1 receptor; DDI=drug-drug interaction; hAME=human absorption, metabolism, and excretion; P-gp=P-glycoprotein; PK=pharmacokinetics; 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.
One participant from the Dose Escalation Phase (Cohort 5), [redacted] re-enrolled into Expansion Cohort B as [redacted]. One participant from the Expansion Phase (Cohort A), [redacted], re-enrolled into Cohort B as [redacted]. These participants were counted as different participants for exposure analyses.
Sources: MOTION Tables 14.1.5.1.1 and 14.1.5.2.1; ISS Table 10.1; Study 002 Table 34; Study 003 Section 12.1; Study 006 Section 12.1; DCC-3014-01-004 Listing 16.2.7.1.1

Pooled Analysis:

Pooled exposure data supporting authorisation for vimseltinib are provided from 2 clinical studies, MOTION and DCC-3014-01-001. Pool 1 includes all TGCT participants in DCC-3014-01-001 and MOTION receiving at least 1 dose of vimseltinib at the recommended dose of 30 mg BIW.

Exposure to vimseltinib across these studies includes 223.1 patient-years of exposure.

Clinical trial exposure data are presented for all participants treated with vimseltinib in MOTION and DCC-3014-01-001 by duration of exposure (Table 4), age group and sex (Table 5), and racial and ethnicity groups (Table 6).

Table 4: Duration of Exposure in Participants with TGCT Treated with Vimseltinib 30 mg BIW in MOTION and Pool 1

Characteristics	Vimseltinib 30 mg BIW in Study DCC-3014-03-001 [a] (N=83)		Vimseltinib 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001 [b] (N=184)	
	Participants n (%)	Person Time (Year)	Participants n (%)	Person Time (Year)
Group by Duration of Exposure (month)				
≥ 3	79 (95.2)	35.4	169 (91.8)	220.8
≥ 6	1(1.2)	0.5	147 (79.9)	212.2
≥ 9	0	0	122 (66.3)	196.5
≥ 12	0	0	101 (54.9)	177.7
≥ 24	0	0	29 (15.8)	75.5
≥ 36	0	0	2 (1.1)	6.0
Group by Duration of Exposure (month)				
< 1	1 (1.2)	0.1	4 (2.2)	0.2
1 - <3	3 (3.6)	0.5	11 (6.0)	2.0
3 - <6	78 (94.0)	34.9	22 (12.0)	8.6
6 - <9	1 (1.2)	0.5	25 (13.6)	15.7
9 - <12	0	0	21 (11.4)	18.7
12 - <24	0	0	72 (39.1)	102.2
24 - <36	0	0	27 (14.7)	69.5
≥36	0	0	2 (1.1)	6.0
Total Person Time (Year)	NA	36.0	NA	223.1

Abbreviations: BIW=Twice Weekly; NA=not applicable; TGCT=Tenosynovial giant cell tumour.
Person time (year) is calculated as the sum of the duration of exposure in days divided by 365.25.
[a] This column presents data in double-blind treatment period of MOTION
[b] This column presents exposure data for all patients in the analysis population (Pool 1)
Note: The analysis population includes patients with Tenosynovial Giant Cell Tumours who were treated with 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001, including 35 patients who originally received placebo and subsequently crossed over to 30 mg BIW in Study DCC-3014-03-001.
One participant from the Expansion Phase (Cohort A), [redacted], re-enrolled into Cohort B as [redacted]. This participant was counted as different participants for the total column.
Source: RMP Source Table 3

Table 5: Exposure by Age Group and Sex in Participants with TGCT Treated with Vimseltinib 30 mg BIW in MOTION and Pool 1

	Vimseltinib 30 mg BIW in Study DCC-3014-03-001 [a] (N=83)				Vimseltinib 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001 [b] (N=184)			
	Participants n (%)		Person Time (Year)		Participants n (%)		Person Time (Year)	
	Male (N=37)	Female (N=46)	Male	Female	Male (N=74)	Female (N=110)	Male	Female
Age Group (year)								
18 - <50	25 (67.6)	29 (63.0)	11.0	12.3	47 (63.5)	68 (61.8)	60.4	71.8
50 - <65	12 (32.4)	12 (26.1)	5.5	5.2	26 (35.1)	32 (29.1)	32.9	49.0
65 - <75	0	3 (6.5)	0	1.0	1 (1.4)	8 (7.3)	1.2	6.1
75 - < 85	0	2 (4.3)	0	0.9	0	2 (1.8)	0	1.7
≥85	0	0	0	0	0	0	0	0
Total Person Time (Year)	NA	NA	16.5	19.5	NA	NA	94.5	128.6

Abbreviations: BIW=Twice Weekly; NA=not applicable; TGCT=Tenosynovial giant cell tumour.
Person time (year) is calculated as the sum of the duration of exposure in days divided by 365.25.
[a] This column presents data in double-blind treatment period of MOTION
[b] This column presents exposure data for all patients in the analysis population (Pool 1)
Note: The analysis population includes patients with Tenosynovial Giant Cell Tumours who were treated with 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001, including 35 patients who originally received placebo and subsequently crossed over to 30 mg BIW in Study DCC-3014-03-001.
One participant from the Expansion Phase (Cohort A), [redacted], re-enrolled into Cohort B as [redacted]. This participant was counted as different participants for the total column.
Source: RMP Source Table 4

Table 6: Exposure by Racial Group and Ethnicity Group in Participants with TGCT Treated with Vimseltinib 30 mg BIW in MOTION and Pool 1

	Vimseltinib 30 mg BIW in Study DCC-3014-03-001 [a] (N=83)		Vimseltinib 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001 [b] (N=184)	
	Participants n (%)	Person Time (Year)	Participants n (%)	Person Time (Year)
Race				
American Indian or Alaska Native	0	0	0	0
Asian	1 (1.2)	0.4	7 (3.8)	9.1
Black or African American	4 (4.8)	1.6	5 (2.7)	3.9

	Vimseltinib 30 mg BIW in Study DCC-3014-03-001 [a] (N=83)		Vimseltinib 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001 [b] (N=184)	
	Participants n (%)	**Person Time (Year)**	**Participants n (%)**	**Person Time (Year)**
Native Hawaiian or Other Pacific Islander	0	0	1 (0.5)	2.7
White	59 (71.1)	25.9	132 (71.7)	160.9
Other	0	0	6 (3.3)	10.4
Not Reported	19 (22.9)	8.0	33 (17.9)	36.1
Ethnicity				
Hispanic or Latino	3 (3.6)	1.2	9 (4.9)	9.4
Not Hispanic or Latino	62 (74.7)	27.1	138 (75.0)	171.1
Not Reported	17 (20.5)	7.3	35 (19.0)	39.7
Unknown	1 (1.2)	0.5	2 (1.1)	2.8
Total Person Time (Year)	NA	36.0	NA	223.1

Abbreviations: BIW=Twice Weekly; NA=not applicable; TGCT=Tenosynovial giant cell tumour.
Person time (year) is calculated as the sum of the duration of exposure in days divided by 365.25.
[a] This column presents data in double-blind treatment period of MOTION
[b] This column presents exposure data for all patients in the analysis population (Pool 1)
Note: The analysis population includes patients with Tenosynovial Giant Cell Tumours who were treated with 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001, including 35 patients who originally received placebo and subsequently crossed over to 30 mg BIW in Study DCC-3014-03-001.
One participant from the Expansion Phase (Cohort A), [redacted], re-enrolled into Cohort B as [redacted]. This participant was counted as different participants for the total column.
Source: RMP Source Table 5

PART II: MODULE SIV POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 Exclusion Criteria in Pivotal Clinical Studies within the Development Programme

Exclusion criteria from pivotal Phase 3 study (MOTION) that are not discussed further as they are common to most clinical trials to ensure standardization of the trial population:

- Known allergy or hypersensitivity to any component of the study drug
- Contraindication to magnetic resonance imaging (MRI)
- 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
- Malabsorption syndrome or other illness that could affect oral absorption as judged by the Investigator

The exclusion criteria that are related to ongoing or recent conditions or treatments that may impact the efficacy assessment of vimseltinib in MOTION are listed below and not discussed further:

- Previous use of systemic therapy (investigational or approved) targeting CSF1 or CSF1R including vimseltinib; previous therapy with imatinib and nilotinib is allowed
- Treatment for TGCT, including investigational therapy, during the screening period
- Known metastatic TGCT or other active cancer that requires concurrent treatment
- 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

The remaining exclusion criteria from MOTION are presented below and may be grouped together:

- 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
- Medications with a known risk of prolonging the QT interval within at least 14 days or 5 x half-life (whichever is longer) prior to the first dose of study drug

  <u>Reason for exclusions:</u>

  While animal studies demonstrated that vimseltinib had no physiologically significant (adverse) effects on PR interval, QRS duration, QT interval, or QTc interval up to 25 hours post-dose, patients with baseline prolongation of the QTcF based on repeated demonstration of QTcF >450ms in males or >470 ms in females or history of long QT syndrome were excluded from clinical trial participation as their inclusion could have affected the efficacy and safety assessment of vimseltinib. Patients on medications with a known risk of prolonging the QT interval were also excluded as a precaution.

Is it considered to be included as missing information? No

Rationale:

Use is likely to be limited in these patients.

The relationship of the QTc interval to vimseltinib plasma concentration and central tendency over time were analysed based on healthy participants (DCC-3014-01-002).

The results from the cardiodynamic evaluation of 40 and 50 mg doses 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.

No participant experienced QTcF prolongation >500 ms and only 3 participants experienced QTcF prolongation above the baseline >60 ms.

No participant experienced QTcF prolongation on multiple occasions. No observation was considered clinically significant, and none led to dose modification or treatment discontinuation.

- Receiving 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 BCRP or OCT2 substrates taken within at least 4 days or 5 x half-life (whichever is longer) prior to the first dose of study drug
  - Prophylactic use of myeloid growth factors (eg, granulocyte colony-stimulating factor, granulocyte macrophage-colony-stimulating factor)

  Reason for exclusion:

  Patients taking any of these prohibited medications were excluded from clinical trial participation as their inclusion could have affected the safety and efficacy assessment of vimseltinib.

  Vimseltinib inhibited BCRP and OCT2 *in vitro i*n clinically relevant concentrations.

  Is it considered to be included as missing information? No

  Rationale:

  Use is likely to be limited in these patients.

  Section 4.5 of the SmPC advises that concomitant use of BCRP and OCT2 substrates should be avoided.

- Active liver or biliary disease including non-alcoholic steatohepatitis (NASH) or cirrhosis

  Reason for exclusion:

  In the animal studies, pathology findings included mildly increased aspartate aminotransferase and CPK activities, which may have resulted from CSF1R inhibition of macrophage function (the mechanism of action for vimseltinib). Patients with active liver or biliary disease including NASH or cirrhosis were excluded from clinical trial participation as their condition could have affected the metabolism and therefore the efficacy and safety assessment of vimseltinib.

Is it considered to be included as missing information? No

Rationale:

Vimseltinib should not be used in patients with moderate and severe hepatic impairment in accordance with Section 4.2 of the vimseltinib SmPC. Therefore, use of vimseltinib in these patients is not expected.

- Known active human immunodeficiency virus (HIV), acute or chronic hepatitis B, acute or chronic hepatitis C, or known active mycobacterium tuberculosis infection

  Reason for exclusion:

  Patients with known active HIV, acute or chronic hepatitis B, acute or chronic hepatitis C, or known active mycobacterium tuberculosis infection were excluded from the clinical development programme as their inclusion may have affected the safety and efficacy assessment of vimseltinib.

  Is it considered to be included as missing information? No

  Rationale:

  Use is likely to be limited in these patients. These patients were excluded due to their underlying condition or concomitant medications required for the infections.

- If female, the participant is pregnant or breastfeeding

  Reason for exclusion:

  In animal studies, vimseltinib administered at a dose of 15 mg/kg/day was a selective developmental toxicant (teratogenic) in rats, producing malformations of the cardiovascular and skeletal systems. Oral administration of vimseltinib resulted in abortions in the 5, 10, and 20 mg/kg/day dose groups in pregnant female rabbits.

  Females who were pregnant or breastfeeding were excluded from clinical trial participation due to potential risk to the foetus.

  Is it considered to be included as missing information? No

  Rationale:

  Embryo-foetal toxicity is considered an important potential risk (Modules SVII.1.2 and SVII.3.1).

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Programmes

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

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Programmes

Table 7: Exposure of Special Populations Included or Not in Clinical Trial Development Programmes

Type of Special Population	Exposure
Pregnant women	While pregnant women were not included in the clinical development programme, there has been one pregnancy reported in the clinical trial programme in Pool 3. The patient was enrolled in DCC-3014-01-001, took an unspecified "morning after pill" and experienced a spontaneous abortion 26 days later (assessed as unrelated to study treatment). There has also been one partner pregnancy reported in the open-label period of MOTION. The pregnancy resulted in a term live birth with no congenital abnormalities reported.
Breastfeeding women	Not included in the clinical development programme
Patients with relevant comorbidities: • Patients with hepatic impairment	Baseline hepatic impairment severity was calculated following the National Cancer Institute hepatic impairment classification using the baseline total bilirubin and aspartate aminotransferase. In the MOTION double-blind period, 1 (1.2%) participant in the vimseltinib arm and 1 participant in the placebo arm had mild hepatic impairment. In Pool 1, 4 (2.2%) participants had mild hepatic impairment (RMP Source Table 2). In DCC-3014-01-004, 8 participants with mild hepatic impairment, according to the Child-Pugh classification, have been exposed to vimseltinib in Part 1. No dose adjustment is recommended for patients with mild hepatic impairment (Child-Pugh A). Dose reductions to 14 mg twice weekly for patients with mild hepatic impairment have not been used and efficacy has not been established. No clinical data are available in patients with moderate and severe hepatic impairment. Therefore, ROMVIMZA should not be used in these patients (Section 4.2 of the SmPC).

Type of Special Population	Exposure
• Patients with renal impairment	Baseline renal impairment severity was determined using the baseline serum creatinine to calculate creatinine clearance using the Cockcroft-Gault equation (Normal: ≥90 mL/min; Mild: 60-89 mL/min; Moderate: 30-59 mL/min; Severe: 15-29 mL/min). Patients with mild and moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥37.7 mL/min/1.73m^2) were permitted in the development programme. In the MOTION double-blind period, 13 (15.7%) participants in the vimseltinib arm had mild renal impairment and 1 (1.2%) participant had moderate renal impairment. In the placebo arm, 8 (20.5%) participants had mild renal impairment and 1 (2.6%) participant had moderate renal impairment. In Pool 1, 30 (16.3%) participants had mild renal impairment and 2 (1.1%) participants had moderate renal impairment (RMP Source Table 2). Renal excretion is not expected to account for a substantial portion of the elimination of unchanged vimseltinib. No dose adjustment is recommended for patients with mild or moderate renal impairment. Patients with severe renal impairment were excluded and no clinical data are available. Therefore, ROMVIMZA should not be used in these patients (Section 4.2 of the SmPC).
• Patients with cardiovascular impairment	There is limited exposure in patients with cardiovascular impairment. Baseline cardiovascular impairment status was based on patients' medical history of any cardiac disorders (by MedDRA System Organ Class). In the MOTION double-blind period, 5 (6%) participants in the vimseltinib arm and 2 (5.1%) participants in the placebo arm had cardiac disorders. In Pool 1, 9 (4.9%) participants had cardiac disorders (RMP Source Table 2).
• Immunocompromised patients	Vimseltinib has not been studied in immunocompromised patients. Patients with known active human immunodeficiency virus (HIV) were excluded from MOTION (Module SIV.1).
• Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme

Type of Special Population	Exposure
Population with relevant different ethnic origin	In the MOTION double-blind period, the main ethnic group in participants receiving vimseltinib was Not Hispanic or Latino (74.7%), with smaller numbers of participants characterised as Not Reported (20.5%), Hispanic or Latino (3.6%) and Unknown (1.2%). In Pool 1, the main ethnic group was Not Hispanic or Latino (75.0%), with smaller numbers of participants characterised as Not Reported (19.0%), Hispanic or Latino (4.9%) and Unknown (1.1%) (Module SIII, Table 6).
Subpopulations carrying relevant genetic polymorphisms	Not applicable
Paediatric patients	Not included in the clinical development programme

PART II: MODULE SV POST-AUTHORISATION EXPERIENCE

Vimseltinib is not authorised in any country at the time of data lock point (22-Feb-2024) of this report.

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Based on the mechanism of action, drug abuse and withdrawal or rebound effects are not anticipated with vimseltinib.

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

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

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

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

- None

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

- None

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

- None

Known risks that do not impact the risk-benefit profile:

- Drug-drug interactions

  Effect of other medicinal products on vimseltinib

  P-gp inhibitors
  Concomitant administration of single-dose vimseltinib with 200 mg of itraconazole (a P-gp inhibitor) once daily showed that peak exposure (C_{max}) of vimseltinib was comparable to that when administered alone, total exposure of vimseltinib (AUC_{0-t} and AUC_{0-inf}) was approximately 17% to 22% higher in the presence of itraconazole. Dose adjustment is not required.

  Proton Pump inhibitors
  Concomitant administration of vimseltinib with rabeprazole (a proton pump inhibitor) 20 mg once daily under fasted conditions reduced C_{max} and AUC_{0-t} and AUC_{0-inf} of

vimseltinib by approximately 21% to 26%, which is not clinically relevant. Dose adjustment is not required.

Effect of vimseltinib on other medicinal products

Breast cancer resistance protein (BCRP) substrates
Vimseltinib is an inhibitor of BCRP *in vitro*. Concomitant use of vimseltinib with BCRP substrates (e.g. rosuvastatin) may increase the concentrations of BCRP substrates and increase the risk of adverse reactions related to these substrates. Clinical studies with BCRP substrates have not been conducted.

The concomitant use of BCRP substrates should be avoided. Refer to the SmPC of the BCRP substrate for dose modifications if concomitant use cannot be avoided.

Organic Cation Transporter 2 (OCT2) substrates
Vimseltinib is an inhibitor of OCT2 *in vitro*. Concomitant use of vimseltinib with OCT2 substrates (e.g. metformin) may increase the concentrations of OCT2 substrates and increase the risk of adverse reactions related to these substrates. Clinical studies with OCT2 substrate have not been conducted.

The concomitant use of OCT2 substrates should be avoided. Refer to the SmPC of the OCT2 substrate for dose modifications if concomitant use cannot be avoided.

P-glycoprotein (P-gp) substrates
Vimseltinib is an inhibitor of P-gp *in vitro*. Concomitant use of vimseltinib with P-gp substrates (e.g. digoxin, dabigatran) may increase the concentrations of P-gp substrates and increase the risk of adverse reactions related to these substrates. Clinical studies with P-gp substrates have not been conducted.

The concomitant use of P-gp substrates should be avoided. Refer to the SmPC of the P-gp substrate for dose modifications if concomitant use cannot be avoided.

Drug-drug interactions do not impact the benefit/risk balance of vimseltinib and can be managed in clinical practice through guidance in the SmPC and are not an important safety concern for vimseltinib.

- *Increased cholesterol* (*including PTs of Hypercholesterolaemia and Blood cholesterol increased*):

  In the MOTION double-blind period, cholesterol elevations were observed as a laboratory abnormality with a notable difference between the vimseltinib arm and the placebo arm. In the vimseltinib arm, 36 (43.4%) participants experienced shifts in cholesterol; none worsened to Grade 3/4. In the placebo arm, 6 (15.4%) participants experienced shifts in cholesterol; none worsened to Grade 3/4. In Pool 1, 95 (51.6%) participants experienced shifts in cholesterol, with a shift to Grade 3 reported in 2 (1.1%) participants. No Grade 4 shifts were observed (RMP Source Table 17).

  In the double-blind period of MOTION, 2 (2.4%) participants experienced TEAEs of Blood cholesterol increased (RMP Source Table 6), both of which were considered related to study treatment (RMP Source Table 11). Both were non-serious (RMP Source Table 8) and Grade 2 in severity (RMP Source Table 9). The median time to

onset of the first event was 17 days (range: 14-120) (RMP Source Table 16) and half of the events resolved (RMP Source Table 10). In the placebo arm, 1 (2.6%) participant experienced a TEAE of Blood cholesterol increased (RMP Source Table 6), which was non-serious (RMP Source Table 8) and Grade 1 in severity (RMP Source Table 9). In Pool 1, 10 (5.5%) participants experienced TEAEs of Blood cholesterol increased (RMP Source Table 6), all of which were considered related to study treatment (RMP Source Table 11). All were non-serious (RMP Source Table 8); 5 (2.7%) were Grade 1 in severity, 4 (2.2%) were Grade 2 in severity and 1 (0.5%) was Grade 3 in severity (RMP Source Table 9). The median time to onset of the first event was 29 days (range: 14-927) (RMP Source Table 16) and 45.5% of all events resolved (RMP Source Table 10).

Blood cholesterol increased is listed in Section 4.8 of the SmPC. All TEAEs of Blood cholesterol increased observed in Pool 1 were non-serious, with the majority reported as Grade 1 or Grade 2 in severity. This laboratory abnormality can be managed in clinical practice and is not an important safety concern for vimseltinib.

- *Decreased neutrophils* (*including PTs of Neutropenia and Neutrophil count decreased*):

  The most frequently reported haematology laboratory abnormality was decreased neutrophils. In the MOTION double-blind period, decreased neutrophils from baseline were observed in 25 (30.1%) of participants in the vimseltinib arm. Of these, 1 (1.2%) worsened to Grade 3/4. In the placebo arm, decreased neutrophils from baseline were observed in 1 (2.6%) participant, and no Grade 3/4 decreases were observed. In Pool 1, decreased neutrophils from baseline were observed in 62 (33.7%) participants. Of these, 5 (2.7%) participants worsened to Grade 3/4 (RMP Source Table 18).

