EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

24 February 2022
EMA/206916/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Kimmtrak

International non-proprietary name: tebentafusp

Procedure No. EMEA/H/C/004929/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

1L	first line
2L+	second line and greater
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
BOR	best overall response
CD	cluster of differentiation
CI	confidence interval
CM	cutaneous melanoma
Cmax	maximum observed concentration
CR	complete response
CRS	cytokine release syndrome
CTLA-4	cytotoxic T-lymphocyte associated antigen-4
DCO	data cutoff
DCR	disease control rate
DOR	duration of response
EMA	European Medicines Agency
ER	exposure-response
FAS	Full Analysis Set
FDA	Food and Drug Administration
gp100	glycoprotein 100
HLA	human leukocyte antigen
HR	hazard ratio
ICR	independent central review
IFN	interferon
IL-6	interleukin-6
IMCgp100	tebentafusp
ITT	Intent-to-treat
IV	intravenous(ly)

LDH	lactate dehydrogenase
LFT	liver function test
MinR	minor response
MoA	mechanism of action
mUM	metastatic uveal melanoma
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death-1
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	preferred term
RAS	Rash Analysis Set
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	serious adverse event
SD	stable disease
SmPC	Summary of Product Characteristics
SOC	system organ class
TCR	T cell receptor
TEAE	treatment-emergent adverse event
TMB	tumour mutational burden
ULN	upper limit of normal
UM	uveal melanoma
US	United States
USPI	United States Prescribing Information

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Immunocore Ireland Limited submitted on 23 July 2021 an application for marketing authorisation to the European Medicines Agency (EMA) for Kimmtrak, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 12 October 2017.

Kimmtrak was designated as an orphan medicinal product EU/3/21/2397 on 19.02.2021 in the following condition: Treatment of uveal melanoma.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Kimmtrak as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website:

https://www.ema.europa.eu/en/medicines/human/EPAR/Kimmtrak.

The applicant applied for the following indication:

Kimmtrak is indicated as monotherapy for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

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

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

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0366/2017 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

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

1.5. Applicant's request(s) for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New Active Substance

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

1.6. Scientific Advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	**Reference**	**SAWP co-ordinators**
13 October 2016	EMEA/H/SAH/067/1/2016/III	Dr Olli Tenhunen and Dr Kerstin Wickström

The Scientific Advice pertained to the following *quality and clinical* aspects:

- *Agreement with formulation change from frozen liquid to the lyophilised formulation after approximately one-half of the enrolment into the pivotal study*
- *Changes in excipients for delivery in the middle of the pivotal trial*
- *Demonstration of product comparability*
- *Product characterisation release and stability tests*
- *In-process control analysis to support production*
- *Shelf-life assignment*
- *Process performance qualification*
- *IMCgp100-202 Clinical Study Design*
- *Conduct of two interim analyses using a three-stage adaptive group sequential design*
- *As a supplemental analysis proposal to combine the results of the randomised, prospective control patient study with historical control data using a Bayesian approach to increase confidence in the outcome of the randomised trial*
- *Safety database*
- *Patient selection approaches*
- *Approach of an expanded access program as a mechanism to collect data in the setting of a conditional MAA*

1.7. Steps taken for the assessment of the product

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

Rapporteur: Sinan B. Sarac Co-Rapporteur: Alexandre Moreau

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Menno van der Elst

The application was received by the EMA on	23 July 2021
Accelerated Assessment procedure was agreed-upon by CHMP on	24 June 2021
The procedure started on	12 August 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	12 October 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	19 October 2021
In accordance with Article 6(3) of Regulation (EC) No 726/2004, the CHMP Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days	
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 October 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	9 November 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	18 December 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	13 January 2022
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	25 January 2022
The applicant submitted the responses to the CHMP List of Outstanding Issues on	01 February 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	10 February 2022
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Kimmtrak on	24 February 2022

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant applied for the following indication:

Kimmtrak is indicated as monotherapy for the treatment of human leukocyte antigen (HLA) A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Uveal melanoma is the most frequent primary intraocular malignancy of the adult eye (~85%; Patel, 2011; Maio, 2013). Uveal melanoma is a rare and highly malignant subset of melanoma, representing < 5% of all melanoma cases in the United States (US; McLaughlin, 2005). The incidence varies by geography, race, and age, ranging from 5.3 to 10.9 cases per million (Singh, 2011). In Europe, the incidence of UM follows a decreasing gradient from north-to-south, ranging from 2 to 8 per million population (Virgili et.al 2007). Despite its rarity (representing ~3% of melanoma cases, approximately 4000 new diagnoses globally per year, any stage), UM is the most frequent primary intraocular malignancy of the adult eye (~85%; Patel 2011; Singh et al, 2011).

2.1.3. Biologic features

Uveal melanoma arises exclusively from melanocytes of the uvea, and it is biologically, clinically, and genetically distinct from cutaneous melanoma (CM; Jager, 2020). BRAF and NRAS mutations dominate the landscape in CM, whereas mutations in guanine nucleotide binding protein, q polypeptide, and alpha 11 dominate in UM (Shoushtari, 2014). The mode of disease spread is distinct between the 2 diseases, with hematogenous spread being most common in UM while lymphatic predominates in CM. Moreover, UM has a highly immunosuppressive tumour microenvironment (Jager, 2020; Rothermel, 2016). Cutaneous melanoma has one of the highest tumour mutational burdens (TMB), whereas the TMB of UM is among the lowest of all cancers (Lee, 2019; Yarchoan, 2017). The low TMB in UM results in few neoantigens, which limits natural antitumour immunity (Violanti, 2019), making UM less sensitive to immune checkpoint inhibitors than CM.

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Uveal melanoma is a life-threatening disease with no effective therapy once it metastasizes. Despite local therapy (radiation and surgery), up to 50% of patients with UM develop systemic metastases, predominantly to the liver (~90% of patients) and less commonly to the lungs and bones (Nathan, 2015). Once patients develop metastatic UM (mUM), the prognosis and outcomes are dismal, with a median survival of ≤ 12 months (Rantala, 2019; Khoja, 2019). Over the past 40 years, there has been no significant improvement in survival for patients with mUM.

2.1.5. Management

In contrast to other melanomas, particularly cutaneous melanoma (CM), current treatment options for mUM are limited and have poor efficacy. Metastatic UM responds poorly to cytotoxic chemotherapy,

radiotherapy, and immunotherapy (Buder, 2013; Pereira, 2013). No systemic or local therapies are approved specifically for the treatment of mUM (Carvajal, 2014; Luke, 2013; Maio, 2013). Treatments introduced for CM over the past decade have not significantly benefited patients with UM, reflecting the distinct biology, genetics, and clinical course of UM. The standard of care for mUM is enrollment in a clinical trial (Carvajal, 2017). When clinical trials are not available, therapies for advanced CM are used.

Representative multicentre clinical studies or case series of at least 20 patients with mUM who received available therapies are summarised in Table 1. Studies with single-agent chemotherapy arms showed a median overall survival of approximately 10 months (Buder, 2013). Single agent immune checkpoint inhibitors exhibited median OS similar to that of cytotoxic therapy in mUM (~ 6-10 months). These data are generally consistent with a global meta-analysis that included > 900 patients in Phase 2 trials in mUM, demonstrating a median OS of approximately 9 months and 1-year OS rate of 43% across treatment modalities and lines of therapy in the metastatic setting (Khoja, 2019). In a meta-analysis of > 2400 first line (1L) mUM patients, median OS was about 12 months with a 1-year OS rate of 52% (Rantala, 2019). Although the combination of anti-CTLA-4 and anti-PD-1 has a numerically higher objective response rate (ORR), this combination has a 1-year OS rate similar to checkpoint monotherapy (Pelster, 2021; Piulats, 2021).