  In the double-blind period of the MOTION study, there were no TEAEs of Neutrophil count decreased in either arm. Four (4.8%) participants experienced TEAEs of Neutropenia (RMP Source Table 6). All Neutropenia TEAEs were non-serious (RMP Source Table 8). One (1.2%) participant experienced a Grade 1 TEAE, 2 (2.4%) participants experienced Grade 2 TEAEs and 1 (1.2%) participant experienced a Grade 3 TEAE (RMP Source Table 9). In the placebo arm, there were no TEAEs of Neutrophil count decreased or Neutropenia (RMP Source Table 6).

  In Pool 1, 5 (2.7%) participants experienced TEAEs of Neutrophil count decreased (RMP Source Table 6), all of which were non-serious, Grade 1 or 2 in severity, and considered related to study treatment (RMP Source Table 8; RMP Source Table 9; RMP Source Table 11). Nine (4.9%) participants experienced TEAEs of Neutropenia (RMP Source Table 6). Of the participants with TEAEs of Neutropenia, 2 (1.1%) participants experienced a Grade 1 TEAE, 6 (3.3%) participants experienced Grade 2 TEAEs and 1 (0.5%) participant experienced a Grade 3 TEAE (RMP Source Table 9); all were non-serious (RMP Source Table 8), with none leading to discontinuation of treatment (ISS Table 12.7.2.1). The median time to onset of the first event of Neutrophil count decreased was 125.5 days (range: 1-862) (RMP Source Table 16) and half of all events resolved (RMP Source Table 10).

  Neutrophil count decreased is listed in Section 4.8 of the SmPC. All TEAEs of Neutrophil count decreased and Neutropenia observed in Pool 1 were non-serious and the majority were Grade 1 or Grade 2 in severity. This laboratory abnormality can be managed in clinical practice and is not an important safety concern for vimseltinib.

- Oedema

  Oedema is an identified risk of vimseltinib. Oedema is a very common TEAE affecting the majority of vimseltinib-treated participants, and is a recognised AE associated with CSF1R inhibition. Oedema events were typically non-serious (RMP Source Table 8) and Grade 1 or Grade 2 in severity (RMP Source Table 9). Four sub-categories were established to describe the risk: periorbital oedema, face oedema, peripheral oedema, and generalised oedema. A summary of TEAEs by sub-category, including the MedDRA PTs within each sub-category, is described in Table 8.

Table 8: Treatment-emergent Adverse Events of Oedema by Preferred Term (All TGCT Participants at 30 mg Twice Weekly)

Oedema Sub-category Preferred Term	Study DCC-3014-03-001 [a]		Vimseltinib 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001 [c] (N=183)
	Placebo [b] (N=39)	Vimseltinib 30 mg BIW (N=83)	
Periorbital oedema	**8 (20.5)**	**50 (60.2)**	**115 (62.8)**
Periorbital oedema	4 (10.3)	35 (42.2)	83 (45.4)
Eyelid oedema	2 (5.1)	11 (13.3)	23 (12.6)
Eye oedema	1 (2.6)	4 (4.8)	8 (4.4)
Periorbital swelling	1 (2.6)	2 (2.4)	6 (3.3)
Swelling of eyelid	0	0	1 (0.5)
Face oedema	**3 (7.7)**	**26 (31.3)**	**51 (27.9)**
Face oedema	3 (7.7)	26 (31.3)	47 (25.7)
Swelling face	0	0	4 (2.2)
Peripheral oedema	**3 (7.7)**	**15 (18.1)**	**41 (22.4)**
Oedema peripheral	3 (7.7)	15 (18.1)	39 (21.3)
Peripheral swelling	0	1 (1.2)	5 (2.7)
Generalised oedema	**0**	**11 (13.3)**	**26 (14.2)**
Generalised oedema	0	11 (13.3)	26 (14.2)
Any oedema	**10 (25.6)**	**68 (81.9)**	**147 (80.3)**

Abbreviations: BIW=Twice Weekly; TGCT=Tenosynovial giant cell tumour.
[a] For Study DCC-3014-03-001, risk data in double-blind treatment period are presented for patient groups 'Placebo' and 'Vimseltinib 30 mg BIW' by treatment initially received.
[b] The 39 placebo patients in Study DCC-3014-03-001 are not a part of the analysis population but the data of these patients in the double-blind treatment period are included in the table to characterise the risks.
[c] This column presents risks data for all patients in the analysis population.
Note 1: The analysis population includes patients with Tenosynovial Giant Cell Tumours who were treated with 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001, including the 35 patients who originally received placebo and subsequently crossed over to 30 mg BIW in Study DCC-3014-03-001.
Patients are counted once for each risk category and once for each Preferred term.
In each column, percentages use the number of treated patients in the corresponding patient group as the denominator.
MedDRA = Medical Dictionary for Regulatory Activities. Adverse events are coded using MedDRA version 26.0.
One participant from the Expansion Phase (Cohort A), [redacted], re-enrolled into Cohort B as [redacted]. This participant was counted as a single participant for the total column
Source: RMP Source Table 6

In the MOTION double-blind period, 66 (79.5%) participants experienced any drug-related TEAE of oedema (RMP Source Table 11). The median time to onset of the

first event was 29 days (range: 1-113) (RMP Source Table 16) and 44.5% of oedema events resolved (RMP Source Table 10).

In Pool 1, 143 (78.1%) participants experienced any drug-related TEAE of oedema (RMP Source Table 11). The median time to onset of the first event was 29 days (range: 1-911) (RMP Source Table 16) and 42.7% of oedema events resolved (RMP Source Table 10).

The oedema events have been grouped into the following four sub-categories to discuss them further:

Periorbital oedema (including PTs of Periorbital oedema, Eyelid oedema, Eye oedema, Periorbital swelling and Swelling of eyelid):

In the MOTION double-blind period, 50 (60.2%) participants in the vimseltinib arm experienced any TEAE of periorbital oedema. The most frequently reported PTs in ≥10% of participants were Periorbital oedema (35 [42.2%]) and Eyelid oedema (11 [13.3%]) (RMP Source Table 6). All TEAEs were non-serious (RMP Source Table 8). The majority were Grade 1 or Grade 2 in severity (Source Table 9). One (1.2%) participant experienced a TEAE of Periorbital oedema that led to discontinuation of treatment (MOTION Table 14.3.1.2.7.1). In the placebo arm, 8 (20.5%) participants experienced any TEAE of periorbital oedema. The most frequently reported PT in ≥10% of participants was Periorbital oedema (4 [10.3%]) (RMP Source Table 6). All TEAEs were non-serious (RMP Source Table 8) and Grade 1 in severity (RMP Source Table 9). None led to discontinuation of treatment.

In Pool 1, 115 (62.8%) participants experienced any TEAE of periorbital oedema. The most frequently reported PTs in ≥10% of participants were Periorbital oedema (83 [45.4%]) and Eyelid oedema (23 [12.6]) (RMP Source Table 6). All TEAEs were non-serious (RMP Source Table 8). The majority Grade 1 or Grade 2 in severity (Source Table 9). Three (1.6%) participants experienced TEAEs of Periorbital oedema and 1 (0.6%) participant experienced a TEAE of Eyelid oedema that led to discontinuation of treatment (ISS Table 12.7.2.1).

Face oedema (including PTs of Face oedema and Swelling face):

In the MOTION double-blind period, 26 (31.3%) participants in the vimseltinib arm experienced any TEAE of face oedema. Face oedema was the only PT reported in MOTION (RMP Source Table 6). All TEAEs were non-serious (RMP Source Table 8). The majority Grade 1 or Grade 2 in severity (RMP Source Table 9). One (0.8%) TEAE of face oedema led to discontinuation of treatment (ISS Table 12.7.2.1). In the placebo arm, 3 (7.7%) participants experienced any TEAE of face oedema (RMP Source Table 6). All TEAEs were non-serious (RMP Source Table 8) and Grade 1 in severity (RMP Source Table 9).

In Pool 1, 51 (27.9%) participants experienced any TEAE of face oedema. The most frequently reported PT in ≥10% of participants was Face oedema (47 [25.7%]) (RMP Source Table 6). All TEAEs were non-serious (RMP Source Table 8). The majority were Grade 1 or Grade 2 in severity (RMP Source Table 9). One (0.5%) participant experienced a TEAE of Face oedema that led to discontinuation of treatment (ISS Table 12.7.2.1).

Peripheral oedema (including PTs of Oedema peripheral and Peripheral swelling):

In the MOTION double-blind period, 15 (18.1%) participants in the vimseltinib arm experienced any TEAE of peripheral oedema (RMP Source Table 6). All were non-serious (RMP Source Table 8) and Grade 1 or Grade 2 in severity (RMP Source Table 9). No TEAEs of peripheral oedema led to discontinuation of treatment (ISS Table 12.7.2.1). In the placebo arm, 3 (7.7%) participants experienced any TEAE of peripheral oedema (RMP Source Table 6). All were non-serious (RMP Source Table 8) and Grade 1 in severity (RMP Source Table 9).

In Pool 1, 41 (22.4%) participants experienced any TEAE of peripheral oedema (RMP Source Table 6). The majority were non-serious (RMP Source Table 8), with the exception of 1 (0.5%) participant that experienced a serious TEAE of Oedema peripheral (RMP Source Table 7); the serious TEAE was reported as Grade 2 and resolving following drug interruption (DCC-3014-01-001 CSR Section 12.3.5). No TEAEs of peripheral oedema led to discontinuation of treatment (ISS Table 12.7.2.1).

Generalised oedema (PT of Generalised oedema):

In the MOTION double blind period, 11 (13.3%) participants in the vimseltinib arm experienced TEAEs of Generalised oedema (RMP Source Table 6). All were non-serious (RMP Source Table 8). The majority Grade 1 or Grade 2 in severity (RMP Source Table 9). One (0.8%) TEAE of generalised oedema led to discontinuation of treatment (ISS Table 12.7.2.1). In the placebo arm, no TEAEs of generalised oedema were reported (RMP Source Table 6).

In Pool 1, 26 (14.2%) participants experienced TEAEs of Generalised oedema (RMP Source Table 6). All were non-serious (RMP Source Table 8). The majority were Grade 1 or Grade 2 in severity (RMP Source Table 9). One (0.5%) participant experienced a TEAE of Generalised oedema that led to discontinuation of treatment (ISS Table 12.7.2.1).

Periorbital oedema, peripheral oedema, face oedema and generalised oedema are adverse reactions that are listed in Section 4.8 of the SmPC. The majority of the reported TEAEs were non-serious and Grade 1 or Grade 2 in severity. Oedema is an adverse reaction that can be managed in clinical practice and is not an important safety concern for vimseltinib.

- Dermatologic effects

  Dermatologic effects including rash, pruritus, and dry skin are an identified risk of vimseltinib and were the most frequently reported TEAEs in the SOC of Skin and subcutaneous tissue disorders in MOTION and Pool 1.

  Rash:

  Rash is a very common TEAE affecting vimseltinib-treated participants, and is a recognised AE associated with CSF1R inhibition. All reported events were non-serious (RMP Source Table 8). The majority were low grade in severity (RMP Source Table 9). The most frequently reported PTs in ≥10% of participants were Rash maculo-papular and Rash. A summary of TEAEs, including the MedDRA PTs used to define the risk of rash, is described in Table 9.

Table 9: Treatment-emergent Adverse Events of Rash by Preferred Term (All TGCT Participants at 30 mg Twice Weekly)

Any Rash Event Preferred Term	Study DCC-3014-03-001 [a]		Vimseltinib 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001 [c] (N=183)
	Placebo [b] (N=39)	Vimseltinib 30 mg BIW (N=83)	
Any Rash Event	**2 (5.1)**	**36 (43.4)**	**93 (50.8)**
Rash maculo-papular	0	16 (19.3)	43 (23.5)
Rash	2 (5.1)	16 (19.3)	39 (21.3)
Dermatitis acneiform	0	6 (7.2)	16 (8.7)
Erythema	0	3 (3.6)	7 (3.8)
Rash pruritic	0	2 (2.4)	6 (3.3)
Rash erythematous	0	2 (2.4)	6 (3.3)
Rash macular	0	1 (1.2)	4 (2.2)
Rash papular	0	0	1 (0.5)

Abbreviations: BIW=Twice Weekly; TGCT=Tenosynovial giant cell tumour.
[a] For Study DCC-3014-03-001, risk data in double-blind treatment period are presented for patient groups 'Placebo' and 'Vimseltinib 30 mg BIW' by treatment initially received.
[b] The 39 placebo patients in Study DCC-3014-03-001 are not a part of the analysis population but the data of these patients in the double-blind treatment period are included in the table to characterise the risks.
[c] This column presents risks data for all patients in the analysis population.
Note 1: The analysis population includes patients with Tenosynovial Giant Cell Tumours who were treated with 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001, including the 35 patients who originally received placebo and subsequently crossed over to 30 mg BIW in Study DCC-3014-03-001.
Patients are counted once for each risk category and once for each Preferred term.
In each column, percentages use the number of treated patients in the corresponding patient group as the denominator.
MedDRA = Medical Dictionary for Regulatory Activities. Adverse events are coded using MedDRA version 26.0.
One participant from the Expansion Phase (Cohort A), [redacted], re-enrolled into Cohort B as [redacted]. This participant was counted as a single participant for the total column
Source: RMP Source Table 6

In the MOTION double-blind period, 36 (43.4%) participants in the vimseltinib arm experienced any TEAE of rash (RMP Source Table 6). All were non-serious (RMP Source Table 8), and the majority were Grade 1 or 2 in severity (RMP Source Table 9). Two (1.7%) participants experienced TEAEs of Rash that led to discontinuation of treatment (ISS Table 12.7.2.1). A total of 35 (42.2%) participants experienced rash events that were considered related to study treatment (RMP Source Table 11). The median time to onset of the first event was 57 days (range: 2-159) (RMP Source Table 16) and 40.9% of all events resolved (RMP Source Table 10). In the placebo arm, 2 (5.1%) participants experienced any TEAE of rash (RMP Source Table 6). Both were non-serious (RMP Source Table 8) and Grade 1 or Grade 2 in severity (RMP Source Table 9) and did not lead to discontinuation of treatment (DCC-3014-03-001 CSR Table 14.3.1.2.7.1).

In Pool 1, 93 (50.8%) participants experienced any TEAE of rash (RMP Source Table 6). All were non-serious (RMP Source Table 7), and the majority were Grade 1 or 2 in severity (RMP Source Table 9). Three (1.6%) participants experienced TEAEs of Rash, 2 (1.1%) participants experienced TEAEs of Rash maculo-papular and 1 (0.5%) participant experienced a TEAE of Dermatitis acneiform that led to

discontinuation of treatment (ISS Table 12.7.2.1). A total of 91 (49.7%) participants experienced rash events that were considered related to study treatment (RMP Source Table 11). The median time to onset of the first event was 78 days (range: 2-512) (RMP Source Table 16) and approximately 42.3% of all events resolved (RMP Source Table 10).

Pruritus (PT of Pruritus):

In the MOTION double-blind period, 24 (28.9%) participants in the vimseltinib arm experienced TEAEs of Pruritus (RMP Source Table 6); 22 (26.5%) participants experienced TEAEs that were considered related to study treatment (RMP Source Table 11). All were non-serious (RMP Source Table 8). Fifteen (18.1%) participants experienced Grade 1 TEAEs, 7 (8.4%) participants experienced Grade 2 TEAEs and 2 (2.4%) participants experienced Grade 3 TEAEs (RMP Source Table 9). The median time to onset of the first event was 12 days (range: 1-185) (RMP Source Table 16) and 76.7% of all events resolved (RMP Source Table 10). Two (1.7%) participants experienced a TEAE that led to discontinuation of treatment (ISS Table 12.7.2.1). In the placebo arm, 3 (7.7%) participants experienced TEAEs of Pruritus (RMP Source Table 6). All were non-serious (RMP Source Table 8) and Grade 1 or 2 in severity (RMP Source Table 9).

In Pool 1, 50 (27.3%) participants experienced TEAEs of Pruritus (RMP Source Table 6); 48 (26.2%) participants experienced TEAEs that were considered related to study treatment (RMP Source Table 11). All were non-serious (RMP Source Table 8). Twenty-five (13.7%) participants experienced Grade 1 TEAEs, 20 (10.9%) participants experienced Grade 2 TEAEs and 5 (2.7%) participants experienced Grade 3 TEAEs (RMP Source Table 9). Two (1.1%) participants experienced TEAEs that led to discontinuation of treatment (ISS Table 12.7.2.1). The median time to onset of the first event was 59.5 days (range: 1-842) (RMP Source Table 16) and approximately 50.6% of all events resolved (RMP Source Table 10).

Dry skin (including PTs of Dry skin and Xeroderma):

In the MOTION double-blind period, 7 (8.4%) participants in the vimseltinib arm experienced TEAEs of Dry skin (RMP Source Table 6); 6 (7.2%) participants experienced TEAEs that were considered related to study treatment (RMP Source Table 11). All were non-serious (RMP Source Table 8) and Grade 1 or 2 in severity (RMP Source Table 9). None led to discontinuation of treatment (MOTION CSR Table 14.3.1.2.7.1). The median time to onset of the first event was 92 days (range: 36-170) (RMP Source Table 16) and 71.4% of all events resolved (RMP source Table 10). In the placebo arm, there were no TEAEs of Dry skin (RMP Source Table 6).

In Pool 1, 22 (12%) participants experienced TEAEs of Dry skin (RMP Source Table 6); 18 (9.8%) participants experienced TEAEs that were considered related to study treatment (RMP Source Table 11). One (0.5%) additional participant experienced a TEAE of Xeroderma (RMP Source Table 6), which was assessed as related to study treatment (RMP Source Table 11). All were non-serious (RMP Source Table 8). The majority were Grade 1 in severity (RMP Source Table 9). None led to discontinuation of treatment (ISS Table 12.7.2.1). The median time to onset of the first event was 143.5 days (range: 15-675) (RMP Source Table 16) and 50% of all events resolved (RMP source Table 10).

Rash, pruritus and dry skin are adverse reactions that are listed in Section 4.8 in the SmPC and pruritus is listed as a warning in Section 4.4 in the SmPC. Most of the TEAEs observed were non-serious and Grade 1 or Grade 2 in severity. Dermatologic effects can be managed in clinical practice and are not an important safety concern for vimseltinib.

- Ophthalmologic effects

  Ophthalmologic effects including lacrimation increased, dry eye and vision blurred are an identified risk of vimseltinib.

  Lacrimation increased (PT of Lacrimation increased):

  In the MOTION double-blind period, 10 (12%) participants in the vimseltinib arm experienced TEAEs of Lacrimation increased (RMP Source Table 6), all of which were assessed as related to study treatment (RMP Source Table 11). All were non-serious (RMP Source Table 8) and Grade 1 severity or 2 in severity (RMP Source Table 9). None led to discontinuation of treatment (MOTION CSR Table 14.3.1.2.7.1). The median time to onset of the first event was 53 days (range: 18-85) (RMP Source Table 16) and 54.5% of all events resolved (RMP Source Table 10). In the placebo arm, no TEAEs of Lacrimation increased were reported (RMP Source Table 6).

  In Pool 1, 19 (10.4%) participants experienced TEAEs of Lacrimation increased (RMP Source Table 6), all of which were assessed as related to study treatment (RMP Source Table 11). All were non-serious (RMP Source Table 8) and Grade 1 or 2 in severity (RMP Source Table 9). None led to discontinuation of treatment (ISS Table 12.7.2.1). The median time to onset of the first event was 66 days (range: 1-224) (RMP Source Table 16) and 47.6% of all events resolved (RMP Source Table 10).

  Dry eye (including PTs of Dry eye and Xerophthalmia):

  In the MOTION double-blind period, 8 (9.6%) participants in the vimseltinib arm experienced Dry eye; 6 (7.2%) participants experienced TEAEs that were assessed as related to study treatment (RMP Source Table 11). One (1.2%) additional participant experienced a TEAE of Xerophthalmia (RMP Source Table 6), which was related to study treatment (RMP Source Table 11). All were non-serious (RMP Source Table 8) and Grade 1 in severity (RMP Source Table 9). None led to discontinuation of treatment (MOTION CSR Table 14.3.1.2.7.1). The median time to onset of the first event was 51.5 days (range: 12-155) (RMP Source Table 16) and 77.8% of all events resolved (RMP Source Table 10). In the placebo arm, no TEAEs of Dry eye were reported (RMP Source Table 6).

  In Pool 1, 13 (7.1%) participants experienced TEAEs of Dry eye; 11 (6.0%) participants experienced TEAEs that were assessed as related to study treatment (RMP Source Table 11). One (0.5%) additional participant experienced a TEAE of Xerophthalmia (RMP Source Table 6), which was related to study treatment (RMP Source Table 11). All were non-serious (RMP Source Table 8) and Grade 1 in severity (RMP Source Table 9). None led to discontinuation of treatment (ISS Table 12.7.2.1). The median time to onset of the first event was 57 days (range: 12-417) (RMP Source Table 16) and 57.1% of all events resolved (RMP Source Table 10).

Vision blurred (PT of Vision blurred):

In the MOTION double-blind period, 5 (6%) participants in the vimseltinib arm experienced TEAEs of Vision blurred (RMP Source Table 6), all of which were assessed as related to study treatment (RMP Source Table 11). All were non-serious (RMP Source Table 8) and Grade 1 in severity (RMP Source Table 9). The median time to onset of the first event was 23 days (range: 13-84) (RMP Source Table 16) and 80% of all events resolved (RMP Source Table 10). In the placebo arm, no TEAEs of Vision blurred were reported (RMP Source Table 6).