Table 1. Efficacy of Current Therapies for Patients with Metastatic Uveal Melanoma

Clinical Study [a]	N [b]	Median Prior Tx Lines (range)	LDH (%)	Response Criteria	ORR n (%)	Median OS (months)	1-yr OS rate (%)	Median PFS (months)
Khoja, 2019	912	(0->3)	NR	Multiple	NR	8.9 (IT) [e] 9.2 (CT) [e]	43	2.8 (IT) [e] 2.6 (CT) [e]
Rantala, 2019	2494	1 (NR)	NR	NR	NR	12.8	52	NR
Single-agent chemotherapy								
Buder, 2013	768	(0-8)	NR	WHO/ RECIST	34 (4.4)	9.3	NR	NR
Anti-CTLA-4 (ipilimumab) monotherapy								
Zimmer, 2015	53	1 (0->3)	NR	RECIST	0	6.8	22	2.8
Luke, 2013	39	1 (0-5)	63	irRECIST	2 (5.1)	9.6	45 [c]	NR
Maio, 2013	82	NR (≥1)	45	irRC	4 (5.0)	6.0	31	3.6
Anti-PD-1 monotherapy								
Algazi, 2016	56	1 (0->4)	70	ir/RECIST [d]	2 (3.6)	7.6	45 [c]	2.6
Karydis, 2016	25	1 (0->3)	72	irRC	2 (8.0)	>225 days	28	91 days
Ipilimumab + nivolumab combination therapy								
Pelster, 2021 [f]	33	NR (0-4)	43	RECIST	6 (18.2)	19.1	56	5.5
Najjar, 2020	89	3 (0->4)	45	NR	10 (11.6)	15.0	NR	2.7
Piulats, 2021	52	0	37	RECIST	6 (11.5)	12.7	52	3.0

CT = chemotherapy; CLTA-4 = cytotoxic T-lymphocyte-associated antigen-4; ir = immune-related; irRC = immune-related Response Criteria; IT = immunotherapy; LDH = lactate dehydrogenase; NR = not reported; ORR = objective response rate; OS = overall survival; PD-1 = programmed cell death-1; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumours; Tx = treatment; UM = uveal melanoma; WHO = World Health Organization.

[a] Studies included if conducted in a multicentre approach and reporting efficacy in at least 20 patients.
[b] Number of UM patients who were evaluable for efficacy, as reported by the publication cited.
[c] OS/PFS rate estimated from published Kaplan-Meier curve.
[d] RECIST implemented with 1 or 2 responses reported following treatment beyond initial RECIST progression.
[e] Meta-analysis (Khoja, 2019) reported some efficacy parameters (median PFS, OS) based on therapy groups (IT or CT).
[f] Single institution study.

Unmet medical need

Uveal melanoma is a life-threatening disease with no effective therapy once it metastasizes. Despite local therapy (radiation and surgery), up to 50% of patients with UM develop systemic metastases, predominantly to the liver (~90% of patients) and less commonly to the lungs and bones (Nathan, 2015). Once patients develop metastatic UM (mUM), the prognosis and outcomes are dismal, with a median survival of ≤ 12 months (Rantala, 2019; Khoja, 2019). Over the past 40 years, there has been no significant improvement in survival for patients with mUM.

2.2. About the product

Tebentafusp is a bispecific protein therapeutic comprised of an affinity-enhanced soluble T cell receptor (TCR) domain fused to an anti-CD3 single-chain variable fragment (scFv). The TCR domain targets the glycoprotein 100 (gp100) peptide fragment (YLEPGPVTA) when presented by human leukocyte antigen (HLA)-A*02:01 on the cell surface. The targeted gp100 peptide is presented by a subset of the population that express a specific variant (serotype) of HLA-A2. This variant is carried by approximately 50% of the population in North American and Western European Populations (Middleton, 2003). Therefore, the anti-tumour activity of tebentafusp is restricted to patients with the HLA A*02:01 allele. An immune synapse is formed when the TCR targeting domain of tebentafusp binds to UM cells and the CD3 effector domain binds to polyclonal T cells. This immune synapse results in redirection, proliferation, and activation of polyclonal T cells regardless of their native TCR specificity. Tebentafusp-activated polyclonal T cells release inflammatory cytokines and cytolytic proteins, which result in direct lysis of UM tumour cells. In addition, tebentafusp-mediated lysis may prime an endogenous anti-tumour immune response via epitope spreading.

The applied indication is as monotherapy for the treatment of human leukocyte antigen (HLA) A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

Patients treated with Kimmtrak must have HLA-A*02:01 genotype determined by any validated HLA genotyping assay. The recommended dose of Kimmtrak is 20 micrograms on Day 1, 30 micrograms on Day 8, 68 micrograms on Day 15, and 68 micrograms once every week thereafter.

2.3. Type of application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the high unmet medical need in the claimed indication of metastatic uveal melanoma and the provided data for tebentafusp support that the medicinal product is of major interest from the point of view of public health. This conclusion is based on the available comparative data from a randomised clinical trial with a relevant comparator (investigators choice due to lack of approved therapies for the targeted patient population), which shows a statistically significant and clinically relevant improvement in OS. Moreover, there is a high unmet medical need in the proposed setting since approximately 50% of patients with newly diagnosed uveal melanoma will develop metastatic disease, which has a poor prognosis and a median OS of less than a year. This unmet need seems to be met by treatment with tebentafusp as the median OS in the tebentafusp arm is 21.7 months.

2.4. Quality aspects

2.4.1. Introduction

Kimmtrak finished product (100 micrograms/0.5 mL) is presented as concentrate for solution for infusion containing 0.2 mg/mL tebentafusp as active substance. Other ingredients are: citric acid monohydrate, di-sodium hydrogen phosphate, mannitol, trehalose, polysorbate 20 and water for injections.

The product is available as a sterile solution in a single-dose type 1 clear glass vial with a bromobutyl rubber stopper and an aluminium/plastic flip-off seal, containing 0.5 mL concentrate.

2.4.2. Active Substance

2.4.2.1. General information

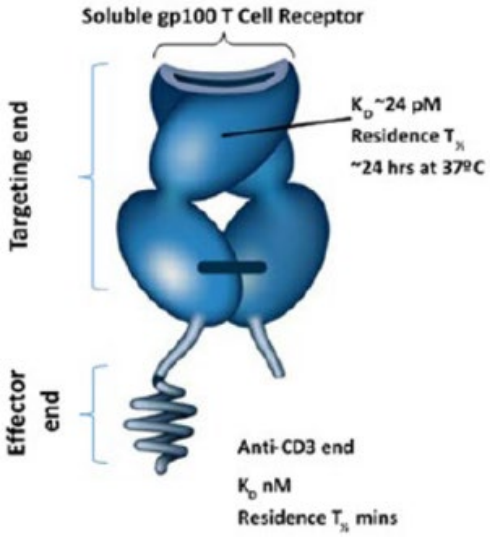
Tebentafusp (INN) is a bispecific fusion protein composed of a high-affinity soluble human T cell receptor (TCR), that binds glycoprotein 100 (gp100) melanoma antigen, fused to a single-chain variable fragment anti-CD3 (scFv) which activates local T cells via interaction with CD3 on the surface of T cells in the tumour environment. The activated T cells kill the target tumour cells directly and trigger an augmentation of a local tumour-directed immune response.

Tebentafusp is composed of an alpha chain and a beta chain subunit. The subunits are linked by an inter-chain disulfide bond. The beta subunit of the TCR is fused with a scFv domain of an anti-CD3 antibody via a short linker (the beta-scFv component is written as beta chain).