In Pool 1, 10 (5.5%) participants experienced TEAEs of Vision blurred (RMP Source Table 6); 9 (4.9%) participants experienced TEAEs that were assessed as related to study treatment (RMP Source Table 11). All were non-serious (RMP Source Table 8) and Grade 1 or 2 in severity (RMP Source Table 9). None led to discontinuation of treatment (ISS Table 12.7.2.1). The median time to onset of the first event was 25.5 days (range: 13-304) (RMP Source Table 16) and 72.7% of all events resolved (RMP Source Table 10).

Lacrimation increased, dry eye, and vision blurred are adverse reactions that are listed in Section 4.8 of the SmPC. All of the TEAEs were non-serious and low grade. Ophthalmologic effects can be managed in clinical practice and are not an important safety concern for vimseltinib.

- *Neuropathy (including PTs of Paraesthesia, Peripheral sensory neuropathy, Hypoaesthesia and Neuropathy peripheral*):

  Overall, in the MOTION double-blind period, 11 (13.3%) participants in the vimseltinib arm experienced TEAEs of Neuropathy (RMP Source Table 6), of which 7 (8.4%) were Grade 1 in severity, 3 (3.6%) were Grade 2 in severity and 1 (1.2%) was Grade 3 in severity (RMP Source Table 9). In Pool 1, 27 (14.8%) participants experienced TEAEs of Neuropathy (RMP Source Table 6) of which 19 (10.4%) were Grade 1 in severity, 7 (3.8%) were Grade 2 in severity and 1 (0.5%) was Grade 3 in severity (RMP Source Table 9).

  In the MOTION double-blind period, 5 (6.0%) participants in the vimseltinib arm experienced TEAEs of Paraesthesia, 3 (3.6%) participants experienced TEAEs of Peripheral sensory neuropathy, 2 (2.4%) participants experienced TEAEs of Neuropathy peripheral and 1 (1.2%) participant experienced a TEAE of Hypoaesthesia (RMP Source Table 6). All were assessed as related to study treatment except for 1 TEAE of Neuropathy peripheral (RMP Source Table 11). All were non-serious (RMP Source Table 8) and the majority were Grade 1 or Grade 2 in severity (RMP Source Table 9). One (0.8%) participant experienced a TEAE of Peripheral sensory neuropathy that led to discontinuation of treatment (MOTION CSR Table 14.3.1.2.7.1). The median duration of the first event was 74 days (range: 6-162) (RMP Source Table 16) and 14.3% of all events resolved. In the placebo arm, 1 (2.6%) participant experienced a TEAE of Paraesthesia (RMP Source Table 6) which was non-serious (RMP Source Table 8), Grade 1 in severity (RMP Source Table 9) and did not lead to discontinuation of treatment (MOTION CSR Table 14.3.1.2.7.1).

  In Pool 1, 17 (9.3%) participants experienced TEAEs of Paraesthesia, 6 (3.3%) participants experienced TEAEs of Peripheral sensory neuropathy, 2 (1.1%) participants experienced TEAEs of Hypoaesthesia and 2 (1.1%) participants experienced TEAEs of Neuropathy peripheral (RMP Source Table 6). The majority

were assessed as related to study treatment (RMP Source Table 11). All were non-serious (RMP Source Table 8) and the majority were Grade 1 or 2 in severity (RMP Source Table 9). One (0.5%) participant experienced a TEAE of Paraesthesia and 1 (0.5%) participant experienced a TEAE of Peripheral sensory neuropathy that led to discontinuation of treatment (ISS Table 12.7.2.1). The median time to onset of the first event was 85 days (range: 1-508) (RMP Source Table 16) and 35% of all events resolved (RMP Source Table 10).

Neuropathy is an adverse reaction of vimseltinib that is listed in Section 4.8 of the SmPC. The TEAEs were primarily non-serious and low grade. Neuropathy can be managed in clinical practice and is not an important safety concern for vimseltinib.

- *Fatigue* (*PT of Fatigue*):

  In the MOTION double-blind period, 28 (33.7%) participants in the vimseltinib arm experienced TEAEs of Fatigue (RMP Source Table 6), 27 (32.5%) of which were assessed as related to study treatment (RMP Source Table 11). All were non-serious (RMP Source Table 8) and Grade 1 or 2 in severity (RMP Source Table 9). The median time to onset of the first event was 29.5 days (range: 1-127) (RMP Source Table 16) and 33.3% of all events resolved (RMP Source Table 10). None led to discontinuation of treatment (MOTION CSR Table 14.3.1.2.7.1). In the placebo arm, 6 (15.4%) participants experienced TEAEs of Fatigue (RMP Source Table 6). All were non-serious (RMP Source Table 8) and Grade 1 in severity (RMP Source Table 9).

  In Pool 1, 55 (30.1%) participants experienced TEAEs of Fatigue (RMP Source Table 6); 52 (28.4%) participants experienced TEAEs that were assessed as related to study treatment (RMP Source Table 11). All were non-serious (RMP Source Table 8). Thirty-seven (20.2%) participants experienced Grade 1 TEAEs, 14 (7.7%) participants experienced Grade 2 TEAEs, and 4 (2.2%) participants experienced Grade 3 TEAEs (RMP Source Table 9). None led to discontinuation of treatment (ISS Table 12.7.2.1). The median time to onset of the first event was 30 days (range: 1-692) (RMP Source Table 16) and 37% of all events resolved (RMP Source Table 10).

  Fatigue is an adverse reaction of vimseltinib that is listed in Section 4.8 of the SmPC. The TEAEs were primarily non-serious and low grade. Fatigue can be managed in clinical practice and is not an important safety concern for vimseltinib.

Other reasons for considering the risks not important:

- None

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk:

Important Identified Risk: Arterial Hypertension

In the non-clinical cardiovascular safety pharmacology study, administration of vimseltinib had no physiologically significant effect on heart rate, systolic, diastolic, mean arterial, or arterial pulse pressure up to 25 hours post-dose.

In the clinical development programme, 15 (18.1%) participants in the vimseltinib arm of MOTION (compared with 4 [10.3%] in the placebo arm) and 39 (21.3%) participants treated with vimseltinib in Pool 1 experienced TEAEs within the Standardised MedDRA Query (SMQ) Hypertension (narrow) (Module SVII.3.1).

Due to the higher frequency of TEAEs of hypertension in participants treated with vimseltinib and the need for new antihypertensive medications in participants who did not have a previous medical history of hypertension, arterial hypertension is considered an important identified risk.

Risk-benefit impact:

The benefit of vimseltinib as an effective treatment for adult patients with TGCT, a rare disease with limited treatment options, outweighs the important identified risk of arterial hypertension that can be managed in routine clinical practice.

Arterial hypertension is described as a warning in Section 4.4 of the SmPC, and hypertension is listed as an adverse reaction in Section 4.8 of the SmPC. Arterial hypertension will be further characterised in a post-authorisation safety study (PASS) (DCC-3014-04-002) (Part III.2).

Important Potential Risks:

Important Potential Risk 1: Embryo-foetal toxicity

No clinical studies have been performed to assess the use of vimseltinib in pregnancy. Although pregnant women were excluded and contraception requirements included in the protocols, one pregnancy while on treatment was reported in Pool 3 from Study DCC-3014-01-001. This pregnancy resulted in a spontaneous abortion following an unspecified “morning after pill,” assessed as unrelated to vimseltinib by the Investigator. There was also one partner pregnancy reported in the open-label period of MOTION. The pregnancy resulted in a term live birth with no congenital abnormalities reported (Table 7, Module SIV.3).

The effect of vimseltinib on embryo-foetal development was characterised in rats (Module SII). Administration of vimseltinib in rats resulted in foetal malformations of the cardiovascular and skeletal systems, as well as additional indications of developmental toxicity, at a maternal dose of 15 mg/kg/day.

Based on non-clinical studies, embryo-foetal toxicity is an important potential risk of vimseltinib.

Risk-benefit impact:

The benefit of vimseltinib as an effective treatment for adult patients with TGCT, a rare disease with limited treatment options, outweighs the important potential risk of embryo-foetal toxicity that has yet to be confirmed in humans and can be managed by advising women 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. The pregnancy status of females of childbearing potential must be verified prior to initiating vimseltinib and during treatment. Effects of vimseltinib on hormonal contraceptives have not been studied. A barrier method should be added if systemic contraceptives are used.

Important Potential Risk 2: Drug-Induced Liver Injury (DILI)

In non-clinical studies, vimseltinib-related pathology results at all dose levels were consistent with inflammation, pancreatic injury and suggestive of hepatocellular injury. Correlating microscopic findings involved several tissues, including the liver, which were found to be fully or partially reversible at doses ≤7.5 mg/kg/day.

There was no evidence of DILI in the clinical development programme, although mild to moderate elevations in hepatic enzymes were observed. In the clinical development programme, 24 (28.9%) participants in the vimseltinib arm of MOTION (compared with 1 [2.6%] participant in the placebo arm), and 58 (31.7%) participants treated with vimseltinib in Pool 1 experienced TEAEs within the SMQ Drug related hepatic disorders (Module SVII.3.1).

Due to the higher frequency of mild to moderate elevations in hepatic enzymes in participants treated with vimseltinib, and the possible association with DILI, this is considered an important potential risk.

Risk-benefit impact:

The benefit of vimseltinib as an effective treatment for adult patients with TGCT, a rare disease with limited treatment options, outweighs the important potential risk of DILI that has yet to be confirmed and can be managed by healthcare professionals being aware that treatment can lead to an increase in AST, ALT and ALP serum enzymes.

Serum enzyme elevations, including AST, ALT and ALP are listed as a warning in Section 4.4 of the SmPC and as adverse reactions in Section 4.8 of the SmPC. DILI will be further characterised in a PASS (DCC-3014-04-002) (Part III.2).

Important Potential Risk 3: Muscle injury/Rhabdomyolysis

In non-clinical studies, vimseltinib-related pathology observations were suggestive of hepatocellular and/or skeletal muscle injury, and mildly increased CPK activities were observed.

There is no evidence of Muscle injury/Rhabdomyolysis in the clinical development programme, although CPK elevations were observed as laboratory abnormalities. In the clinical development programme, 25 (30.1%) participants in the vimseltinib arm of MOTION (compared to 4 (10.3%) participants in the placebo arm) and 90 (49.2%) participants treated with vimseltinib in Pool 1 experienced TEAEs within the SMQ Rhabdomyolysis/myopathy (Module SVII.3.1). The majority of the reported TEAEs referred to laboratory abnormalities.

Due to the higher frequency of CPK increase in participants treated with vimseltinib, and the limited long-term data, Muscle injury/Rhabdomyolysis is considered an important potential risk.

Risk-benefit impact:

The benefit of vimseltinib as an effective treatment for adult patients with TGCT, a rare disease with limited treatment options, outweighs the important potential risk of Muscle injury/Rhabdomyolysis that has yet to be confirmed and can be managed by healthcare professional awareness that treatment with vimseltinib can lead to an increase in CPK.

Serum enzyme elevations including CPK are listed as a warning in Section 4.4 of the SmPC and as an adverse reaction in Section 4.8 of the SmPC. Muscle injury/Rhabdomyolysis will be further characterised in a PASS (DCC-3014-04-002) (Part III.2).

Important Potential Risk 4: Nephrotoxicity

Non-clinical studies showed chronic progressive nephropathy (CPN) in animals administered ≥2.5 mg/kg/day vimseltinib.

There is no evidence of Nephrotoxicity in the clinical development programme, although blood creatinine elevations were observed as a laboratory abnormality. In the clinical development programme, 2 (2.4%) participants in the vimseltinib arm of MOTION (compared with no participants in the placebo arm) and 6 (3.3%) participants treated with vimseltinib in Pool 1 experienced TEAEs within the SMQ Acute renal failure (Module SVII.3.1).

Due to the higher frequency of increased blood creatinine in participants treated with vimseltinib and the limited long-term data, Nephrotoxicity is considered an important potential risk.

Risk-benefit impact:

The benefit of vimseltinib as an effective treatment for adult patients with TGCT, a rare disease with limited treatment options, outweighs the important potential risk of Nephrotoxicity that has yet to be confirmed and can be managed by healthcare professional awareness that treatment with vimseltinib can lead to an increase in blood creatinine. Increased blood creatinine is listed as an adverse reaction in Section 4.8 of the SmPC. Nephrotoxicity will be further characterised in a PASS (DCC-3014-04-002) (Part III.2).

Important Potential Risk 5: Cognitive Disorders/ CNS Adverse Events

In vivo distribution studies demonstrated CNS penetration of vimseltinib. In the rat blood brain barrier PK study (DCC-3014-03-0015), the brain:plasma ratio was 0.73 after a 1 mg/kg intravenous dose. CNS penetration was determined to be lower in the rat mass balance study (DCC-3014-03-0022). After a single oral dose of 10 mg/kg (100 μCi/kg) [^{14}C]-vimseltinib, brain accumulation was considered low from 0.5-672 hours, as determined by QWBA. No neurobehavioral observations were attributable to vimseltinib administration in safety pharmacology or repeated-dose toxicity studies.In the clinical development programme, 4 (4.8%) participants in the vimseltinib arm of MOTION (compared to 0 participants in the placebo arm) and 9 (4.9%) participants treated with vimseltinib in Pool 1 experienced TEAEs within the HLGT Deliria (incl confusion) and HLGT Mental impairment disorders (Module SVII.3.1).

As vimseltinib was brain penetrant in non-clinical studies and cognitive disorders (including memory impairment, amnesia, confusional state, disturbance in attention, and attention deficit/hyperactivity disorder) have been observed following administration of other CSF1R inhibitors, cognitive disorders/CNS adverse events are considered an important potential risk.

Risk-benefit impact:

The benefit of vimseltinib as an effective treatment for adult patients with TGCT, a rare disease with limited treatment options, outweighs the important potential risk of Cognitive disorders/CNS adverse events that has yet to be confirmed and can be managed as part of routine clinical practice. Cognitive disorders/CNS adverse events will be further characterised in a PASS (DCC-3014-04-002) (Part III.2).

Important Potential Risk 6: Malignancies

In a 2-year oral rat carcinogenicity study (DCC-3014-04-0025), 2 out of 60 (3%) male rats receiving 1.0 mg/kg/day (approximately 1.4 times the total vimseltinib exposure at the

recommended dose and less than the unbound [free] vimseltinib exposure for patients with TGCT based on AUC) were identified as having histomorphologically different sarcomas in the synovium of the femorotibial joint. Both were classified as sarcoma, not otherwise specified.

In the clinical development programme, 4 (4.8%) participants in the vimseltinib arm of MOTION (compared with 0 in the placebo arm) experienced TEAEs within the SMQ Malignancies (Module SVII.3.1), all of which were assessed as unrelated to vimseltinib. In Pool 1, 6 (3.3%) participants experienced TEAEs within the SMQ Malignancies (broad) (Module SVII.3.1). 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. However, considering all available clinical and non-clinical data, the carcinogenic risk after vimseltinib administration is considered low.

Risk-benefit impact:

The benefit of vimseltinib as an effective treatment for adult patients with TGCT, a rare disease with limited treatment options, outweighs the important potential risk of Malignancies that has yet to be confirmed. Considering all available clinical and non-clinical data, the carcinogenic risk after vimseltinib administration is considered low. Malignancies will be further characterised in a PASS (DCC-3014-04-002) (Part III.2).

Missing information: Long-term safety

Long term safety is an area of missing information due to the limited duration of patient exposure to vimseltinib to date. While the available data from MOTION and DCC-3014-01-001 provide a comprehensive understanding of the safety profile, the effects of prolonged exposure has not yet been fully characterised.

Available exposure data is presented in Part II: Module SIII, Table 4. In Pool 1, 101 (54.9%) participants had more than 1 year exposure, with 72 (39.1%) participants having 12 - <24 months exposure. Total vimseltinib exposure in Pool 1 was 223.1 patient-years of exposure. Additionally in Pool 3 (all participants who received at least one dose of vimseltinib in MOTION and Study DCC-3014-01-001 regardless of tumour type or dose of vimseltinib), 122 (48.2%) participants had more than 1 year exposure; total vimseltinib exposure was 294.4 patient-years of exposure (RMP Source Table 3.1).

Risk-benefit impact:

The benefit of vimseltinib as an effective treatment for adult patients with symptomatic TGCT, a rare disease with limited treatment options, is considered to outweigh long-term safety, an area of missing information, where data is limited but where the safety profile is expected to be comparable to the safety profile observed thus far in the clinical development programme. A review of safety data by years of exposure found that overall TEAEs occurred more frequently in Year 1 compared to Year 2 and Year 3 and did not identify any new safety concerns associated with long latency (Section SVII.3.2) (ISS Table 14.10.1).

The anticipated long-term use of vimseltinib makes long-term safety relevant for inclusion in the RMP and is considered missing information, as further characterisation is needed. A PASS (DCC-3014-04-002) will further characterise long-term safety (Part III.2).

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

None

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Important Identified Risk: Arterial Hypertension

Potential Mechanisms:

Vimseltinib is a CSF1R inhibitor. CSF1R inhibitors may be associated with hypertension due to off-target inhibition of receptors such as VEGFR or pathways regulating vascular tone, leading to hypertension (Scott et al, 2013).

Evidence source and strength of evidence:

In the clinical development programme, 15 (18.1%) in the vimseltinib arm of MOTION (compared with 4 [10.3%] in the placebo arm) and 39 (21.3%) participants treated with vimseltinib in Pool 1 experienced TEAEs within the Standardised MedDRA Query (SMQ) of Hypertension (narrow). In the double-blind period of the MOTION study, approximately 60% of participants with TEAEs of hypertension who did not have previous medical history of hypertension were treated with antihypertensive medications.

Due to the higher frequency of TEAEs of hypertension in participants treated with vimseltinib and the need for new antihypertensive medications in participants who did not have previous medical history of hypertension, arterial hypertension is considered an important identified risk.

Characterisation of the risk:

The SMQ Hypertension (narrow) identified the following PTs, as presented in Table 10: Hypertension, Blood pressure increased, and Hypertensive emergency.

Table 10 Overall Summary of Hypertension SMQ TEAEs in Participants with TGCT in MOTION and Pool 1

	DCC-3014-03-001 [a]		
	Placebo [b] (N=39)	**Vimseltinib 30 mg BIW (N=83)**	**Vimseltinib 30 mg BIW in DCC-3014-03-001 and DCC-3014-01-001 [c] (N=183)**
Hypertension SMQ, n (%)	4 (10.3)	15 (18.1)	39 (21.3)
Hypertension	4 (10.3)	15 (18.1)	38 (20.8)
Blood pressure increased	0	0	1 (0.5)
Hypertensive emergency	0	0	1 (0.5)
Related TEAEs, n (%)	3 (7.7)	11 (13.3)	29 (15.8)
Seriousness, n (%)			
Serious TEAEs	0	0	1 (0.5)

Non-serious TEAEs	4 (10.3)	15 (18.1)	39 (21.3)
Serious related TEAEs	0	0	1 (0.5)
Non-serious related TEAEs	3 (7.7)	11 (13.3)	29 (15.8)
Severity, n (%)			
Grade 3 TEAEs	1 (2.6)	4 (4.8)	15 (8.2)
Grade 4 TEAEs	0	0	1 (0.5)
Grade 3 related TEAEs	1 (2.6)	4 (4.8)	13 (7.1)
Grade 4 related TEAEs	0	0	1 (0.5)
Outcome, E	7	20	92
Fatal	0	0	0
Not recovered/not resolved	4 (57.1)	6 (30.0)	39 (42.4)
Recovered/resolved	3 (42.9)	11 (55.0)	32 (34.8)
Recovered/resolved with sequelae	0	0	0
Recovering/resolving	0	3 (15.0)	20 (21.7)
Unknown	0	0	1 (1.1)
Related TEAEs, Outcome, E	6	16	77
Fatal	0	0	0
Not recovered/not resolved	3 (50.0)	6 (37.5)	30 (39.0)
Recovered/resolved	3 (50.0)	7 (43.8)	28 (36.4)
Recovered/resolved with sequelae	0	0	0
Recovering/resolving	0	3 (18.8)	18 (23.4)
Unknown	0	0	1 (1.3)
Time to First Onset (days)			
Mean (SD)	27.0 (27.94)	70.3 (54.42)	107.2 (146.74)
Median	20.5	57	57
Min, Max	1, 66	1, 172	1, 803
TEAEs leading to Treatment Discontinuation	0	0	0

Abbreviations: BIW=Twice Weekly; MedDRA = Medical Dictionary for Regulatory Activities; Max = maximum; Min = minimum; N = number of subjects in safety analysis set; SD = standard deviation; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event; TGCT=Tenosynovial giant cell tumour.
[a] For Study DCC-3014-03-001, SMQs data in double-blind treatment period are presented for patients groups 'Placebo' and 'Vimseltinib 30 mg BIW' by treatment initially received.
[b] The 39 placebo patients in Study DCC-3014-03-001 are not a part of the analysis population but the data of these patients in the double-blind treatment period are included in the table to characterize the SMQs.
[c] This column presents SMQs data for all patients in the analysis population.
Note 1: The analysis population includes patients with Tenosynovial Giant Cell Tumours who were treated with 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001, including the 35 patients who originally received placebo and subsequently crossed over to 30 mg BIW in Study DCC-3014-03-001.
For n (%) patients are counted once for each SMQ category and once for each preferred term.