The alpha chain and the beta chain are composed of 195 and 500 amino acid residues, respectively.

Tebentafusp active substance is a heterodimeric protein manufactured by the refolding of alpha and beta chain polypeptides, which are produced in recombinant *Escherichia coli* (*E. coli*) as intracellular, insoluble inclusion bodies (IBs).

Figure 1. Tebentafusp structure and functional domains



2.4.2.2. Manufacture, characterisation and process controls

Description of manufacturing process and process controls

Manufacturing of the active substance is carried out by AGC Biologics A/S, Denmark. Testing sites and responsibilities have been included and provided. Master Cell bank (MCB) and working cell banks (WCB) have been established under GMP conditions. GMP compliance is confirmed for all relevant sites.

Tebentafusp is a heterodimeric protein manufactured by the refolding of alpha and beta chain polypeptides.

The commercial manufacturing process for tebentafusp consists of three phases (culture, recovery of the alpha and beta chain polypeptides, and, refolding and purification) and 11 steps.

The protein is manufactured in separate fermentations of recombinant *E. coli*, (1) for the alpha, and (2) for the beta-scFv fusion polypeptides. The separate chains are then combined and allowed to refold into the correct protein structure. The correctly folded protein is then purified via several chromatography steps.

The manufacturing is based on a seed lot system.

There are no process intermediates in the active substance manufacturing process. No reprocessing of the active substance is proposed. The active substance batch scale is properly defined. The batch numbering system is described in sufficient detail and allows adequate identification and appropriate traceability of the active substance batches.

The control strategy for the tebentafusp active substance manufacturing process was established in line with ICH Q11 guidance. The tebentafusp active substance manufacturing process is controlled by a number of process parameters with defined targets / limits, and a large number of in-process controls (IPCs) and in-process monitorings (IPMs) with defined acceptance criteria / expected ranges.

For each process step, process parameters have been evaluated and defined in relation to their impact on critical quality attributes (CQAs) (critical process parameters (CPPs) and process performance attributes (key process parameters (KPPs)) and a justification for the classification has been provided. Furthermore, a risk assessment of the tebentafusp active substance manufacturing process, Process Failure Mode and Effects Analysis (FMEA) has been performed.

Overall, the manufacturing process is considered adequately described and the applied process parameters and IPCs, as well as their ranges, and the control of starting materials are considered adequate to control the process and ensure formation of active substance of adequate and consistent quality.

Control of materials

The MCB and WCBs have been characterised according to current guideline. No evidence of microbial contamination was observed.

Stability of the cell banks and the genetic integrations were demonstrated through end of production (EOP) and Limit of In-Vitro Cell Age (LIVCA) testing. Purity testing, genetic characterisation and expression data performed on the LIVCA cell banks showed that extending the number of generations up to the defined LIVCA should not negatively impact the upstream manufacturing process.

Overall, the generation and characterisation of the MCBs, WCBs, EOP cell banks and LIVCA cell banks comply with the requirements set in the ICH Q5D guideline. Post commercial launch of tebentafusp, the MCB will be retested for viability every 10 years whereas the WCB stability monitoring will be performed routinely. The stability monitoring protocol is found adequate. The applicant also provided sufficient and information on the procedures to establish new MCBs and WCBs.

Process validation

Three consecutive commercial scale tebentafusp active substance validation batches have been manufactured according to a validation protocol and pre-defined process performance qualification (PPQ) acceptance criteria. The IPC and IPM results, the unit operating ranges during the three PPQ runs, and the PPQ batch release data confirm that the control strategy performs as intended to consistently manufacture active substance meeting predetermined quality attributes. All PPQ release data comply with the proposed active substance specification. Efficient clearance of process related impurities was consistently demonstrated in all three PPQ runs.

Sterilisation and cleaning of the equipment used for each of the process steps was validated. Shipping validation has been accomplished for the shipment of tebentafusp active substance from the active substance manufacturer to the finished product manufacturer. The ongoing process verification approach has been presented and is considered acceptable.

Overall, the approach taken to validate tebentafusp active substance manufacturing process is considered adequate. The process is demonstrated to perform consistently and tebentafusp active substance meets all the biochemical, functional and microbiological acceptance criteria.

Manufacturing process development

A number of comparability studies have been performed. Overall, comparability assessment is considered covered by the studies and analyses performed and comparability is overall supported by the data presented.

Method bridging studies have been performed where relevant and method bridging studies demonstrate that methods are comparable.

Overall, the approaches taken for process characterisation and development of the control strategy including acceptable ranges are adequately described and considered acceptable and compliant to ICH guideline Q11.

In conclusion, the process development, including development of the control strategy, is overall considered adequately described and justified. A large number of thorough comparability studies have been made, indicating product comparability.

Characterisation

Overall, the structural and physiochemical characterisation of tebentafusp active substance is considered comprehensive and sufficient.

An overview of the batches included in the different characterisation studies has been provided.

The characterisation studies include release testing using the proposed commercial release analytical methods and extended characterisation methods to assess the primary, secondary and higher order structure, as well as post-translational modifications. Physicochemical characteristics have also been sufficiently addressed. In addition, the biological and immunological characteristics have been sufficiently addressed.

2.4.2.3. Specification

Specifications

The active substance specification includes general tests (appearance (color and clarity), pH, osmolality), test for identity, purity and impurity tests for product-related impurities, test for process-related impurities, test for protein content, potency, as well as tests for safety (endotoxin and bioburden). In addition, tests for excipients are included on the specification.

Overall, the parameters included in the active substance specification are found adequate to control the quality of the tebentafusp active substance at release and shelf life.

The justification of the acceptance criteria for tebentafusp active substance is based on batch data from several active substance batches manufactured representing the commercial manufacturing process.

Overall the approach to setting the acceptance criteria is in line with ICH Q6B and the acceptance criteria are in general found appropriate.

Analytical procedures

The panel of methods used to assure the quality of the active substance is in accordance with ICH Q6B, Ph. Eur. 2031, and EMA/CHMP/BWP/532517/2008. The analytical procedures are in general described in sufficient detail. Information on the reference standard is included where relevant. The methods are considered suitable for their intended use.

The compendial analytical procedures are performed in accordance with the methods described in the relevant pharmacopoeia. Bioburden and Bacterial endotoxin test methods were qualified for use with the active substance, in-process samples and in-process buffers, demonstrating recovery of challenge organisms in the presence of the different samples.

The applicant has provided a summary of validation for the non-compendial methods. The non-compendial analytical methods have in general been sufficiently validated according to ICH Q2 to control active substance and finished product where relevant.

Batch Analysis

Batch data from several batches manufactured according to the proposed commercial manufacturing process has been provided. These batches include several PPQ batches and GMP batches used for method validation, stability studies and clinical and non-clinical studies.

The provided batch data demonstrates adequate batch-to-batch consistency.

Reference standard

A two-tiered reference material system has been established. The applicant provided batch information about the primary reference standard, the working reference standard and historical reference standards. Qualification includes active substance release methods as well as additional characterisation.

The applicant outlines the characterisation of future working reference standards which consists of active substance release tests and extended characterisation.

Container closure

Tebentafusp active substance is filled into sterile bottles and stored at the recommended temperature. The bottles and closures are supplied sterile. Based on the information provided the proposed container-closure is accepted.

2.4.2.4. Stability

The stability studies are designed in accordance with ICH Q5C Stability testing of biotechnological/biological products. Long-term stability studies are on-going for several tebentafusp active substance batches.

Trends were not observed at the intended storage temperature for any test. The stability samples are stored in a container closure system (CCS) that is representative of the commercial product. Based on the stability results the proposed shelf life for the active substance is acceptable when stored at the recommended storage conditions.