In each column, percentages use the number of treated patients in the corresponding patient group as the denominator.
Adverse events are coded using MedDRA version 26.0. The severity of adverse event was assessed using CTCAE Version 5.0, defining Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4=life threatening, and Grade 5=death.
For each SMQ category or a SMQ term, 'E' represents the total number of occurrences of the treatment-emergent adverse events; 'n' represents the number of occurrences of the treatment-emergent adverse events for each type of outcome; percentages are calculated as n/Ex100 in each column.
One participant from the Expansion Phase (Cohort A), [redacted], re-enrolled into Cohort B as [redacted]. This participant was counted as a single participant for the total column.
Data Cut-off Date for Study DCC-3014-01-001: 27DEC2023; Data Cut-off Date for Study MOTION: 22FEB2024.
Source: RMP Source Table 6.2, RMP Source Table 7.2, RMP Source Table 8.2, RMP Source Table 9.2, RMP Source Table 10.2, RMP Source Table 11.2, RMP Source Table 12.2, RMP Source Table 13.2, RMP Source Table 14.2, RMP Source Table 15.2, RMP Source Table 20.2

In the MOTION double-blind period, 15 (18.1%) participants in the vimseltinib arm experienced TEAEs within the SMQ Hypertension (narrow) (Table 10), with a total of 11 (13.3%) participants experiencing events that were related to study treatment. With the exception of 1 SAE, all were non-serious and the majority were Grade 1 or 2 in severity. The median time to onset of the first event was 57 days (range: 1-172 days). Of the reported events, 55.0% of all events resolved. The only reported PT was Hypertension. In the placebo arm, 4 (10.3%) participants experienced TEAEs within the SMQ Hypertension (narrow). The majority were non-serious and Grade 1 or 2 in severity. Of the reported events, 42.9% of events resolved.

In Pool 1, 39 (21.3%) participants treated with vimseltinib experienced TEAEs within the SMQ Hypertension (narrow) (Table 10), with a total of 29 (15.8%) participants experiencing events that were related to study treatment. There was 1 (0.5%) participant who experienced a serious TEAE related to study treatment; 15 (8.2%) participants experienced TEAEs which were Grade 3 in severity and 1 (0.5%) participant experienced a TEAEs which was Grade 4 in severity. The median time to onset of the first event was 57 days (range: 1 – 803 days). Of the reported events, 34.8% of all events resolved. The most frequently reported PT was Hypertension; 38 (20.8%) participants experienced TEAEs of Hypertension.

Risk factors and risk groups:

Risk factors associated with arterial hypertension are age, obesity, family history of hypertension, genetics, lifestyle habits, male sex, other medical conditions, social and economic factors.

Preventability:

In the clinical development programme, TEAEs of hypertension were observed. The events were predominantly low grade, non-serious, and managed with pharmaceutical intervention when necessary. Arterial hypertension is listed as a warning in Section 4.4 of the SmPC, and hypertension is an adverse reaction of vimseltinib that is listed in Section 4.8 of the SmPC. The risk of hypertension can be minimised by healthcare professional awareness at the time of product initiation to ensure appropriate medical management.

Impact on the risk-benefit balance of the product:

The benefit of vimseltinib as an effective treatment for adult patients with TGCT, a rare disease with limited treatment options, outweighs the important identified risk of arterial hypertension that can be managed in routine clinical practice.

Arterial hypertension will be further characterised in a PASS (DCC-3014-04-002) (Part III.2).

Public health impact:

As TGCT is a very rare condition (Part II: Module SI), and hypertension can be managed clinically, the potential impact on public health is expected to be low.

Important Potential Risk: Embryo-foetal toxicity

Potential Mechanisms:

The embryo-foetal toxicity of vimseltinib was characterised in non-clinical studies (Part II: Module SII). One potential mechanism by which vimseltinib may cause embryo-foetal toxicity when administered to pregnant women is by inhibiting CSF-1R signalling. CSF-1R deficiency has been demonstrated in mouse strains to cause embryonic or perinatal death while surviving mice exhibit multiple developmental and functional deficits (Chitu and Stanley, 2017).

Evidence source and strength of evidence:

No clinical studies have been performed to assess the use of vimseltinib in pregnancy. Although pregnant women were excluded and contraception requirements included in the protocols, one pregnancy while on treatment was reported in Study DCC-3014-01-001. This resulted in a spontaneous abortion following an unspecified “morning after pill,” assessed as unrelated to vimseltinib by the Investigator. There was also one partner pregnancy reported in the open-label period of MOTION that resulted in a term live birth with no congenital abnormalities reported. In animal embryo-foetal toxicity studies, vimseltinib was teratogenic in rats with malformations observed in the cardiovascular and skeletal systems.

Non-clinical findings may be relevant for humans and in the absence of clinical data suggest a potential safety concern that awaits clinical confirmation.

Characterisation of the risk:

There are limited data available for vimseltinib exposure in pregnant women. Use of vimseltinib during pregnancy has not been evaluated in the clinical development programme.

Vimseltinib toxicity was observed in a fertility and early embryonic development study in female rats given oral doses of vimseltinib at 2.5, 5 and 10 mg/kg/day (5.3, 10.7, and 20-times the exposure at the recommended human dose) (Part II: Module SII). Post-implantation loss and increased uterine weights were observed at doses of 10 mg/kg/day. Administration of vimseltinib in rats resulted in foetal malformations of the cardiovascular and skeletal systems, as well as additional indications of developmental toxicity, at a maternal dose of 15 mg/kg/day (~23-times the exposure at the recommended human dose).

Additional indications of developmental toxicity, observed only at this dose, included anatomic variations, and reduced foetal body weight. The maternal NOAEL for vimseltinib in rats was 15 mg/kg/day, the highest dose tested. The developmental NOAEL for vimseltinib was 5 mg/kg/day.

Risk factors and risk groups:

Females of childbearing potential not using effective contraception.

Preventability:

The risk of embryo-foetal toxicity can be minimised by adhering to the guidance provided in the SmPC that warns that based on data from animal studies, vimseltinib may cause foetal harm when administered to pregnant women. Healthcare professionals are recommended to advise women 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. The pregnancy status of females of childbearing potential must be verified prior to initiating vimseltinib and during treatment. Effects of vimseltinib on hormonal contraceptives have not been studied. A barrier method should be added if systemic contraceptives are used.

Additional risk minimisation measures in the form of a healthcare professional (HCP) guide and a Patient card will be used to highlight the important potential risk of embryo-foetal toxicity to prescribers and patients, respectively, with a reminder that vimseltinib should not be used in pregnancy and of the need for effective contraception and regular pregnancy testing for women of childbearing potential (Module V.2).

Impact on the risk-benefit balance of the product:

Vimseltinib is used for treating adult patients with TGCT, a rare disease with limited treatment options. The risk of embryo-foetal toxicity can be managed in clinical practice by adhering to the guidance in the product information that warns against use during pregnancy and advises females of childbearing potential that vimseltinib may cause foetal harm and that effective contraception (including a barrier method if systemic contraceptives are used) should be used during treatment and for 30 days after the final dose.

Public health impact:

No clinical studies have been performed to assess the use of vimseltinib in pregnancy, (Module SIV.3) but non-clinical findings suggest a potential risk to the foetus (Part II: Module SII). However, as TGCT is a very rare condition (Part II: Module SI), the potential impact on public health is expected to be low.

Important Potential Risk: Drug-Induced Liver Injury (DILI):

Potential Mechanisms:

Vimseltinib is a CSF1R inhibitor. CSF1R inhibitors are known to reduce macrophages in the liver (Kupffer cells) and other tissues. Kupffer cells clear enzymes such as AST from circulation. Consequently, depletion of Kupffer cells due to an on-target effect of vimseltinib leads to serum enzyme elevations, but without organ injury (Radi et al, 2011; Wang et al, 2011; Smith et al, 2021).

Evidence source and strength of evidence:

Vimseltinib is a CSF1R inhibitor and a pharmacological effect within this class is to reduce macrophages in the liver (Kupffer cells).

There was no evidence of DILI in the clinical development programme, although mild to moderate elevations in hepatic enzymes were observed. In the MOTION double-blind period, 24 (28.9%) participants in the vimseltinib arm experienced TEAEs within the SMQ Drug related hepatic disorders compared with 1 (2.6%) participant in the placebo arm. In Pool 1, 58 (31.7%) participants treated with vimseltinib experienced TEAEs within the SMQ Drug related hepatic disorders (RMP Source Table 6.2). The majority of the TEAEs were non-serious, mild to moderate in severity and none led to discontinuation of treatment.

In non-clinical studies, vimseltinib-related pathology observations, including minimally increased AST, were suggestive of hepatocellular and/or skeletal muscle injury. Correlating microscopic findings involved several tissues, including the liver, which were found to be fully or partially reversible at doses ≤7.5 mg/kg/day.

Characterisation of the risk:

The SMQ Drug related hepatic disorders identified the following PTs, as presented in Table 11 [redacted] Overall Summary of Drug Related Hepatic Disorders SMQ TEAEs in Participants with TGCT in MOTION and Pool 1: Aspartate aminotransferase increased, Alanine aminotransferase increased, Hypertransaminasaemia, Blood alkaline phosphatase increased, Gamma-glutamyltransferase increased, Blood bilirubin increased, Bilirubin conjugated increased, International normalised ratio increased, Prothrombin time prolonged and Transaminases increased.

Table 11 Overall Summary of Drug Related Hepatic Disorders SMQ TEAEs in Participants with TGCT in MOTION and Pool 1

	DCC-3014-03-001 [a]		
	Placebo [b] (N=39)	**Vimseltinib 30 mg BIW (N=83)**	**Vimseltinib 30 mg BIW in DCC-3014-03-001 and DCC-3014-01-001 [c] (N=183)**
Drug Related Hepatic Disorders SMQ, n (%)	1 (2.6)	24 (28.9)	58 (31.7)
Aspartate aminotransferase increased	1 (2.6)	19 (22.9)	50 (27.3)
Alanine aminotransferase increased	1 (2.6)	9 (10.8)	29 (15.8)
Hypertransaminasaemia	0	1 (1.2)	6 (3.3)
Blood alkaline phosphatase increased	1 (2.6)	1 (1.2)	3 (1.6)
Gamma-glutamyltransferase increased	0	1 (1.2)	3 (1.6)
Blood bilirubin increased	0	0	2 (1.1)
Bilirubin conjugated increased	0	0	1 (0.5)
International normalised ratio increased	0	1 (1.2)	1 (0.5)
Prothrombin time prolonged	0	1 (1.2)	1 (0.5)
Transaminases increased	0	1 (1.2)	1 (0.5)
Related TEAEs, n (%)	1 (2.6)	21 (25.3)	55 (30.1)
Seriousness, n (%)			
Serious TEAEs	0	0	0
Non-serious TEAEs	1 (2.6)	24 (28.9)	58 (31.7)
Serious related TEAEs	0	0	0
Non-serious related TEAEs	1 (2.6)	21 (25.3)	55 (30.1)
Severity, n (%)			
Grade 3 TEAEs	0	1 (1.2)	1 (0.5)

	DCC-3014-03-001 [a]		
	Placebo [b] (N=39)	**Vimseltinib 30 mg BIW (N=83)**	**Vimseltinib 30 mg BIW in DCC-3014-03-001 and DCC-3014-01-001 [c] (N=183)**
Grade 4 TEAEs	0	0	0
Grade 3 related TEAEs	0	1 (1.2)	1 (0.5)
Grade 4 related TEAEs	0	0	0
Outcome, E	3	45	157
Fatal	0	0	0
Not recovered/not resolved	0	12 (26.7)	51 (32.5)
Recovered/resolved	3 (100.0)	24 (53.3)	81 (51.6)
Recovered/resolved with sequelae	0	0	0
Recovering/resolving	0	9 (20.0)	24 (15.3)
Unknown	0	0	1 (0.6)
Related TEAEs Outcome, E	3	42	153
Fatal	0	0	0
Not recovered/not resolved	0	11 (26.2)	49 (32.0)
Recovered/resolved	3 (100.0)	22 (52.4)	79 (51.6)
Recovered/resolved with sequelae	0	0	0
Recovering/resolving	0	9 (21.4)	24 (15.7)
Unknown	0	0	1 (0.7)
Time to First Onset (days)			
Mean (SD)	133.0 (NA)	46.0 (42.88)	54.6 (86.71)
Median	133	29	27
Min, Max	133, 133	14, 141	1, 560
TEAEs leading to Treatment Discontinuation	0	0	0

Abbreviations: BIW=Twice Weekly; MedDRA = Medical Dictionary for Regulatory Activities; Max = maximum; Min = minimum; N = number of subjects in safety analysis set; SD = standard deviation; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event; TGCT=Tenosynovial giant cell tumour; NA = Not Applicable.
[a] For Study DCC-3014-03-001, SMQs data in double-blind treatment period are presented for patients groups 'Placebo' and 'Vimseltinib 30 mg BIW' by treatment initially received.
[b] The 39 placebo patients in Study DCC-3014-03-001 are not a part of the analysis population but the data of these patients in the double-blind treatment period are included in the table to characterize the SMQs.
[c] This column presents SMQs data for all patients in the analysis population.
Note 1: The analysis population includes patients with Tenosynovial Giant Cell Tumours who were treated with 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001, including the 35 patients who originally received placebo and subsequently crossed over to 30 mg BIW in Study DCC-3014-03-001.
For n (%) patients are counted once for each SMQ category and once for each preferred term.
In each column, percentages use the number of treated patients in the corresponding patient group as the denominator.
Adverse events are coded using MedDRA version 26.0. The severity of adverse event was assessed using CTCAE Version 5.0, defining Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4=life threatening, and Grade 5=death.

For each SMQ category or a SMQ term, 'E' represents the total number of occurrences of the treatment-emergent adverse events; 'n' represents the number of occurrences of the treatment-emergent adverse events for each type of outcome; percentages are calculated as (n/E)x100 in each column.
One participant from the Expansion Phase (Cohort A), [redacted], re-enrolled into Cohort B as [redacted]. This participant was counted as a single participant for the total column.
Data Cut-off Date for Study DCC-3014-01-001: 27DEC2023; Data Cut-off Date for Study MOTION: 22FEB2024.
Source: RMP Source Table 6.2, RMP Source Table 7.2, RMP Source Table 8.2, RMP Source Table 9.2, RMP Source Table 10.2, RMP Source Table 11.2, RMP Source Table 12.2, RMP Source Table 13.2, RMP Source Table 14.2, RMP Source Table 15.2, RMP Source Table 20.2

In the MOTION double-blind period, 24 (28.9%) participants in the vimseltinib arm experienced TEAEs within the SMQ Drug related hepatic disorders (Table 11), with a total of 21 (25.3%) participants experiencing events that were related to study treatment. All were non-serious and the majority were Grade 1 or 2 in severity. The median time to onset of the first event was 29 days (range: 14-141 days). Of the reported events, 53.3% of all events resolved. The most frequently reported PTs were Aspartate aminotransferase increased and Alanine aminotransferase increased; 19 (22.9%) participants experienced TEAEs of Aspartate aminotransferase increased and 9 (10.8%) participants experienced TEAEs of Alanine aminotransferase increased. In the placebo arm, 1 (2.6%) participant experienced a TEAE within the SMQ Drug related hepatic disorder, which was non-serious and resolved.

In Pool 1, 58 (31.7%) participants treated with vimseltinib experienced TEAEs within the SMQ Drug related hepatic disorders (Table 11), with a total of 55 (30.1%) participants experiencing events that were related to study treatment. All were non-serious and the majority were Grade 1 or 2 in severity. The median time to onset of the first event was 27 days (range: 1 – 560 days). Of the reported events 51.6% of all events resolved. The most frequently reported PTs were Aspartate aminotransferase increased and Alanine aminotransferase increased; 50 (27.3%) participants experienced TEAEs of Aspartate aminotransferase increased and 29 (15.8%) participants experienced TEAEs of Alanine aminotransferase increased.

Chemistry laboratory abnormalities were also evaluated in the clinical development programme.

In the MOTION double-blind period, elevations in ALT, AST and ALP were observed as laboratory abnormalities with a notable difference between the vimseltinib arm and the placebo arm. Most of the shifts were from normal at baseline to Grade 1 at worst post-baseline. In the vimseltinib arm, shifts in AST were observed in 76 (91.6%) participants, shifts in ALT were observed in 20 (24.1%) participants and shifts in ALP were observed in 12 (14.5%) participants. None showed worsening to Grade 3/4. In the placebo arm, shifts in AST were observed in 4 (10.3%) participants, shifts in ALT were observed in 6 (15.4%) participants and shifts in ALP were observed in 3 (7.7%) participants. None showed worsening to Grade 3/4. Similarly, in Pool 1, shifts in AST were observed in 169 (91.8%) participants, shifts in ALT were reported in 50 (27.2%) participants and shifts in ALP were observed in 20 (10.9%) participants. Of these, AST was the only parameter with an observed shift to Grade 3 in 1 (0.5%) participant. No Grade 4 shifts were observed (RMP Source Table 17).

Most of the detected laboratory abnormalities were not reported with associated TEAEs and none led to discontinuation of treatment (MOTION CSR Table 14.3.1.2.7.1 and ISS Table 12.7.2.1).

No cases of Hy's Law or cholestatic liver injury were observed in any participant treated with vimseltinib. Additional analyses of participants with ALT or AST ≥3x upper limit of normal (ULN), participants with ALP ≥2x ULN, and participants with bilirubin >1x ULN were performed and are summarized below.

Participants with ALT or AST ≥3x ULN (Temple's Corollary)

In Pool 3, 29 (11.5%) participants experienced ALT or AST elevations ≥3x ULN, none of which were associated with bilirubin >1x ULN. In total, one participant discontinued treatment with vimseltinib due to elevated ALT or AST. This participant experienced a non-serious TEAE of Grade 3 Aspartate aminotransferase increased that was considered resolving within one week of onset.

Participants with ALP ≥2x ULN

In Pool 3, 11 (4.3%) participants experienced ALP elevations ≥2x ULN, 7 of which occurred in participants with MST, Of the 7 participants with MST, 6 had metastases to the liver at baseline; the 1 remaining participant initiated vimseltinib treatment with elevated ALP at baseline. Of the 4 TGCT participants with ALP ≥2x ULN, 2 initiated vimseltinib treatment with elevated ALP at baseline; the remaining 2 participants experienced Grade 1 ALP elevations lasting 1-2 cycles that returned to normal range without any subsequent elevations. No participants modified or discontinued treatment due to TEAEs of Alkaline phosphatase increased.

Participants with Bilirubin >1x ULN

In Pool 3, 5 (2.0%) participants experienced bilirubin >1x ULN, 1 of which occurred in an MST participant with metastases to the liver. Of the 4 TGCT participants with bilirubin >1x ULN, 1 initiated vimseltinib treatment with elevated bilirubin at baseline; the remaining 3 participants experienced Grade 1 bilirubin elevations <1.5x ULN lasting 1-3 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, and no other relevant TEAEs were observed.

Risk factors and risk groups:

Risk factors associated with DILI include age, female gender, pre-existing liver disease, and obesity.

Preventability:

In the clinical development programme, mild to moderate elevations in hepatic enzymes were observed. Serum enzyme elevations including AST, ALT and ALP are listed as a warning in Section 4.4 of the SmPC and as adverse reactions in Section 4.8 of the SmPC. In addition, Section 5.1 of the SmPC describes that a decline in the number of hepatic Kupffer cells due to CSF1R inhibition leads to decreased clearance of serum enzymes, including AST, ALT and ALP which results in an increase in the serum levels of these enzymes.

The risk of DILI can be minimised by healthcare professional awareness of these elevations, as described in the SmPC.

Impact on the risk-benefit balance of the product:

Vimseltinib is used for treating adult patients with TGCT, a rare disease with limited treatment options. The risk of DILI can be managed in clinical practice through healthcare

professional awareness that laboratory abnormalities may occur due to decreased clearance of serum enzymes.

The hepatic enzyme elevations were generally non-serious and mild to moderate in severity and did not lead to discontinuation of treatment.

DILI will be further characterised in a PASS (DCC-3014-04-002) (Part III.2).

Public health impact:

DILI has not been observed in the clinical development programme. As TGCT is a very rare condition (Part II: Module SI), the potential impact on public health is expected to be low.

Important Potential Risk: Muscle injury/Rhabdomyolysis

Potential Mechanisms:

Vimseltinib is a CSF1R inhibitor. CSF1R inhibitors are known to reduce macrophages in the liver (Kupffer cells) and other tissues. Kupffer cells clear enzymes such as CPK from circulation. Consequently, depletion of Kupffer cells due to an on-target effect of vimseltinib leads to serum enzyme elevations, but without organ injury (Radi et al, 2011; Wang et al, 2011; Smith et al, 2021).

Evidence source and strength of evidence:

Vimseltinib is a CSF1R inhibitor and CSF1R inhibitors are known to reduce macrophages in the liver and other tissues.

There is no evidence of Muscle injury/Rhabdomyolysis in the clinical development programme, although CPK elevations were observed as laboratory abnormalities. In the MOTION double-blind period, 25 (30.1%) participants in the vimseltinib arm experienced TEAEs within the SMQ Rhabdomyolysis/Myopathy compared with 4 (10.3%) participants in the placebo arm. In Pool 1, 90 (49.2%) participants treated with vimseltinib experienced TEAEs within the SMQ Rhabdomyolysis/Myopathy (RMP Source Table 6.2). The majority of the TEAEs were non-serious, mild to moderate in severity and none led to discontinuation of treatment.

In the non-clinical studies, mildly increased CPK activities were seen.

Characterisation of the risk:

The SMQ Rhabdomyolysis/Myopathy identified the following PTs, as presented in Table 12: Blood creatinine phosphokinase increased, Myalgia, Blood creatine increased, Musculoskeletal pain, Hypocalcaemia, Hypercreatininaemia, Muscle fatigue, Muscular weakness and Musculoskeletal discomfort.