The post-approval stability protocol and stability commitment are acceptable.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Description of the product

The finished product is an aqueous solution of tebentafusp, which is clear, colourless to slightly yellowish.

The tebentafusp finished product is supplied as a sterile 0.2 mg/mL concentrate for solution for infusion in a single-dose vial. The other ingredients are: disodium hydrogen phosphate, citric acid monohydrate, mannitol, trehalose, polysorbate 20 and water for injections. All excipients are compendial. No overages are added to the tebentafusp finished product.

The CCS consists of a Type 1 glass vial with a bromobutyl, rubber stopper and a aluminum overseal with a blue flip-off cap. Vial and stopper are compliant with Ph. Eur 3.2.1 and 3.2.9, respectively.

Pharmaceutical development

Tebentafusp is a recombinant bispecific fusion protein solubilised at 0.20 mg/mL in a formulation buffer of disodium hydrogen phosphate, citric acid, trehalose, mannitol, polysorbate 20, pH 6.5.

Excipients include disodium hydrogen phosphate and citric acid monohydrate, mannitol and trehalose and polysorbate 20. No novel excipients or excipients of human or animal origin have been identified. Compatibility of active substance with the excipients is considered demonstrated.

Two different formulations were used to support the Phase 1/2 clinical studies. Formulation development included studies to support adjustments in active substance concentration, buffers, excipients, pH and surfactants and the changes considered justified.

The tebentafusp finished product manufacturing process consists of a thaw of tebentafusp bulk active substance, a compounding step, filtration, fill into glass vials, stoppering and capping before 100% visual inspection. No excipients are added in the manufacture of tebentafusp finished product. The finished product manufacturing process development has mainly consisted in increasing the batch size and adjustment of the fill volume. The IPCs have been adjusted during the development.

Analytical comparability is presented for all batches of the different development stages back to the primary reference. All batches are considered comparable across formulations and manufacturing sites.

The proposed sets of process and release controls are reasonable and similar to common industry practice.

The tebentafusp finished product does not contain preservatives or antioxidants. The finished product is sterile filtered using an aseptic filling process. Satisfactory microbiological testing and container closure an integrity testing (CCIT) is proposed as release and stability testing.

Container closure

The container closure system for the tebentafusp finished product consists of a Type 1 glass vial closed with a bromobutyl, rubber stopper and secured with an aluminum overseal with a plastic flip-off cap. The primary packaging components of the vial and stopper are of compendial quality. Compatibility of the primary packaging materials with the finished product has been demonstrated by long-term and accelerated stability data.

The secondary cardboard packaging protects the finished product from light as it is shown to be light sensitive.

Comprehensive extractables and leachables studies have been performed on the CCS. All of the identified extractables and leachables are below the defined threshold permitted daily exposure (PDE) values. The proposed container closure system is adequate for the finished product.

Compatibility

The compatibility of the tebentafusp finished product with the infusion set and bag has been evaluated. The product is stable in a range of commercially available saline infusion bags with the addition of albumin (human serum) with a PVC infusion set.

2.4.3.2. Manufacture of the product and process controls

Manufacture

GMP compliance is confirmed for all relevant sites.

The finished product manufacturing process is standard and consists of thawing of the active substance, pooling and mixing, sterile filtration, filling and capping, external washing of the vials, visual inspection and cold storage. The description is comprehensive and acceptable.

Process controls

The proposed controls are considered adequate.

Process validation

The PPQ was performed on several commercial scale batches. The PPQ protocol specifies relevant tests in addition to the controls defined in sections 3.2.P.3.3 and 3.2.P.3.4: thawing time of the active substance, mixing time during compounding, hold time study of compounded active substance, hold time of first filled vials, filter and line flush, homogeneity during filling, CCIT, capping pressure.

The submitted data demonstrate that the process is generally well controlled with little variation in the reported results.