Table 12 Overall Summary of Rhabdomyolysis/Myopathy SMQ TEAEs in Participants with TGCT in MOTION and Pool 1

	DCC-3014-03-001 [a]		
	Placebo [b] (N=39)	**Vimseltinib 30 mg BIW (N=83)**	**Vimseltinib 30 mg BIW in DCC-3014-03-001 and DCC-3014-01-001 [c] (N=183)**
Rhabdomyolysis Myopathy SMQ, n (%)	4 (10.3)	25 (30.1)	90 (49.2)

	DCC-3014-03-001 [a]		
	Placebo [b] (N=39)	**Vimseltinib 30 mg BIW (N=83)**	**Vimseltinib 30 mg BIW in DCC-3014-03-001 and DCC-3014-01-001 [c] (N=183)**
Blood creatinine phosphokinase increased	0	21 (25.3)	78 (42.6)
Myalgia	2 (5.1)	7 (8.4)	31 (16.9)
Blood creatine increased	1 (2.6)	4 (4.8)	13 (7.1)
Musculoskeletal pain	0	1 (1.2)	4 (2.2)
Hypocalcaemia	0	1 (1.2)	2 (1.1)
Hypercreatininaemia	0	0	1 (0.5)
Muscle fatigue	0	1 (1.2)	1 (0.5)
Muscular weakness	1 (2.6)	0	1 (0.5)
Musculoskeletal discomfort	0	0	1 (0.5)
Related TEAEs, n (%)	3 (7.7)	22 (26.5)	85 (46.4)
Seriousness, n (%)			
Serious TEAEs	0	0	1 (0.5)
Non-serious TEAEs	4 (10.3)	25 (30.1)	90 (49.2)
Serious related TEAEs	0	0	1 (0.5)
Non-serious related TEAEs	3 (7.7)	22 (26.5)	85 (46.4)
Severity, n (%)			
Grade 3 TEAEs	0	6 (7.2)	32 (17.5)
Grade 4 TEAEs	0	2 (2.4)	12 (6.6)
Grade 3 related TEAEs	0	6 (7.2)	32 (17.5)
Grade 4 related TEAEs	0	2 (2.4)	12 (6.6)
Outcome, E	4	75	447
Fatal	0	0	0
Not recovered/not resolved	0	27 (36.0)	171 (38.3)
Recovered/resolved	4 (100)	29 (38.7)	148 (33.1)
Recovered/resolved with sequelae	0	2 (2.7)	3 (0.7)
Recovering/resolving	0	17 (22.7)	124 (27.7)
Unknown	0	0	1 (0.2)
Related TEAEs Outcome, E	3	68	430
Fatal	0	0	0
Not recovered/not resolved	0	24 (35.3)	168 (39.1)
Recovered/resolved	3 (100)	25 (36.8)	134 (31.2)
Recovered/resolved with sequelae	0	2 (2.9)	3 (0.7)
Recovering/resolving	0	17 (25)	1 (0.2)
Unknown	0	0	1 (0.2)
Time to First Onset (days)			
Mean (SD)	18.8 (26.13)	36.5 (32.57)	54.9 (82.29)
Median	8.5	29	29

	DCC-3014-03-001 [a]		
	Placebo [b] (N=39)	**Vimseltinib 30 mg BIW (N=83)**	**Vimseltinib 30 mg BIW in DCC-3014-03-001 and DCC-3014-01-001 [c] (N=183)**
Min, Max	1, 57	9, 142	1, 414
TEAEs leading to Treatment Discontinuation	0	0	0

Abbreviations: BIW=Twice Weekly; MedDRA = Medical Dictionary for Regulatory Activities; Max = maximum; Min = minimum; N = number of subjects in safety analysis set; SD = standard deviation; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event; TGCT=Tenosynovial giant cell tumour.
[a] For Study DCC-3014-03-001, SMQs data in double-blind treatment period are presented for patients groups 'Placebo' and 'Vimseltinib 30 mg BIW' by treatment initially received.
[b] The 39 placebo patients in Study DCC-3014-03-001 are not a part of the analysis population but the data of these patients in the double-blind treatment period are included in the table to characterize the SMQs.
[c] This column presents SMQs data for all patients in the analysis population.
Note 1: The analysis population includes patients with Tenosynovial Giant Cell Tumours who were treated with 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001, including the 35 patients who originally received placebo and subsequently crossed over to 30 mg BIW in Study DCC-3014-03-001.
For n (%) patients are counted once for each SMQ category and once for each preferred term.
In each column, percentages use the number of treated patients in the corresponding patient group as the denominator.
Adverse events are coded using MedDRA version 26.0. The severity of adverse event was assessed using CTCAE Version 5.0, defining Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4=life threatening, and Grade 5=death.
For each SMQ category or a SMQ term, 'E' represents the total number of occurrences of the treatment-emergent adverse events; 'n' represents the number of occurrences of the treatment-emergent adverse events for each type of outcome; percentages are calculated as (n/E)x100 in each column.
One participant from the Expansion Phase (Cohort A), [redacted], re-enrolled into Cohort B as [redacted]. This participant was counted as a single participant for the total column.
Data Cut-off Date for Study DCC-3014-01-001: 27DEC2023; Data Cut-off Date for Study MOTION: 22FEB2024.
Source: RMP Source Table 6.2, RMP Source Table 7.2, RMP Source Table 8.2, RMP Source Table 9.2, RMP Source Table 10.2, RMP Source Table 11.2, RMP Source Table 12.2, RMP Source Table 13.2, RMP Source Table 14.2, RMP Source Table 15.2, RMP Source Table 20.2

In the MOTION double-blind period, 25 (30.1%) participants in the vimseltinib arm experienced TEAEs within the SMQ Rhabdomyolysis/Myopathy (Table 12), with a total of 22 (26.5%) participants experiencing events that were related to study treatment. All were non-serious and the majority were Grade 1 or 2 in severity. The median time to onset of the first event was 29 days (range: 9-142 days). Of the reported events, 38.7% of all events resolved. The most frequently reported PTs were Blood creatinine phosphokinase increased, Myalgia and Blood creatine increased; 21 (25.3%) participants experienced TEAEs of Blood creatinine phosphokinase increased, 7 (8.4%) participants experienced TEAEs of Myalgia and 4 (4.8%) participants experienced TEAEs of Blood creatine increased. In the placebo arm, 4 (10.3%) participants experienced TEAEs within the SMQ Rhabdomyolysis/Myopathy. All were non-serious and Grade 1 or 2 in severity. Of the reported events, all events resolved.

In Pool 1, 90 (49.2%) participants treated with vimseltinib experienced TEAEs within the SMQ Rhabdomyolysis/Myopathy (Table 12), with a total of 85 (46.4%) participants experiencing events that were related to study treatment. There was 1 (0.5%) participant who experienced a serious TEAE related to study treatment; 32 (17.5%) participants experienced TEAEs which were Grade 3 in severity and 12 (6.6%) participants experienced TEAEs which

were Grade 4 in severity. The median time to onset of the first event was 29 days (range: 1 – 414 days). Of the reported events, 33.1% of all events resolved. The most frequently reported PTs were Blood creatinine phosphokinase increased, Myalgia, Blood creatine increased and Musculoskeletal pain; 78 (42.6%) participants experienced TEAEs of Blood creatinine phosphokinase increased, 31 (16.9%) participants experienced TEAEs of Myalgia, 13 (7.1%) participants experienced TEAEs of Blood creatine increased and 4 (2.2%) participants experienced TEAEs of Musculoskeletal pain.

Elevations in CPK were observed as laboratory abnormalities in the clinical development programme. This laboratory parameter was not systematically collected at baseline in MOTION, and the frequency of CPK elevations in MOTION cannot be determined. In Study DCC-3014-01-001, increased CPK was observed as a laboratory abnormality that worsened from baseline in 66 (100%) of participants receiving 30 mg of vimseltinib twice weekly. Of these, 38 (57.6%) worsened to Grade 3/4 (RMP Source Table 19.1).

Although CPK elevations were frequently observed in participants who received vimseltinib, no evidence of muscle injury has been reported.

Risk factors and risk groups:

Risk factors associated with Muscle injury/Rhabdomyolysis include extreme temperatures, dehydration, infections, trauma, strenuous exercise, and underlying medical conditions.

Preventability:

In the clinical development programme, and consistent with the mechanism of action, CPK elevations were reported. Elevations in serum enzymes, including CPK, is listed as a warning in Section 4.4 of the SmPC and as an adverse reaction in Section 4.8 of the SmPC. In addition, Section 5.1 of the SmPC describes that a decline in the number of hepatic Kupffer cells due to CSF1R inhibition leads to decreased clearance of serum enzymes, including CPK which results in an increase in the serum levels of these enzymes. The risk of Muscle injury/Rhabdomyolysis can be minimised by healthcare professional awareness of these elevations as described in the SmPC.

Impact on the risk-benefit balance of the product:

The benefit of vimseltinib as an effective treatment for adult patients with TGCT, a rare disease with limited treatment options, outweighs the important potential risk of Muscle injury/Rhabdomyolysis that has not been observed in the clinical development programme. Vimseltinib reduces the number of hepatic Kupffer cells leading to decreased clearance of CPK, resulting in an increase in serum CPK. The majority of the CPK elevations were non-serious and did not lead to discontinuation of treatment.

Muscle injury/Rhabdomyolysis will be further characterised in a PASS (DCC-3014-04-002) (Part III.2).

Public health impact:

Muscle injury/Rhabdomyolysis has not been observed in the clinical development programme. As TGCT is a very rare condition (Part II: Module SI), the potential impact on public health is expected to be low.

Important Potential Risk: Nephrotoxicity

Potential Mechanisms:

Some TKIs (e.g., crizotinib, gefitinib, imatinib) reversibly inhibit renal creatinine transporters, leading to an increase in serum creatinine without renal impairment (Omote et al, 2018). OCT2 and MATE-1 function as renal transporters of cationic drugs and endogenous compounds (e.g., creatinine) (Koepsell, 2020). Pseudo-kidney injury has been described in association with inhibition of renal transporters, characterized by a rapid elevation of creatinine levels, stabilization within 2 weeks of treatment initiation, and a quick return to baseline on discontinuation (Tanizaki and Hayashi, 2024).

In vitro data demonstrated that vimseltinib inhibited OCT2 at clinically relevant concentrations. The creatinine elevations observed with vimseltinib are likely to be pseudo-kidney injury caused by excretion effect (i.e., a disruption in renal excretion due to inhibition of renal transporters without damage to kidney tissue).

Evidence source and strength of evidence:

There is no evidence of nephrotoxicity in the clinical development programme, although elevations in creatinine were observed as a laboratory abnormality. In the MOTION double-blind period, 2 (2.4%) participants in the vimseltinib arm experienced TEAEs within the SMQ Acute renal failure, compared with 0 participants in the placebo arm. In Pool 1, 6 (3.3%) participants treated with vimseltinib experienced TEAEs within the SMQ Acute renal failure (RMP Source Table 6.2). All of the TEAEs were non-serious, mild to moderate in severity and none led to discontinuation of treatment.

In the non-clinical studies, CPN was observed in animals administered ≥2.5 mg/kg/day vimseltinib.

Characterisation of the risk:

The SMQ Acute renal failure identified the following PTs, as presented in Table 13: Proteinuria and Azotaemia.

Table 13 Overall Summary of Acute Renal Failure SMQ TEAEs in Participants with TGCT in MOTION and Pool 1

	DCC-3014-03-001 [a]		
	Placebo [b] (N=39)	**Vimseltinib 30 mg BIW (N=83)**	**Vimseltinib 30 mg BIW in DCC-3014-03-001 and DCC-3014-01-001 [c] (N=183)**
Acute Renal Failure SMQ, n (%)	0	2 (2.4)	6 (3.3)
Proteinuria	0	2 (2.4)	6 (3.3)
Azotaemia	0	1 (1.2)	1 (0.5)
Related TEAEs, n (%)	0	2 (2.4)	5 (2.7)
Seriousness, n (%)			
Serious TEAEs	0	0	0
Non-serious TEAEs	0	2 (2.4)	6 (3.3)
Serious related TEAEs	0	0	0
Non-serious related TEAEs	0	2 (2.4)	5 (2.7)
Severity, n (%)			
Grade 3 TEAEs	0	0	0

	DCC-3014-03-001 [a]		
	Placebo [b] (N=39)	**Vimseltinib 30 mg BIW (N=83)**	**Vimseltinib 30 mg BIW in DCC-3014-03-001 and DCC-3014-01-001 [c] (N=183)**
Grade 4 TEAEs	0	0	0
Grade 3 related TEAEs	0	0	0
Grade 4 related TEAEs	0	0	0
Outcome, E	0	3	10
Fatal	0	0	0
Not recovered/not resolved	0	0	3 (30.0)
Recovered/resolved	0	3 (100.0)	6 (60.0)
Recovered/resolved with sequelae	0	0	0
Recovering/resolving	0	0	1 (10.0)
Unknown	0	0	0
Related TEAEs Outcome, E	0	3	7
Fatal	0	0	0
Not recovered/not resolved	0	0	2 (28.6)
Recovered/resolved	0	3 (100.0)	4 (57.1)
Recovered/resolved with sequelae	0	0	0
Recovering/resolving	0	0	1 (14.3)
Unknown	0	0	0
Time to First Onset (days)			
Mean (SD)	-	99.5 (99.70)	143.3 (111.55)
Median	-	99.5	127.5
Min, Max	-	29, 170	29, 337
TEAEs leading to Treatment Discontinuation	0	0	0

Abbreviations: BIW=Twice Weekly; MedDRA = Medical Dictionary for Regulatory Activities; Max = maximum; Min = minimum; N = number of subjects in safety analysis set; SD = standard deviation; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event; TGCT=Tenosynovial giant cell tumour.
[a] For Study DCC-3014-03-001, SMQs data in double-blind treatment period are presented for patients groups 'Placebo' and 'Vimseltinib 30 mg BIW' by treatment initially received.
[b] The 39 placebo patients in Study DCC-3014-03-001 are not a part of the analysis population but the data of these patients in the double-blind treatment period are included in the table to characterize the SMQs.
[c] This column presents SMQs data for all patients in the analysis population.
Note 1: The analysis population includes patients with Tenosynovial Giant Cell Tumours who were treated with 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001, including the 35 patients who originally received placebo and subsequently crossed over to 30 mg BIW in Study DCC-3014-03-001.
For n (%) patients are counted once for each SMQ category and once for each preferred term.
In each column, percentages use the number of treated patients in the corresponding patient group as the denominator.
Adverse events are coded using MedDRA version 26.0. The severity of adverse event was assessed using CTCAE Version 5.0, defining Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4=life threatening, and Grade 5=death.

For each SMQ category or a SMQ term, 'E' represents the total number of occurrences of the treatment-emergent adverse events; 'n' represents the number of occurrences of the treatment-emergent adverse events for each type of outcome; percentages are calculated as (n/E)x100 in each column.
One participant from the Expansion Phase (Cohort A), [redacted], re-enrolled into Cohort B as [redacted]. This participant was counted as a single participant for the total column.
Data Cut-off Date for Study DCC-3014-01-001: 27DEC2023; Data Cut-off Date for Study MOTION: 22FEB2024.
Source: RMP Source Table 6.2, RMP Source Table 7.2, RMP Source Table 8.2, RMP Source Table 9.2, RMP Source Table 10.2, RMP Source Table 11.2, RMP Source Table 12.2, RMP Source Table 13.2, RMP Source Table 14.2, RMP Source Table 15.2, RMP Source Table 20.2

In the MOTION double-blind period, 2 (2.4%) participants in the vimseltinib arm experienced TEAEs within the SMQ Acute renal failure (Table 13). Both participants experienced events that were related to study treatment. All were non-serious and Grade 1 or 2 in severity. The median time to onset of the first event was 99.5 days (range: 29 - 170 days). Of the reported events, all events resolved. Two [2 (2.4%)] participants experienced TEAEs of proteinuria and 1 (1.2%) participant experienced a TEAE of azotaemia. In the placebo arm, no participants experienced TEAEs within the SMQ Acute renal failure.

In Pool 1, 6 (3.3%) participants treated with vimseltinib experienced TEAEs within the SMQ Acute renal failure (Table 13), with a total of 5 (2.7%) participants experiencing events that were related to study treatment. All were non-serious and Grade 1 or 2 in severity. The median time to onset of the first event was 27.5 days (range: 29 – 337 days). Of the reported events, 60% of all events resolved. Six [6 (3.3%)] participants experienced TEAEs of Proteinuria and 1 (0.5%) participant experienced a TEAE of Azotaemia.

Chemistry laboratory abnormalities were also evaluated in the clinical development programme. In the MOTION double-blind period, creatinine elevations were observed as a laboratory abnormality with a notable difference between the vimseltinib arm and the placebo arm. In the vimseltinib arm, 13 (15.7%) participants experienced shifts in creatinine; none worsened to Grade 3/4. In the placebo arm, 1 (2.6%) participant experienced a Grade 1/2 shift in creatinine; none worsened to Grade 3/4. In Pool 1, 79 (42.9%) participants experienced shifts in creatinine. None worsened to Grade 3/4 (RMP Source Table 17).

Although creatinine elevations were observed in participants who received vimseltinib, no evidence of nephrotoxicity has been observed. Increased blood creatinine is listed in Section 4.8 of the SmPC. All TEAEs of Blood creatinine increased observed in MOTION and Pool 1 were non-serious and Grade 1. This laboratory abnormality can be managed in clinical practice.

Risk factors and risk groups:

Risk factors associated with nephrotoxicity include comorbidities, volume depletion, liver dysfunction, sepsis, renal dysfunction, hypokalaemia, hypomagnesaemia, and advanced age.

Preventability:

In the clinical development programme, creatinine elevations were observed as a laboratory abnormality. Increases in creatinine are described as a warning in Section 4.4 of the SmPC to ensure awareness of the need to monitor renal function using alternative means and as an adverse reaction in Section 4.8 of the SmPC. No evidence of nephrotoxicity has been observed. The risk of nephrotoxicity can be minimised by increased healthcare professional awareness of these elevations as described in the SmPC.

Impact on the risk-benefit balance of the product:

The benefit of vimseltinib as an effective treatment for adult patients with TGCT, a rare disease with limited treatment options, outweighs the important potential risk of Nephrotoxicity that has not been observed in the clinical development programme. The creatinine elevations observed with vimseltinib were all non-serious, Grade 1 in severity and did not lead to discontinuation of treatment.

Nephrotoxicity will be further characterised in a PASS (DCC-3014-04-002) (Part III.2).

Public health impact:

Nephrotoxicity has not been observed in the clinical development programme. As TGCT is a very rare condition (Part II: Module SI), the potential impact on public health is expected to be low.

Important Potential Risk: Cognitive Disorders/CNS Adverse Events

Potential Mechanisms:

In vivo distribution studies demonstrated CNS penetration of vimseltinib.

Evidence source and strength of evidence:

In the rat blood brain barrier PK study (DCC-3014-03-0015), the brain:plasma ratio was 0.73 after a 1 mg/kg intravenous dose. CNS penetration was determined to be lower in the rat mass balance study (DCC-3014-03-0022). After a single oral dose of 10 mg/kg (100 µCi/kg) [^{14}C]-vimseltinib, brain accumulation was considered low from 0.5-672 hours, as determined by QWBA. No neurobehavioral observations were attributable to vimseltinib administration in safety pharmacology or repeated-dose toxicity studies.

As vimseltinib was brain penetrant in non-clinical studies and cognitive disorders (including memory impairment, amnesia, confusional state, disturbance in attention, and attention deficit/hyperactivity disorder) have been observed following administration of other CSF1R inhibitors, cognitive disorders/CNS adverse events are considered an important potential risk.

Characterisation of the risk:

The HLGT Deliria (incl confusion) and HLGT Mental impairment disorders identified the following PTs, as presented in Table 14: Disturbance in attention, Memory impairment, Cognitive disorder, Confusional state, and Memory impairment.

Table 14 Overall Summary of TEAEs from HLGT Deliria (incl confusion) and HLGT Mental Impairment Disorders in Participants with TGCT in MOTION and Pool 1

	DCC-3014-03-001 [a]		
	Placebo [b] (N=39)	**Vimseltinib 30 mg BIW (N=83)**	**Vimseltinib 30 mg BIW in DCC-3014-03-001 and DCC-3014-01-001 [c] (N=183)**
Cognitive Disorder TEAEs (HLGT Deliria (incl confusion) and HLGT Mental Impairment Disorders), n (%)	0	4 (4.8)	9 (4.9)
Disturbance in attention	0	1 (1.2)	4 (2.2)
Memory impairment	0	2 (2.4)	2 (1.1)

Cognitive disorder	0	1 (1.2)	1 (0.5)
Confusional state	0	0	1 (0.5)
Mental impairment	0	0	1 (0.5)
Related TEAEs, n (%)	0	2 (2.4)	6 (3.3)
Seriousness, n (%)			
Serious TEAEs	0	0	0
Non-serious TEAEs	0	4 (4.8)	9 (4.9)
Serious related TEAEs	0	0	0
Non-serious related TEAEs	0	2 (2.4)	6 (3.3)
Severity, n (%)			
Grade 3 TEAEs	0	0	0
Grade 4 TEAEs	0	0	0
Grade 3 related TEAEs	0	0	0
Grade 4 related TEAEs	0	0	0
Outcome, E	0	4	9
Fatal	0	0	0
Not recovered/not resolved	0	4 (100.0)	7 (77.8)
Recovered/resolved	0	0	2 (22.2)
Recovered/resolved with sequelae	0	0	0
Recovering/resolving	0	0	0
Unknown	0	0	0
Related TEAEs Outcome, E	0	2	6
Fatal	0	0	0
Not recovered/not resolved	0	2 (100.0)	5 (83.3)
Recovered/resolved	0	0	1 (16.7)
Recovered/resolved with sequelae	0	0	0
Recovering/resolving	0	0	0
Unknown	0	0	0
Time to First Onset (days)			
Mean (SD)	-	30.8 (25.93)	81.6 (119.05)
Median	-	28	29
Min, Max	-	2, 65	2, 360
TEAEs leading to Treatment Discontinuation	0	0	0

Abbreviations: BIW=Twice Weekly; MedDRA = Medical Dictionary for Regulatory Activities; Max = maximum; Min = minimum; N = number of subjects in safety analysis set; SD = standard deviation; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event; TGCT=Tenosynovial giant cell tumour.

[a] For Study DCC-3014-03-001, SMQs data in double-blind treatment period are presented for patients groups 'Placebo' and 'Vimseltinib 30 mg BIW' by treatment initially received.
[b] The 39 placebo patients in Study DCC-3014-03-001 are not a part of the analysis population but the data of these patients in the double-blind treatment period are included in the table to characterize the SMQs.
[c] This column presents SMQs data for all patients in the analysis population.
Note 1: The analysis population includes patients with Tenosynovial Giant Cell Tumours who were treated with 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001, including the 35 patients who originally received placebo and subsequently crossed over to 30 mg BIW in Study DCC-3014-03-001.
For n (%) patients are counted once for each SMQ category and once for each preferred term.
In each column, percentages use the number of treated patients in the corresponding patient group as the denominator.
Adverse events are coded using MedDRA version 26.0. The severity of adverse event was assessed using CTCAE Version 5.0, defining Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4=life threatening, and Grade 5=death.
For each SMQ category or a SMQ term, 'E' represents the total number of occurrences of the treatment-emergent adverse events; 'n' represents the number of occurrences of the treatment-emergent adverse events for each type of outcome; percentages are calculated as (n/E)x100 in each column.
One participant from the Expansion Phase (Cohort A), [redacted], re-enrolled into Cohort B as [redacted]. This participant was counted as a single participant for the total column.
Data Cut-off Date for Study DCC-3014-01-001: 27DEC2023; Data Cut-off Date for Study MOTION: 22FEB2024.
Source: RMP Source Table 6.3, RMP Source Table 7.3, RMP Source Table 8.3, RMP Source Table 9.3, RMP Source Table 10.3, RMP Source Table 11.3, RMP Source Table 12.3, RMP Source Table 13.3, RMP Source Table 14.3, RMP Source Table 15.3, RMP Source Table 16.3

In the MOTION double-blind period, 4 (4.8%) participants in the vimseltinib arm experienced TEAEs within the HLGT Deliria (incl confusion) and HLGT Mental impairment disorders (Table 14), with a total of 2 (2.4%) participants experiencing events that were related to study treatment. All were non-serious and Grade 1. The median time to onset of the first event was 28 days (range: 2-65 days). Of the reported events, none of the events resolved. Reported PTs included Memory impairment, Disturbance in attention, and Cognitive disorder. No participants in the placebo arm experienced TEAEs within the HLGT Deliria (incl confusion) or HLGT Mental impairment disorders.

In Pool 1, 9 (4.9%) participants treated with vimseltinib experienced TEAEs within the HLGT Deliria (incl confusion) or HLGT Mental impairment disorders (Table 14), with a total of 6 (3.3%) participants experiencing events that were related to study treatment. All were non-serious and Grade 1. The median time to onset of the first event was 29 days (range: 2-360 days). Of the reported events, 22.2% of the events resolved. The most frequently reported PTs were Disturbance in attention (4 [2.2%] participants) and memory impairment (2 [1.1%] participants); all remaining PTs were reported in one participant each.

Risk factors and risk groups:

Risk factors associated with cognitive disorders/CNS adverse events are currently unknown.

Preventability:

The preventability of this risk is currently unknown.

Impact on the risk-benefit balance of the product:

The benefit of vimseltinib as an effective treatment for adult patients with TGCT, a rare disease with limited treatment options, outweighs the important potential risk of cognitive disorders/CNS adverse events, in which all events were low grade and non-serious.

Cognitive disorders/CNS adverse events will be further characterised in a PASS (DCC-3014-04-002) (Part III.2).

Public health impact:

As TGCT is a very rare condition (Part II: Module SI), and the cognitive disorders/CNS adverse events observed to date were low grade and manageable in clinical practice, the potential impact on public health is expected to be low.

Important Potential Risk: Malignancies

Potential Mechanisms:

Unknown. Vimseltinib is unlikely to be genotoxic. In humans, vimseltinib effectively treats a joint neoplasia. Other CSF1R inhibitors have no identified carcinogenicity risk.

Evidence source and strength of evidence:

In a 2-year oral rat carcinogenicity study (DCC-3014-04-0025), 2 out of 60 (3%) male rats receiving 1.0 mg/kg/day (approximately 1.4 times the total vimseltinib exposure at the recommended dose and less than the unbound [free] vimseltinib exposure for patients with TGCT based on AUC) were identified as having histomorphologically different sarcomas in the synovium of the femorotibial joint. Both were classified as sarcoma, not otherwise specified.

The relevance of the observed non-clinical finding is unknown but considering all available clinical and non-clinical data, the carcinogenic risk after vimseltinib administration is considered low.

Characterisation of the risk:

The SMQ Malignancies identified the following PTs, as presented in Table 15[redacted] Overall Summary of Rhabdomyolysis/Myopathy SMQ TEAEs in Participants with TGCT in MOTION and Pool 1: Basal cell carcinoma, Breast cancer, Malignant melanoma, Papillary thyroid cancer, Plasma cell myeloma, Squamous cell carcinoma of skin, and Tumour pain.

Table 15: Overall Summary of Malignancies SMQ TEAEs in Participants with TGCT in MOTION and Pool 1

	DCC-3014-03-001 [a]		
	Placebo [b] (N=39)	**Vimseltinib 30 mg BIW (N=83)**	**Vimseltinib 30 mg BIW in DCC-3014-03-001 and DCC-3014-01-001 [c] (N=183)**
Malignancies SMQ, n (%)	0	4 (4.8)	6 (3.3)
Basal cell carcinoma	0	0	1 (0.5)
Breast cancer	0	0	1 (0.5)
Malignant melanoma	0	1 (1.2)	1 (0.5)
Papillary thyroid cancer	0	1 (1.2)	1 (0.5)
Plasma cell myeloma	0	1 (1.2)	1 (0.5)
Squamous cell carcinoma of skin	0	0	1 (0.5)
Tumour pain	0	1 (1.2)	1 (0.5)
Related TEAEs, n (%)	0	0	1 (0.5)

Seriousness, n (%)			
Serious TEAEs	0	2 (2.4)	4 (2.2)
Non-serious TEAEs	0	2 (2.4)	2 (1.1)
Serious related TEAEs	0	0	1 (0.5)
Non-serious related TEAEs	0	0	0
Severity, n (%)			
Grade 3 TEAEs	0	1 (1.2)	2 (1.1)
Grade 4 TEAEs	0	1 (1.2)	1 (0.5)
Grade 3 related TEAEs	0	0	0
Grade 4 related TEAEs	0	0	0
Outcome, E	0	5	9
Fatal	0	0	0
Not recovered/not resolved	0	2 (40.0)	4 (44.4)
Recovered/resolved	0	3 (60.0)	5 (55.6)
Recovered/resolved with sequelae	0	0	0
Recovering/resolving	0	0	0
Unknown	0	0	0
Related TEAEs Outcome, E	0	0	3
Fatal	0	0	0
Not recovered/not resolved	0	0	1 (33.3)
Recovered/resolved	0	0	2 (66.7)
Recovered/resolved with sequelae	0	0	0
Recovering/resolving	0	0	0
Unknown	0	0	0
Time to First Onset (days)			
Mean (SD)	-	65.0 (44.97)	267.5 (321.98)
Median	-	68	97
Min, Max	-	8, 116	8, 773
TEAEs leading to Treatment Discontinuation	0	0	0

Abbreviations: BIW=Twice Weekly; MedDRA = Medical Dictionary for Regulatory Activities; Max = maximum; Min = minimum; N = number of subjects in safety analysis set; SD = standard deviation; SMQ = Standardised MedDRA Query; TEAE = treatment-emergent adverse event; TGCT=Tenosynovial giant cell tumour.
[a] For Study DCC-3014-03-001, SMQs data in double-blind treatment period are presented for patients groups 'Placebo' and 'Vimseltinib 30 mg BIW' by treatment initially received.
[b] The 39 placebo patients in Study DCC-3014-03-001 are not a part of the analysis population but the data of these patients in the double-blind treatment period are included in the table to characterize the SMQs.
[c] This column presents SMQs data for all patients in the analysis population.

Note 1: The analysis population includes patients with Tenosynovial Giant Cell Tumours who were treated with 30 mg BIW in Study DCC-3014-03-001 and Study DCC-3014-01-001, including the 35 patients who originally received placebo and subsequently crossed over to 30 mg BIW in Study DCC-3014-03-001.
For n (%) patients are counted once for each SMQ category and once for each preferred term.
In each column, percentages use the number of treated patients in the corresponding patient group as the denominator.
Adverse events are coded using MedDRA version 26.0. The severity of adverse event was assessed using CTCAE Version 5.0, defining Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe, Grade 4=life threatening, and Grade 5=death.
For each SMQ category or a SMQ term, 'E' represents the total number of occurrences of the treatment-emergent adverse events; 'n' represents the number of occurrences of the treatment-emergent adverse events for each type of outcome; percentages are calculated as (n/E)x100 in each column.
One participant from the Expansion Phase (Cohort A), [redacted], re-enrolled into Cohort B as [redacted] This participant was counted as a single participant for the total column.
Data Cut-off Date for Study DCC-3014-01-001: 27DEC2023; Data Cut-off Date for Study MOTION: 22FEB2024.
Source: RMP Source Table 6.2, RMP Source Table 7.2, RMP Source Table 8.2, RMP Source Table 9.2, RMP Source Table 10.2, RMP Source Table 11.2, RMP Source Table 12.2, RMP Source Table 13.2, RMP Source Table 14.2, RMP Source Table 15.2, RMP Source Table 16.2

In the MOTION double-blind period, 4 (4.8%) participants in the vimseltinib arm experienced TEAEs within the SMQ Malignancies (Table 15), none of which were related to study treatment. Two participants experienced SAEs (not related), and one participant experienced an event that was ≥Grade 3. The median time to onset of the first event was 68 days (range: 8-116 days). Of the reported events, 60.0% of all events resolved. PTs included Malignant melanoma, Papillary thyroid cancer, Plasma cell myeloma and Tumour pain, each of which was reported in 1 participant. No participants in the placebo arm experienced TEAEs within the SMQ Malignancies.

In Pool 1, 6 (3.3%) participants treated with vimseltinib experienced TEAEs within the SMQ Malignancies (Table 15), one of which experienced events that were related to study treatment; this related event referred to a participant with prior medical history of squamous cell carcinoma who experienced SAEs of basal cell carcinoma and squamous cell carcinoma of skin. Two (1.1%) participants experienced TEAEs which were Grade 3 in severity and 1 (0.5%) participant experienced a TEAE which was Grade 4 in severity. The median time to onset of the first event was 97 days (range: 8-773 days). Of the reported events, 55.6% of all events resolved. Each PT was reported in 1 (0.5%) participant each.

All of the events observed in clinical trials were either assessed as unrelated to study treatment or were confounded by prior medical history.

Risk factors and risk groups:

Risk factors are unknown.

Preventability:

Preventability is unknown. The carcinogenic risk after vimseltinib administration is considered low.

Impact on the risk-benefit balance of the product:

The benefit of vimseltinib as an effective treatment for adult patients with TGCT, a rare disease with limited treatment options, outweighs the important potential risk of Malignancies that has yet to be confirmed. Considering all available clinical and non-clinical data, the carcinogenic risk after vimseltinib administration is considered low.

Malignancies will be further characterised in a PASS (DCC-3014-04-002) (Part III.2).

Public health impact:

Considering all available clinical and non-clinical data, the carcinogenic risk after vimseltinib administration is considered low. As TGCT is a very rare condition (Part II: Module SI), the potential impact on public health is expected to be low.

SVII.3.2 Presentation of the Missing Information

Missing information: Long-term safety

Evidence source:

Vimseltinib is expected to be used as long-term treatment for adult patients with TGCT who are not amenable to surgery.

Long-term exposure to vimseltinib in the clinical development programme is limited. In Pool 1, 101 (54.9%) participants had ≥1 year exposure and 29 (15.8%) participants had ≥2 years exposure; 2 (1.1%) participants had ≥3 years exposure. Total vimseltinib exposure in Pool 1 was 223.1 patient-years of exposure (Table 4, Module SIII). In Pool 3, 122 (48.2%) participants had ≥1 year exposure and 46 (18.2%) participants had ≥2 years exposure; with 15 (5.9%) participants having ≥3 years exposure (RMP Table 3.1). Total vimseltinib exposure for Pool 3 was 294.4 patient-years of exposure.

A review of safety data for Pool 1 by years of exposure found that the TEAEs occurred more frequently during Year 1 (N=183) compared to Year 2 (N=112) and Year 3 (N=31) (Table 14.10.1). The proportion of patients with TEAEs in Year 1, Year 2, and Year 3 is presented for the SOCs with the most frequently reported TEAEs: General disorders and administration site conditions (78.1% [Year 1], 17.9% [Year 2], and 16.1% [Year 3]), Eye disorders (72.1% [Year 1], 14.3% [Year 2], and 3.2% [Year 3]), and Skin and subcutaneous tissue disorders SOC (65.0% [Year 1], 14.3% [Year 2], and 16.1% [Year 3]), respectively. This is consistent for the vast majority of SOCs. The number of participants in the Year 4 group (N=4) is currently too small to provide a meaningful comparison. Overall, no new safety concerns associated with long latency have been identified.

Population in need of further characterisation:

Long-term safety will be further characterised in a PASS (DCC-3014-04-002) (Part III.2).

SUMMARY OF THE SAFETY CONCERNS

Table 16 Summary of 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

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

III.1 Routine Pharmacovigilance Activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires for safety concerns:

- Drug-Induced Liver Injury (DILI)
- Muscle injury/Rhabdomyolysis
- Nephrotoxicity

Other forms of routine pharmacovigilance activities for safety concerns:

- All important risks will undergo thorough follow-up as a part of individual case safety report (ICSR) processing. For the important identified risk of arterial hypertension and the important potential risks of embryofoetal toxicity, malignancies, and cognitive disorders/CNS adverse events, follow-up queries will be tailored to the specific nature and context of the reported event.
- All important risks will be subject to continuous surveillance as a part of routine signal detection. Safety signals will be assessed in accordance with applicable regulatory requirements, and pertinent findings will be summarised in the PSUR.

III.2 Additional Pharmacovigilance Activities

DCC-3014-04-002 (Category 3 PASS)

A PASS 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.

The study design and objectives will be determined following a comprehensive feasibility assessment.

III.3 Summary Table of Additional Pharmacovigilance Activities

Table 17 Ongoing and Planned Additional Pharmacovigilance Activities

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				

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
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 Cognitive disorders/CNS adverse events Malignancies Long-term safety	Study start date	To be determined (TBD)
			Study end date	TBD
			Final study report	TBD

PART IV PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are no planned post-authorisation efficacy studies.

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

Risk Minimisation Plan

V.1 Routine Risk Minimisation Measures

Table 18 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Arterial Hypertension (Important identified risk)	Routine risk communication: • *SmPC sections 4.4 and 4.8* • *Package leaflet section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *None* Other routine risk minimisation measures beyond SmPC/Product information: • *Prescription medicine*
Embryo-foetal toxicity (Important potential risk)	Routine risk communication: • *SmPC sections 4.3, 4.4, 4.5, 4.6 and 5.3* • *Package leaflet section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *Recommendation for women to avoid pregnancy while taking vimseltinib, and to advise pregnant women on the potential risk to foetus. Female patients of childbearing potential must use effective contraception during treatment with vimseltinib and for 30 days after the final dose. The pregnancy status of females of childbearing potential must be verified prior to initiating vimseltinib and during treatment. Effects of vimseltinib on hormonal contraceptives have not been studied. A barrier method contraception should be added if systemic contraceptives are used.* Other routine risk minimisation measures beyond SmPC/Product information: • *Prescription medicine*
Drug-induced liver injury (DILI) (Important potential risk)	Routine risk communication: • *SmPC sections 4.4 and 5.1* • *Package leaflet section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk:

	• *Recommendation to avoid ROMVIMZA in patients with pre-existing serum enzyme 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.* Other routine risk minimisation measures beyond SmPC/Product information: • *Prescription medicine*
Muscle injury/Rhabdomyolysis (Important potential risk)	Routine risk communication: • *SmPC sections 4.4 and 5.1* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *None* Other routine risk minimisation measures beyond SmPC/Product information: • *Prescription medicine*
Nephrotoxicity (Important potential risk)	Routine risk communication: • *SmPC section 4.4* • *Package leaflet section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *None* Other routine risk minimisation measures beyond SmPC/Product information: • *Prescription medicine*
Cognitive disorders/CNS adverse events (Important potential risk)	Routine risk communication: • *SmPC section 4.4* • *Package leaflet section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *None* Other routine risk minimisation measures beyond SmPC/Product information: • *Prescription medicine*
Malignancies (Important potential risk)	Routine risk communication: • *SmPC section 5.3* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *None* Other routine risk minimisation measures beyond SmPC/Product information: • *Prescription medicine*

Long-term safety (Missing information)	Routine risk communication: • *SmPC section 4.4* • *Package leaflet section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *None* Other routine risk minimisation measures beyond SmPC/Product information: • *None*

V.2 Additional Risk Minimisation Measures

Additional risk minimisation 1: HCP guide

Objectives:

The objective of the HCP guide is to inform and educate prescribers about the important potential risk of embryo-foetal toxicity associated with the use of vimseltinib. The guide aims to support risk minimisation through appropriate patient selection and contraceptive guidance.

Rationale for the additional risk minimisation activity:

In animal embryo-foetal toxicity studies, vimseltinib was teratogenic in rats with malformations observed in the cardiovascular and skeletal systems.

Vimseltinib toxicity was observed in a fertility and early embryonic development study in female rats given oral doses of vimseltinib at 2.5, 5 and 10 mg/kg/day (5.3, 10.7, and 20-times the exposure at the recommended human dose) (Part II: Module SII). Post-implantation loss and increased uterine weights were observed at doses of 10 mg/kg/day. Administration of vimseltinib in rats resulted in foetal malformations of the cardiovascular and skeletal systems, as well as additional indications of developmental toxicity, at a maternal dose of 15 mg/kg/day (~23-times the exposure at the recommended human dose).

No clinical studies have been performed to assess the use of vimseltinib in pregnancy. Although pregnant women were excluded and contraception requirements were included in the clinical protocols, one pregnancy while on treatment was reported in Study DCC-3014-01-001. This resulted in a spontaneous abortion following an unspecified “morning after pill,” assessed as unrelated to vimseltinib by the Investigator. There was also one partner pregnancy reported in the open-label period of MOTION that resulted in a term live birth with no congenital abnormalities reported.

The SmPC contraindicates use of vimseltinib in pregnancy and instructs that women of childbearing potential must use effective contraception (including a barrier method if systemic contraceptives are used) during treatment with vimseltinib and for 30 days after the final dose, and that the pregnancy status of females of childbearing potential must be verified prior to initiating vimseltinib and during treatment. Due to possible severe outcomes for the foetus and that the target population for vimseltinib includes females of childbearing potential, an HCP guide is deemed necessary to act as a reminder of the risk and the guidance to use effective contraception and regularly test for pregnancy.

Target audience and planned distribution path:

The HCP guide will be provided to prescribers. The educational materials as well as the implementation plan will be agreed at local level with the national competent authorities.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness of the HCP guide will be evaluated through the reporting of any identified pregnancy cases and their outcomes in the periodic safety update reports (PSURs).

Additional risk minimisation 2: Patient Card

Objectives:

The objective of the patient card is to notify patients of the important potential risk of embryo-foetal toxicity with a reminder that vimseltinib should not be used in pregnancy and of the need for effective contraception and regular pregnancy testing for women of childbearing potential.

Rationale for the additional risk minimisation activity:

In animal embryo-foetal toxicity studies, vimseltinib was teratogenic in rats with malformations observed in the cardiovascular and skeletal systems.

Vimseltinib toxicity was observed in a fertility and early embryonic development study in female rats given oral doses of vimseltinib at 2.5, 5 and 10 mg/kg/day (5.3, 10.7, and 20-times the exposure at the recommended human dose) (Part II: Module SII). Post-implantation loss and increased uterine weights were observed at doses of 10 mg/kg/day. Administration of vimseltinib in rats resulted in foetal malformations of the cardiovascular and skeletal systems, as well as additional indications of developmental toxicity, at a maternal dose of 15 mg/kg/day (~23-times the exposure at the recommended human dose).

No clinical studies have been performed to assess the use of vimseltinib in pregnancy. Although pregnant women were excluded and contraception requirements included in the protocols, one pregnancy while on treatment was reported in Study DCC-3014-01-001. This resulted in a spontaneous abortion following an unspecified “morning after pill,” assessed as unrelated to vimseltinib by the Investigator. There was also one partner pregnancy reported in the open-label period of MOTION that resulted in a term live birth with no congenital abnormalities reported.

The SmPC contraindicates use of vimseltinib in pregnancy and instructs that women of childbearing potential must use effective contraception (including a barrier method if systemic contraceptives are used) during treatment with vimseltinib and for 30 days after the final dose, and that the pregnancy status of females of childbearing potential must be verified prior to initiating vimseltinib and during treatment. Due to possible severe outcomes for the foetus and that the target population for vimseltinib includes females of childbearing potential, a patient card is deemed necessary to act as a reminder of the risk and the guidance to use effective contraception and regularly test for pregnancy.

Target audience and planned distribution path:

The patient card will be included in the secondary packaging for ROMVIMZA. The patient card will be provided to all patients treated with vimseltinib via their healthcare professional. The intention is for the patient to keep the patient card as a reminder of the guidance concerning the risk of embryo-foetal toxicity.

Plans to evaluate the effectiveness of the interventions and criteria for success:

The effectiveness of the patient card will be evaluated through the reporting of any identified pregnancy cases and their outcomes in the PSURs.

Removal of additional risk minimisation activities

Not applicable.

V.3 Summary of Risk Minimisation Measures

Table 19 Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

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: • *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)*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
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* Additional risk minimisation measures: • *None*	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
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)*

PART VI SUMMARY OF THE RISK MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR ROMVIMZA (VIMSELTINIB)

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

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

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

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

I THE MEDICINE AND WHAT IT IS USED FOR

ROMVIMZA is authorised 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 (see SmPC for the full indication). It contains vimseltinib as the active substance and it is given orally.

Further information about the evaluation of ROMVIMZA's benefits can be found in ROMVIMZA's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

II RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERISE THE RISKS

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

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

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

Together, these measures constitute *routine risk minimisation* measures.

In the case of ROMVIMZA, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

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

If important information that may affect the safe use of ROMVIMZA is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

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

Table 20 List of Important Risks and Missing Information

List of important risks and missing information	
Important identified risks	Arterial Hypertension
Important potential risks	Embryo-foetal toxicity Drug-Induced Liver Injury (DILI) Muscle injury/Rhabdomyolysis Nephrotoxicity Cognitive Disorders/CNS Adverse Events Malignancies
Missing information	Long-term safety

II.B Summary of Important Risks

Table 21 Summary of Important Risks

Important Identified Risk: Arterial Hypertension	
Evidence for linking the risk to the medicine	There may be an association of CSF1R inhibitors and hypertension through off-target receptor inhibition that has been observed with tyrosine kinase inhibitors, even those not targeting VEGF directly. In the clinical development programme, 15 (18.1%) in the vimseltinib arm of MOTION (compared with 4 [10.3%] in the placebo arm) and 39 (21.3%) participants treated with vimseltinib in Pool 1 experienced TEAEs within the

	Standardised MedDRA Query (SMQ) of Hypertension (narrow) (Module SVII.3.1). Due to the higher frequency of TEAEs of hypertension in participants treated with vimseltinib and the need for new antihypertensive medications in participants who did not have previous medical history of hypertension, arterial hypertension is considered an important identified risk.
Risk factors and risk groups	Risk factors associated with arterial hypertension are age, obesity, family history of hypertension, genetics, lifestyle habits, male sex, other medical conditions, social and economic factors.
Risk minimisation measures	Routine risk communication: • *SmPC sections 4.4 and 4.8* • *Package leaflet section 2* Routine risk minimisation activities recommending specific clinical measures to address the risk: • *None* Other routine risk minimisation measures beyond SmPC/Product information: • *Prescription medicine*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *PASS (DCC-3014-04-002)* See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Embryo-foetal toxicity	
Evidence for linking the risk to the medicine	No clinical studies have been performed to assess the use of vimseltinib in pregnancy. Although pregnant women were excluded and contraception requirements included in the protocols, one pregnancy while on treatment was reported in Study DCC-3014-01-001. This resulted in a spontaneous abortion following an unspecified “morning after pill,” assessed as unrelated to vimseltinib by the Investigator. There was also one partner pregnancy reported in the open-label period of MOTION that resulted in a term live birth with no congenital abnormalities reported. In animal embryo-foetal toxicity studies, vimseltinib was teratogenic in rats with malformations observed in the cardiovascular and skeletal systems. Non-clinical findings may be relevant for humans and in the absence of clinical data suggest a potential safety concern that awaits clinical confirmation.
Risk factors and risk groups	Females of childbearing potential not using effective contraception.
Risk minimisation measures	Routine risk minimisation measures • *SmPC sections 4.3, 4.4, 4.5, 4.6 and 5.3*

	• *Package leaflet section 2* • *Prescription medicine* Additional risk minimisation measures • *Patient card* • *HCP guide*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *None*
Important potential risk: Drug-Induced Liver Injury (DILI)	
Evidence for linking the risk to the medicine	Vimseltinib is a CSF1R inhibitor and a pharmacological effect within this class is to reduce macrophages in the liver (Kupffer cells). There was no evidence of DILI in the clinical development programme, although mild to moderate elevations in hepatic enzymes were observed. In the MOTION double-blind period, 24 (28.9%) participants in the vimseltinib arm experienced TEAEs within the Drug related hepatic disorders SMQ compared with 1 (2.6%) participant in the placebo arm. In Pool 1, 58 (31.7%) participants treated with vimseltinib experienced TEAEs Drug related hepatic disorders SMQ (RMP Source Table 6.2). All of the TEAEs referred to laboratory abnormalities. The majority of the TEAEs were non-serious, mild to moderate in severity, and did not lead to discontinuation of treatment. In non-clinical studies, vimseltinib-related pathology observations were suggestive of hepatocellular and/or skeletal muscle injury. Correlating microscopic findings involved several tissues, including the liver which were found to be fully or partially reversible at doses ≤7.5 mg/kg/day. Pathology findings included minimally increased aspartate aminotransferase.
Risk factors and risk groups	Risk factors associated with DILI include age, female gender, pre-existing liver disease, and obesity.
Risk minimisation measures	Routine risk minimisation measures • *SmPC sections 4.4 and 5.1* • *Package leaflet section 2* • *Prescription medicine* Additional risk minimisation measures • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *PASS (DCC-3014-04-002)* See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Muscle injury/Rhabdomyolysis	
Evidence for linking the risk to the medicine	Vimseltinib is a CSF1R inhibitor. CSF1R inhibitors are known to reduce macrophages in the liver and other tissues.

	There is no evidence of Muscle injury/Rhabdomyolysis in the clinical development programme, although CPK elevations were observed as laboratory abnormalities. In the MOTION double-blind period, 25 (30.1%) participants in the vimseltinib arm experienced TEAEs within the SMQ Rhabdomyolysis/Myopathy compared with 4 (10.3%) participants in the placebo arm. In Pool 1, 90 (49.2%) participants treated with vimseltinib experienced TEAEs within the SMQ Rhabdomyolysis/Myopathy (RMP Source Table 6.2). The majority of the TEAEs were non-serious, mild to moderate in severity and did not lead to discontinuation of treatment. In the non-clinical studies, mildly increased CPK activities were seen.
Risk factors and risk groups	Risk factors associated with Muscle injury/Rhabdomyolysis include extreme temperatures, dehydration, infections, trauma, strenuous exercise, and underlying medical conditions.
Risk minimisation measures	Routine risk minimisation measures • *SmPC sections 4.4 and 5.1* • *Prescription medicine* Additional risk minimisation measures • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *PASS (DCC-3014-04-002)* See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Nephrotoxicity	
Evidence for linking the risk to the medicine	There is no evidence of nephrotoxicity in the clinical development programme, although creatinine elevations were observed as a laboratory abnormality. In the MOTION double-blind period, 2 (2.4%) participants in the vimseltinib arm experienced TEAEs within the SMQ Acute renal failure, compared with 0 participants in the placebo arm. In Pool 1, 6 (3.3%) participants treated with vimseltinib experienced TEAEs within the SMQ Acute renal failure (RMP Source Table 6.2). All of the TEAEs were non-serious, mild to moderate in severity and did not lead to discontinuation of treatment. In the non-clinical studies, CPN was observed in animals administered ≥2.5 mg/kg/day vimseltinib.
Risk factors and risk groups	Risk factors associated with nephrotoxicity include comorbidities, volume depletion, liver dysfunction, sepsis, renal dysfunction, hypokalaemia, hypomagnesaemia, and advanced age.
Risk minimisation measures	Routine risk minimisation measures • *SmPC section 4.4* • *Package leaflet section 2*

	• *Prescription medicine* Additional risk minimisation measures • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *PASS (DCC-3014-04-002)* See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Cognitive Disorders/ CNS Adverse Events	
Evidence for linking the risk to the medicine	As vimseltinib was brain penetrant in non-clinical studies and cognitive disorders (including memory impairment, amnesia, confusional state, disturbance in attention, and attention deficit/hyperactivity disorder) have been observed following administration of other CSF1R inhibitors, cognitive disorders/CNS adverse events are considered an important potential risk
Risk factors and risk groups	Risk factors associated with cognitive disorders/CNS adverse events are currently unknown
Risk minimisation measures	Routine risk minimisation: • *SmPC section 4.4* • *Package leaflet section 2* • *Prescription medicine* Additional risk minimisation measures • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *PASS (DCC-3014-04-002)* See section II.C of this summary for an overview of the post-authorisation development plan.
Important potential risk: Malignancies	
Evidence for linking the risk to the medicine	In a 2-year oral rat carcinogenicity study (DCC-3014-04-0025), 2 out of 60 (3%) male rats receiving 1.0 mg/kg/day (approximately 1.4 times the total vimseltinib exposure at the recommended dose and less than the unbound [free] vimseltinib exposure for patients with TGCT based on AUC) were identified as having histomorphologically different sarcomas in the synovium of the femorotibial joint. Both were classified as sarcoma, not otherwise specified. The relevance of the observed non-clinical finding is unknown but considering all available clinical and non-clinical data, the carcinogenic risk after vimseltinib administration is considered low.
Risk factors and risk groups	Risk factors are unknown.
Risk minimisation measures	Routine risk minimisation:

	• *SmPC section 5.3* • *Prescription medicine* Additional risk minimisation measures: • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *PASS (DCC-3014-04-002)* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Long-term safety	
Risk minimisation measures	Routine risk minimisation measures • *SmPC section 4.4* • *Package leaflet section 2* Additional risk minimisation measures • *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • *PASS (DCC-3014-04-002)* See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-Authorisation Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligations of vimseltinib.

II.C.2 Other Studies in Post-Authorisation Development Plan

Study short name: DCC-3014-04-002

Purpose of the study:

A PASS 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.

The study design and objectives will be determined following a comprehensive feasibility assessment.

PART VII ANNEXES

LIST OF ANNEXES

ANNEX 1 EUDRAVIGILANCE INTERFACE

ANNEX 2 TABULATED SUMMARY OF PLANNED, ONGOING, AND COMPLETED PHARMACOVIGILANCE STUDY PROGRAMME

Table 22 Planned and Ongoing Studies

Study	Summary of objectives	Safety concerns addressed	Milestones
DCC-3014-04-002 Category 3	• 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 Cognitive Disorders/Central Nervous System (CNS) Adverse Events Malignancies Long-term safety	Study start date: TBD Study end date: TBD Final study report: TBD

Completed Studies

Not applicable

ANNEX 3 PROTOCOLS FOR PROPOSED, ONGOING AND COMPLETED STUDIES IN THE PHARMACOVIGILANCE PLAN

Table of contents

Part A: Requested protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

Part B: Requested amendments of previously approved protocols of studies in the Pharmacovigilance Plan, submitted for regulatory review with this updated version of the RMP

Not applicable

Part C: Previously agreed protocols for ongoing and final protocols not reviewed by the competent authority

Not applicable

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents

Follow-up forms

Specific adverse reaction follow-up questionnaires for safety concerns:

- Drug-Induced Liver Injury (DILI)
- Muscle injury/Rhabdomyolysis
- Nephrotoxicity

ROMVIMZA DRUG-INDUCED LIVER INJURY (DILI) FOLLOW-UP QUESTIONNAIRE

Safety tracking ID: <ID>

DD-MMM-YYYY

Dear [name of recipient],

You are receiving this questionnaire because an adverse event was reported for your patient following treatment with Romvimza. The reported adverse event of [verbatim term (PT)] that occurred on DD-MMM-YYYY requires further information.

We request your help in investigating the event and determining if there may have been other underlying causes. This questionnaire is focused on drug-induced liver injury (DILI).

Please help us answer as many questions as you can. Any details you provide will be useful and very much appreciated.

We understand that the questionnaire is extensive, and that you might not have all the information. Please answer as many questions as you can, according to the available information.

All the information and personal data you share with us will be protected and kept confidential in line with applicable privacy and data laws, including the European Union General Data Protection Regulation (GDPR) and US Health Insurance Portability and Accessibility Act (“HIPAA”), and any other applicable local laws that regulate the storage, processing, access and transfer of personal data. The information provided will be used for the purpose of drug safety pharmacovigilance and may be shared with health authorities to meet relevant legal obligations. The patient has a right to access his/her personal data that we hold about him/her.

Thank you in advance for your assistance in providing Deciphera with this information.

Please fax or scan and email the completed form (and additional pages, if necessary) or send an email with your answers using the contact information below:

Email: <Email address>
Fax number: <Fax Number>

Deciphera use only			
Manufacturer's Control Number (MCN):	☐ Initial	☐ Follow-up	Date of Notification:
Study Number (if applicable):	Patient Number (if applicable):		Date of Initial Notification:

Patient Information:		
Patient's Initials/ID:	Year of birth: ____	Age: years
Gender: ☐ Male ☐ Female	Current height: cm	Current weight: kg

Product information: Please provide the following information on ROMVIMZA/Other Suspect Product(s)

Product	Indication	Dosing Details (strength and frequency)	Form / Route	Start date	Stop date / ongoing	Lot/Batch#
ROMVIMZA				__/___/____	__/___/____ ☐ Ongoing	
				__/___/____	__/___/____ ☐ Ongoing	
				__/___/____	__/___/____ ☐ Ongoing	

Event information: Please list the hepatic event(s) and all other relevant event(s) experienced by the patient at the time of the hepatic event(s) and provide the following information

	Event(s) (Please describe the clinical course in the 'Narrative' section)	Event seriousness	Event onset date	Outcome	Event end date (if applicable) / ongoing	Was any corrective treatment received? (Yes/No)	Causality for each suspect product***
1		☐ Death ☐ Life-threatening ☐ Congenital anomaly ☐ Significant incapacity / Disability ☐ Hospitalized (new and prolonged)** ☐ Medically significant ☐ Non-serious	__/___/____	☐ Fatal* ☐ Not recovered / Resolved ☐ Recovering / Resolving ☐ Recovered/ Resolved ☐ Recovered with sequelae ☐ Unknown	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s): ☐ Not related Suspect product(s): If not related to ROMVIMZA, please provide alternative etiology(ies):
2		☐ Death ☐ Life-threatening ☐ Congenital anomaly	__/___/____	☐ Fatal* ☐ Not recovered / Resolved	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s):

Event information: Please list the hepatic event(s) and all other relevant event(s) experienced by the patient at the time of the hepatic event(s) and provide the following information							
	Event(s) (Please describe the clinical course in the 'Narrative' section)	**Event seriousness**	**Event onset date**	**Outcome**	**Event end date** (if applicable) / **ongoing**	**Was any corrective treatment received?** (Yes/No)	**Causality for each suspect product*****
		☐ Significant incapacity / Disability ☐ Hospitalized (new and prolonged)** ☐ Medically significant ☐ Non-serious		☐ Recovering / Resolving ☐ Recovered/ Resolved ☐ Recovered with sequelae ☐ Unknown			☐ Not related Suspect product(s): If not related to ROMVIMZA, please provide alternative etiology(ies):

*Please provide the autopsy report, if available. ** Please provide hospital discharge summary. ***Please provide the relationship between the event and each of the suspect products.

Action taken information: Please provide the following details for ROMVIMZA and any other suspect product(s)				
Product	**Action taken with the suspect product in response to the hepatic event(s)**	**Date of action taken** (if applicable)	**Did the hepatic event(s) resolve following this action?** (Yes/No)	**If the product was re-introduced, did the hepatic event(s) re-occur (positive rechallenge)?**
ROMVIMZA	☐ Dose Increased ☐ No Change ☐ Dose decreased ☐ Interrupted ☐ Withdrawn ☐ Not applicable (product stopped before event) ☐ Unknown	__/___/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)
(Please describe other suspect products in the 'Narrative' section)	☐ Dose Increased ☐ No Change ☐ Dose decreased ☐ Interrupted ☐ Withdrawn ☐ Not applicable (product stopped before event) ☐ Unknown	__/___/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)

Targeted queries	
Did the patient experience any of the following signs and symptoms at the time of (or close to) the occurrence of the above-reported hepatic event(s)? If yes, please provide details in the appropriate sections ('Event information', 'Investigations' and 'Narrative').	Fatigue and weakness ☐ Yes ☐ No Loss of appetite ☐ Yes ☐ No Nausea ☐ Yes ☐ No Vomiting ☐ Yes ☐ No Jaundice ☐ Yes ☐ No Abdominal pain and swelling ☐ Yes ☐ No Dark urine ☐ Yes ☐ No Pale or clay-colored stools ☐ Yes ☐ No Itching ☐ Yes ☐ No Rash ☐ Yes ☐ No Fever ☐ Yes ☐ No Swelling in legs and ankles ☐ Yes ☐ No Confusion and disorientation ☐ Yes ☐ No Bruising or bleeding ☐ Yes ☐ No Other If yes, please specify: ☐ Yes ☐ No
Has the patient experienced any recent infection(s)? If yes, please provide details in the appropriate section ('Patient's Medical History').	☐ Yes ☐ No
Does the patient have any alcohol or substance abuse issues? If yes, please provide details in the appropriate section ('Patient's Medical History').	☐ Yes ☐ No
Does the patient have any of the following past or ongoing medical history? If yes, please provide details in the appropriate section ('Patient's Medical History').	Jaundice ☐ Yes ☐ No MELD-Na score ≥ 12 ☐ Yes ☐ No Hepatorenal syndrome ☐ Yes ☐ No Ascites ☐ Yes ☐ No Variceal bleeds ☐ Yes ☐ No Hepatic encephalopathy ☐ Yes ☐ No Spontaneous bacterial peritonitis ☐ Yes ☐ No Other If yes, please specify: ☐ Yes ☐ No
Does the patient have any family history of liver disease? If yes, please provide details.	☐ Yes ☐ No

Patient's Medical History: Please provide any relevant medical history information including any pre-existing hepatic disorders prior to initiation of ROMVIMZA treatment (specifying start (diagnosis) and end dates, if available)	
Current (ongoing)	
Previous	

Investigations: Please provide results of any relevant investigations (laboratory tests, physical examinations, imaging, etc.) from prior to, during and after the hepatic event(s) (including baseline results prior to ROMVIMZA initiation, if available)				
Test / examination name	**Was the test performed** (Yes/No/Unknown)*	**Test / examination date**	**Test / examination result** (quantitative or qualitative)**	**Normal range** (if applicable)
Blood alkaline phosphatase (ALP)				
Total bilirubin (TB)				
Direct (conjugated) bilirubin (DB)				
Blood urea nitrogen (BUN)				
Blood creatinine				
Blood glucose				
Blood calcium				
Blood potassium				
Blood phosphate				
Blood sodium				
Blood chloride				
Blood uric acid				
Blood albumin				
Aspartate aminotransferase (AST)				
Alanine aminotransferase (ALT)				
Gamma-glutamyl transferase (GGT)				
Complete blood count (CBC)				
C reactive protein (CRP)				
Viral serology				
Gamma globulin (Immunoglobulin G (IgG))				
Prothrombin time (PT)				
International normalized ratio (INR)				
Liver ultrasound				
Liver scan				
Liver biopsy				
Any other relevant test / examination (If done, please provide results in the 'Narrative' section.)				

*Please attach any relevant test/examination report. **Please describe in 'Narrative' section if abnormal.

Product information: Please list relevant concomitant medications and provide the following information – Please note all relevant medications the patient was taking at the time of the event(s) (including prescribed or over-the-counter medications, herbal products, supplements, and/or vitamins) and indicate for each medication whether it was suspect (i.e., whether it may have contributed to the hepatic event(s)) **Please attach any relevant concomitant medications report.**

	Product (brand name if known or generic)	**Suspect?** (Yes/No)	**Indication**	**Dose**	**Frequency**	**Form / Route**	**Start date**	**Stop date / ongoing**
1		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
2		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
3		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
4		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
5		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
6		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing

Narrative: Please describe the clinical course of the hepatic event(s)

ROMVIMZA MUSCLE INJURY/RHABDOMYOLYSIS FOLLOW-UP QUESTIONNAIRE

Safety tracking ID: <ID>

DD-MMM-YYYY

Dear [name of recipient],

You are receiving this questionnaire because an adverse event was reported for your patient following treatment with Romvimza. The reported adverse event of [verbatim term (PT)] that occurred on DD-MMM-YYYY requires further information.

We request your help in investigating the event and determining if there may have been other underlying causes. This questionnaire is focused on muscle injury/rhabdomyolyis.

Please help us answer as many questions as you can. Any details you provide will be useful and very much appreciated.

We understand that the questionnaire is extensive, and that you might not have all the information. Please answer as many questions as you can, according to the available information.

All the information and personal data you share with us will be protected and kept confidential in line with applicable privacy and data laws, including the European Union General Data Protection Regulation (GDPR) and US Health Insurance Portability and Accessibility Act ("HIPAA"), and any other applicable local laws that regulate the storage, processing, access and transfer of personal data. The information provided will be used for the purpose of drug safety pharmacovigilance and may be shared with health authorities to meet relevant legal obligations. The patient has a right to access his/her personal data that we hold about him/her.

Thank you in advance for your assistance in providing Deciphera with this information.

Please fax or scan and email the completed form (and additional pages, if necessary) or send an email with your answers using the contact information below:

Email: <Email address>
Fax number: <Fax Number>

Manufacturer's Control Number (MCN):	☐ Initial	☐ Follow-up	Date of Notification:
Study Number (if applicable):	Patient Number (if applicable):		Date of Initial Notification:

Patient Information:		
Patient's Initials/ID:	Year of birth: ____	Age: years
Gender: ☐ Male ☐ Female	Current height: cm	Current weight: kg

Product information: Please provide the following information on ROMVIMZA/Other Suspect Product(s)

Product	Indication	Dosing Details (strength and frequency)	Form / Route	Start date	Stop date / ongoing	Lot/Batch#
ROMVIMZA				__/___/____	__/___/____ ☐ Ongoing	
				__/___/____	__/___/____ ☐ Ongoing	
				__/___/____	__/___/____ ☐ Ongoing	

Event information: Please list the muscle-related event(s) and all other relevant event(s) experienced by the patient at the time of the muscle-related event(s) and provide the following information

	Event(s) (Please describe the clinical course in the 'Narrative' section)	Event seriousness	Event onset date	Outcome	Event end date (if applicable) / ongoing	Was any corrective treatment received? (Yes/No)	Causality for each suspect product***
1		☐ Death ☐ Life-threatening ☐ Congenital anomaly ☐ Significant incapacity / Disability ☐ Hospitalized (new and prolonged)** ☐ Medically significant ☐ Non-serious	__/___/____	☐ Fatal* ☐ Not recovered / Resolved ☐ Recovering / Resolving ☐ Recovered/ Resolved ☐ Recovered with sequelae ☐ Unknown	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s): ☐ Not related Suspect product(s): If not related to ROMVIMZA, please provide alternative etiology(ies):
2		☐ Death ☐ Life-threatening ☐ Congenital anomaly ☐ Significant incapacity / Disability	__/___/____	☐ Fatal* ☐ Not recovered / Resolved ☐ Recovering / Resolving	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s): ☐ Not related

Event information: Please list the muscle-related event(s) and all other relevant event(s) experienced by the patient at the time of the muscle-related event(s) and provide the following information							
	Event(s) (Please describe the clinical course in the 'Narrative' section)	**Event seriousness**	**Event onset date**	**Outcome**	**Event end date** (if applicable) / **ongoing**	**Was any corrective treatment received?** (Yes/No)	**Causality for each suspect product*** **
		☐ Hospitalized (new and prolonged)** ☐ Medically significant ☐ Non-serious		☐ Recovered/ Resolved ☐ Recovered with sequelae ☐ Unknown			Suspect product(s): If not related to ROMVIMZA, please provide alternative etiology(ies):

*Please provide the autopsy report, if available. **Please provide hospital discharge summary. ***Please provide the relationship between the event and each of the suspect products.

Action taken information: Please provide the following details for ROMVIMZA and any other suspect product(s)				
Product	**Action taken with the suspect product in response to the muscle-related event(s)**	**Date of action taken** (if applicable)	**Did the muscle-related event(s) resolve following this action?** (Yes/No)	**If the product was re-introduced, did the muscle-related event(s) re-occur (positive rechallenge)?**
ROMVIMZA	☐ Dose Increased ☐ No Change ☐ Dose decreased ☐ Interrupted ☐ Withdrawn ☐ Not applicable (product stopped before event) ☐ Unknown	__/___/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)
(Please describe other suspect products in the 'Narrative' section)	☐ Dose Increased ☐ No Change ☐ Dose decreased ☐ Interrupted ☐ Withdrawn ☐ Not applicable (product stopped before event) ☐ Unknown	__/___/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)

Targeted queries	
Did the patient experience any of the following signs and symptoms at the time of (or close to) the occurrence of the above-reported muscle-related event(s)? If yes, please provide details in the appropriate sections ('Event information', 'Investigations' and 'Narrative').	Myalgia ☐ Yes ☐ No Generalized muscle weakness ☐ Yes ☐ No Muscle swelling ☐ Yes ☐ No Muscle tenderness ☐ Yes ☐ No Marked increase in muscle CPK values ☐ Yes ☐ No Myoglobinuria ☐ Yes ☐ No Urine pigmentation (darkened urine) ☐ Yes ☐ No Fever ☐ Yes ☐ No Nausea ☐ Yes ☐ No Vomiting ☐ Yes ☐ No Other ☐ Yes ☐ No If yes, please specify:
Were there any signs of rhabdomyolysis complications (including acute kidney injury)? If yes, please provide details in the appropriate sections ('Event information' and 'Narrative').	☐ Yes ☐ No
Was the patient practicing a sustained physical activity of high intensity at the time of (or close to) the occurrence of the above-reported muscle-related event(s)? If yes, please provide details in the appropriate section ('Narrative').	☐ Yes ☐ No
Did the patient experience any traumatic injuries (e.g., fall, electrical injury, burn injury) before or at the time of (or close to) the occurrence of the above-reported muscle-related event(s)? If yes, please provide details in the appropriate sections ('Event information' and 'Narrative') including circumstances/cause.	☐ Yes ☐ No
Did the patient experience any hyperthermia or hypothermia at the time of (or close to) the occurrence of the above-reported muscle-related event(s)? If yes, please provide details in the appropriate sections ('Event information' and 'Narrative').	Hyperthermia ☐ Yes ☐ No Hypothermia ☐ Yes ☐ No
Was the patient taking any statins or other medications potentially linked to muscle injury at the time of (or close to) the occurrence of the above-reported muscle-related event(s)? If yes, please provide details in the appropriate section ('Product information').	☐ Yes ☐ No
Has the patient experienced any recent infection(s)? If yes, please provide details in the appropriate section ('Patient's Medical History').	☐ Yes ☐ No
Does the patient have any alcohol or substance abuse issues? If yes, please provide details in the appropriate section ('Patient's Medical History').	☐ Yes ☐ No

Targeted queries		
Does the patient have any of the following past or ongoing medical history? If yes, please provide details in the appropriate section ('Patient's Medical History').	Myalgia	☐ Yes ☐ No
	Generalized muscle weakness	☐ Yes ☐ No
	Muscle swelling	☐ Yes ☐ No
	Muscle tenderness	☐ Yes ☐ No
	Marked increase in muscle CPK values	☐ Yes ☐ No
	Myoglobinuria	☐ Yes ☐ No
	Urine pigmentation (darkened urine)	☐ Yes ☐ No
	Rhabdomyolysis	☐ Yes ☐ No
	Inflammatory myopathy	☐ Yes ☐ No
	Endocrine myopathies	☐ Yes ☐ No
	Muscular dystrophy	☐ Yes ☐ No
	Other chronic muscle disease If yes, please specify:	☐ Yes ☐ No
	Muscle phosphorylase deficiency	☐ Yes ☐ No
	Other enzyme deficiency If yes, please specify:	☐ Yes ☐ No

Patient's Medical History: Please provide any relevant medical history information including any pre-existing muscle-related disorders prior to initiation of ROMVIMZA treatment (specifying start (diagnosis) and end dates, if available)	
Current (ongoing)	
Previous	

Investigations: Please provide results of any relevant investigations (laboratory tests, physical examinations, imaging, etc.) from prior to, during and after the muscle-related event(s) (including baseline results prior to ROMVIMZA initiation, if available)

Test / examination name	Was the test performed (Yes/No/Unknown)*	**Test / examination date**	**Test / examination result** (quantitative or qualitative)**	**Normal range** (if applicable)
Blood creatine phosphokinase (CPK)				
Urine myoglobin				
Complete blood count (CBC)				
Blood urea nitrogen (BUN)				
Blood creatinine				
Blood glucose				
Blood calcium				
Blood potassium				
Blood phosphate				
Blood sodium				

Investigations: Please provide results of any relevant investigations (laboratory tests, physical examinations, imaging, etc.) from prior to, during and after the muscle-related event(s) (including baseline results prior to ROMVIMZA initiation, if available)				
Blood chloride				
Blood uric acid				
Blood alkaline phosphatase (ALP)				
Alanine aminotransferase (ALT)				
Aspartate aminotransferase (AST)				
Gamma-glutamyl transferase (GGT)				
Total bilirubin (TB)				
Direct (conjugated) bilirubin (DB)				
Thyroid tests				
Serum albumin				
Total serum protein				
Blood aldolase				
Lactate dehydrogenase (LDH)				
Estimated glomerular filtration rate (eGFR)				
Electrocardiogram (ECG)				
Electromyogram (EMG)				
Muscle biopsy				
Any other relevant test / examination (If done, please provide results in the 'Narrative' section.)				

*Please attach any relevant test/examination report. **Please describe in 'Narrative' section if abnormal.

Product information: Please list relevant concomitant medications and provide the following information – Please note all relevant medications the patient was taking at the time of the event(s) (including prescribed or over-the-counter medications, herbal products, supplements, and/or vitamins) and indicate for each medication whether it was suspect (i.e., whether it may have contributed to the muscle-related event(s)) **Please attach any relevant concomitant medications report.**

	Product (brand name if known or generic)	**Suspect?** (Yes/No)	**Indication**	**Dose**	**Frequency**	**Form / Route**	**Start date**	**Stop date / ongoing**
1		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
2		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
3		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
4		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
5		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing

Product information: Please list relevant concomitant medications and provide the following information – Please note all relevant medications the patient was taking at the time of the event(s) (including prescribed or over-the-counter medications, herbal products, supplements, and/or vitamins) and indicate for each medication whether it was suspect (i.e., whether it may have contributed to the muscle-related event(s)) **Please attach any relevant concomitant medications report.**

	Product (brand name if known or generic)	**Suspect?** (Yes/No)	**Indication**	**Dose**	**Frequency**	**Form / Route**	**Start date**	**Stop date / ongoing**
6		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing

Narrative: Please describe the clinical course of the muscle-related event(s)

ROMVIMZA NEPHROTOXICITY FOLLOW-UP QUESTIONNAIRE

Safety tracking ID: <ID>

DD-MMM-YYYY

Dear [name of recipient],

You are receiving this questionnaire because an adverse event was reported for your patient following treatment with Romvimza. The reported adverse event of [verbatim term (PT)] that occurred on DD-MMM-YYYY requires further information.

We request your help in investigating the event and determining if there may have been other underlying causes. This questionnaire is focused on nephrotoxicity.

Please help us answer as many questions as you can. Any details you provide will be useful and very much appreciated.

We understand that the questionnaire is extensive, and that you might not have all the information. Please answer as many questions as you can, according to the available information.

All the information and personal data you share with us will be protected and kept confidential in line with applicable privacy and data laws, including the European Union General Data Protection Regulation (GDPR) and US Health Insurance Portability and Accessibility Act ("HIPAA"), and any other applicable local laws that regulate the storage, processing, access and transfer of personal data. The information provided will be used for the purpose of drug safety pharmacovigilance and may be shared with health authorities to meet relevant legal obligations. The patient has a right to access his/her personal data that we hold about him/her.

Thank you in advance for your assistance in providing Deciphera with this information.

Please fax or scan and email the completed form (and additional pages, if necessary) or send an email with your answers using the contact information below:

Email: <Email address>
Fax number: <Fax Number>

Manufacturer's Control Number (MCN):	☐ Initial	☐ Follow-up	Date of Notification:
Study Number (if applicable):	Patient Number (if applicable):		Date of Initial Notification:

Patient Information:		
Patient's Initials/ID:	Year of birth: ____	Age: years
Gender: ☐ Male ☐ Female	Current height: cm	Current weight: kg

Product information: Please provide the following information on ROMVIMZA/ Other suspect product(s)

Product	Indication	Dosing details (strength and frequency)	Form / Route	Start date	Stop date / ongoing	Lot/Batch#
ROMVIMZA				__/___/____	__/___/____ ☐ Ongoing	
				__/___/____	__/___/____ ☐ Ongoing	
				__/___/____	__/___/____ ☐ Ongoing	

Event information: Please list the renal event(s) and all other relevant event(s) experienced by the patient at the time of the renal event(s) and provide the following information

	Event(s) (Please describe the clinical course in the 'Narrative' section)	Event seriousness	Event onset date	Outcome	Event end date (if applicable) / ongoing	Was any corrective treatment received? (Yes/No)	Causality for each suspect product***
1		☐ Death ☐ Life-threatening ☐ Congenital anomaly ☐ Significant incapacity / Disability ☐ Hospitalized (new and prolonged)** ☐ Medically significant ☐ Non-serious	__/___/____	☐ Fatal* ☐ Not recovered / Resolved ☐ Recovering / Resolving ☐ Recovered/ Resolved ☐ Recovered with sequelae ☐ Unknown	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s): ☐ Not related Suspect product(s): If not related to ROMVIMZA, please provide alternative etiology(ies):
2		☐ Death ☐ Life-threatening ☐ Congenital anomaly ☐ Significant incapacity / Disability	__/___/____	☐ Fatal* ☐ Not recovered / Resolved ☐ Recovering / Resolving	__/___/____ ☐ Ongoing	☐ Yes ☐ No If yes, please provide details:	☐ Related Suspect product(s): ☐ Not related

Event information: Please list the renal event(s) and all other relevant event(s) experienced by the patient at the time of the renal event(s) and provide the following information							
	Event(s) (Please describe the clinical course in the 'Narrative' section)	**Event seriousness**	**Event onset date**	**Outcome**	**Event end date** (if applicable) / **ongoing**	**Was any corrective treatment received?** (Yes/No)	**Causality for each suspect product*****
		☐ Hospitalized (new and prolonged)** ☐ Medically significant ☐ Non-serious		☐ Recovered/ Resolved ☐ Recovered with sequelae ☐ Unknown			Suspect product(s): If not related to ROMVIMZA, please provide alternative etiology(ies):

*Please provide the autopsy report, if available. ** Please provide hospital discharge summary. ***Please provide the relationship between the event and each of the suspect products.

Action taken information: Please provide the following details for ROMVIMZA and any other suspect product(s)				
Product	**Action taken with the suspect product in response to the renal event(s)**	**Date of action taken** (if applicable)	**Did the renal event(s) resolve following this action?** (Yes/No)	**If the product was re-introduced, did the renal event(s) re-occur (positive rechallenge)?**
ROMVIMZA	☐ Dose Increased ☐ No Change ☐ Dose decreased ☐ Interrupted ☐ Withdrawn ☐ Not applicable (product stopped before event) ☐ Unknown	__/___/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)
(Please describe other suspect products in the 'Narrative' section)	☐ Dose Increased ☐ No Change ☐ Dose decreased ☐ Interrupted ☐ Withdrawn ☐ Not applicable (product stopped before event) ☐ Unknown	__/___/____	☐ Yes ☐ No ☐ Not applicable (product continued without change)	☐ Yes ☐ No ☐ Not applicable (product not re-introduced)

Targeted queries	
Did the patient experience any of the following signs and symptoms at the time of (or close to) the occurrence of the above-reported renal event(s)? If yes, please provide details in the appropriate sections ('Event information', 'Investigations' and 'Narrative').	Decreased urine output ☐ Yes ☐ No Hypertension ☐ Yes ☐ No Oedema ☐ Yes ☐ No Fatigue and weakness ☐ Yes ☐ No Nausea ☐ Yes ☐ No Vomiting ☐ Yes ☐ No Dehydration (acute) ☐ Yes ☐ No Loss of appetite ☐ Yes ☐ No Dyspnea ☐ Yes ☐ No Confusion and drowsiness ☐ Yes ☐ No Chest pain or pressure ☐ Yes ☐ No Seizures or coma ☐ Yes ☐ No Uremic fetor ☐ Yes ☐ No Uremic pruritus ☐ Yes ☐ No Uremic frost ☐ Yes ☐ No Muscle cramps ☐ Yes ☐ No Blood or pus in urine ☐ Yes ☐ No Jaundice ☐ Yes ☐ No Acute liver disease ☐ Yes ☐ No Acute kidney injury ☐ Yes ☐ No Acute pancreatitis ☐ Yes ☐ No Sepsis ☐ Yes ☐ No Haemorrhage ☐ Yes ☐ No Anaemia (Hb<9 g/dL ☐ Yes ☐ No Other ☐ Yes ☐ No If yes, please specify:
Did the patient experience any snakebite, wasp or bee stings or was exposed to other nephrotoxins before or at the time of (or close to) the occurrence of the above-reported renal event(s)? If yes, please provide details in the appropriate sections ('Event information' and 'Narrative') including circumstances/cause.	☐ Yes ☐ No
Did the patient experience any recent injuries (e.g. crush injury) before or at the time of (or close to) the occurrence of the above-reported renal event(s)? If yes, please provide details in the appropriate sections ('Event information' and 'Narrative') including circumstances/cause.	☐ Yes ☐ No
Did the patient experience any adverse environmental or occupational exposures (e.g. Prolonged physical work in hot climate) at the time of (or close to) the occurrence of the above-reported renal event(s)? If yes, please provide details in the appropriate sections ('Event information' and 'Narrative').	☐ Yes ☐ No

Targeted queries	
Was the patient taking any medications potentially linked to nephrotoxicity (e.g. gentamicin, vancomycin, naproxen, cisplatin, amphotericin B, iodinated contrast dye, ACE-inhibitor or ARB or SGLT2) at the time of (or close to) the occurrence of the above-reported renal event(s)? If yes, please provide details in the appropriate section ('Product information').	☐ Yes ☐ No
Has the patient experienced any recent infection(s)? (tropical acute febrile illnesses, diarrheal illnesses) If yes, please provide details in the appropriate section ('Patient's Medical History').	☐ Yes ☐ No
Does the patient have any alcohol or substance abuse issues? If yes, please provide details in the appropriate section ('Patient's Medical History').	☐ Yes ☐ No
Does the patient have any of the following past or ongoing medical history? If yes, please provide details in the appropriate section ('Patient's Medical History').	

Diabetes	☐ Yes ☐ No
Hypertension	☐ Yes ☐ No
Glomerulonephritis	☐ Yes ☐ No
Other nephritis If yes, please specify:	☐ Yes ☐ No
Polycystic kidney disease	☐ Yes ☐ No
Other genetic kidney disease If yes, please specify:	☐ Yes ☐ No
Lupus	☐ Yes ☐ No
Other autoimmune disease If yes, please specify:	☐ Yes ☐ No
Other kidney injury If yes, please specify:	☐ Yes ☐ No
HIV infection	☐ Yes ☐ No
Urinary tract infections	☐ Yes ☐ No
Urinary tract obstruction	☐ Yes ☐ No
Heart failure	☐ Yes ☐ No
Chronic liver disease	☐ Yes ☐ No
Chronic lung disease	☐ Yes ☐ No
Anaemia (Hb<9 g/dL	☐ Yes ☐ No
Cancer treatment associated with a high risk of tumor lysis syndrome	☐ Yes ☐ No
Other If yes, please specify:	☐ Yes ☐ No

Patient's Medical History: Please provide any relevant medical history information including any pre-existing renal disorders prior to initiation of ROMVIMZA treatment (specifying start (diagnosis) and end dates, if available)	
Current (ongoing)	

Patient's Medical History: Please provide any relevant medical history information including any pre-existing renal disorders prior to initiation of ROMVIMZA treatment (specifying start (diagnosis) and end dates, if available)	
Previous	

Investigations: Please provide results of any relevant investigations (laboratory tests, physical examinations, imaging, etc.) from prior to, during and after the renal event(s) (including baseline results prior to ROMVIMZA initiation, if available)

Test / examination name	Was the test performed (Yes/No/Unknown)*	**Test / examination date**	**Test / examination result** (quantitative or qualitative)**	**Normal range** (if applicable)
Blood/serum cystatin C				
Blood creatine phosphokinase (CPK)				
Urine myoglobin				
Complete blood count (CBC)				
Blood urea nitrogen (BUN)				
Blood creatinine				
Blood glucose				
Blood calcium				
Blood potassium				
Blood phosphate				
Blood sodium				
Blood chloride				
Blood uric acid				
Blood alkaline phosphatase (ALP)				
Alanine aminotransferase (ALT)				
Aspartate aminotransferase (AST)				
Gamma-glutamyl transferase (GGT)				
Total bilirubin (TB)				
Direct (conjugated) bilirubin (DB)				
Thyroid tests				
Serum albumin				
Total serum protein				
Estimated glomerular filtration rate (eGFR)				
Urinalysis				
Urine albumin				
Electrocardiogram (ECG)				
Abdominal scan				

Investigations: Please provide results of any relevant investigations (laboratory tests, physical examinations, imaging, etc.) from prior to, during and after the renal event(s) (including baseline results prior to ROMVIMZA initiation, if available)				
Kidney biopsy				
Systemic Blood Pressure measurement				
Any other relevant test / examination (If done, please provide results in the 'Narrative' section.)				

*Please attach any relevant test/examination report. **Please describe in 'Narrative' section if abnormal.

Product information: Please list relevant concomitant medications and provide the following information – Please note all relevant medications the patient was taking at the time of the event(s) (including prescribed or over-the-counter medications, herbal products, supplements, and/or vitamins) and indicate for each medication whether it was suspect (i.e., whether it may have contributed to the renal event(s)) **Please attach any relevant concomitant medications report.**

	Product (brand name if known or generic)	**Suspect?** (Yes/No)	**Indication**	**Dose**	**Frequency**	**Form / Route**	**Start date**	**Stop date / ongoing**
1		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
2		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
3		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
4		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
5		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing
6		☐ Yes ☐ No					__/___/____	__/___/____ ☐ Ongoing

Narrative: Please describe the clinical course of the renal event(s)

ANNEX 5 PROTOCOLS FOR PROPOSED AND ONGOING STUDIES IN RMP PART IV

Not applicable

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Key messages of the additional risk minimisation measures

The educational programme is aimed at patients with TGCT prescribed ROMVIMZA, to highlight the important potential risk of embryo-foetal toxicity with a reminder that ROMVIMZA should not be used in pregnancy and of the need for effective contraception and regular pregnancy testing for women of childbearing potential.

The MAH shall ensure that in each Member State where ROMVIMZA is marketed, all healthcare professionals and patients who are expected to prescribe or use ROMVIMZA have access to/are provided with the following educational materials:

- Prescriber educational materials
- Patient information pack

Prescriber educational materials:

- Summary of product characteristics
- Healthcare professional guide:
    - 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.

The patient information pack:

- Package leaflet
- Patient card:
    - 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 immediately

The patient card will be integrated in the packaging and the content will be agreed as part of the labelling (Annex 3).

ANNEX 7 OTHER SUPPORTING DATA (INCLUDING REFERENCED MATERIAL)

List of References

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ANNEX 8 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

Not applicable

Signature Page for Vimseltinib EU RMP v0.7 - Clean

Approval Task	Wendy Huisman Consultant, EU, Qualified Person for Pharmacovigilance (EU- QPPV) Deciphera Pharmaceuticals, LLC 23-Jul-2025 19:30:33 GMT+0000

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Veeva Vault RIM Document ID Number DCC-PVG-000807