Equipment, utilities and sterilising processes were adequately qualified prior to the PPQ. Ongoing process verification and annual product review principles are described and follow relevant guidelines.

2.4.3.3. Product specification

The finished product specification includes general tests (visual inspection, appearance (color and clarity), pH, osmolality, extractable volume), test for identity, purity and impurity tests for product related impurities, test for protein content, potency and test for excipients, as well as tests for safety (visible particles, subvisible particulates, endotoxin and test for sterility/CCIT).

Overall, the parameters included in the finished product specification are found adequate to control the quality of the tebentafusp finished product at release. The shelf-life specification has been provided and is clearly described and justified which tests are not to be performed during shelf-life.

The justification of the acceptance criteria for tebentafusp finished product is based on batch data from several finished product batches manufactured representing the commercial manufacturing process.

Overall, the approach to setting the acceptance criteria is in line with ICH Q6B.

Batch Analysis

Batch data are provided for several batches of the 0.2 mg/ml formulation using the proposed commercial process.

All results are compliant with established limits and are consistent across the batches with an acceptable batch-to-batch variation.

Characterisation of impurities

The tebentafusp finished product is manufactured by thawing of the active substance, pooling and homogenisation, sterile filtration and aseptic filling into finished product vials. No formulation takes place during finished product manufacturing and hence the formulation of the finished product is identical to the active substance formulation. No new impurities are generated during the finished product manufacturing process and all impurities observed in the finished product were characterised for the active substance.

The nitrosamine risk evaluation document has been provided and the nitrosamine risk is found negligible.

The risk assessment of elemental impurities contamination from the components used for manufacturing of the active substance and finished product, has been provided. The outcome of the risk assessment, indicate that all elemental impurities are below the permitted daily exposure limits and no additional routine process testing or controls are deemed necessary. The assumptions used in the risk assessment were confirmed by testing three separate batches in line with ICH Q3D for elemental impurities content. This is acceptable.

Analytical procedures

The suitability of the methods was demonstrated sufficiently. The analytical procedures used are the same as for active substance. The description and validation of these methods can be found in the active substance section.

Reference standards

The same reference standards used for the active substance analyses also apply to relevant analyses of finished product. Refer to the description of the reference standards in the active substance section.

2.4.3.4. Stability of the product

A shelf-life of 36 months when stored at 2°C to 8°C is claimed for the finished product. This is supported by the data presented.

An in-use time of 4 hours at room temperature (below 30°C) or 24 hours at 2°C to 8°C is proposed in saline infusion bags prepared with human albumin. This is supported by the data presented.

The protocols are in accordance with current guidelines.

Generally, no unusual trends are observed at 5°C even if some parameters display a high degree of scatter. Slight increases of impurities and decrease of purity is observed and this is confirmed by the data at accelerated conditions. At accelerated conditions a decrease is also seen in activity.

Furthermore, photostability and freeze/thaw studies have been conducted on the PPQ batches, showing that the tebentafusp finished product is light sensitive whereas, there is no measurable effect from up to 5 freeze/thaw cycles, including on container closure integrity.

Due to the high dilutions of samples in the in-use stability studies and therefore low concentration of the tebentafusp finished product for administration, specific methods were used for the in-use stability studies. The qualification of these methods is found acceptable.

Based on the stability data the shelf-life of 36 months when stored at 5°C ± 3°C claimed for the finished product is acceptable.

After opening and from a microbiological point of view, once opened, the medicinal product should be diluted and infused immediately. After preparation of solution for infusion, chemical and physical in-use stability has been demonstrated for 4 hours at room temperature (below 30°C) or 24 hours at 2 °C to 8 °C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

2.4.3.5. Adventitious agents

Non-viral agents.

No animal or human derived raw materials are used for the manufacture of tebentafusp. Microbial purity and absence of bacteriophages is confirmed for the cell banks. The manufacturers have provided statements confirming that active substance and finished product are manufactured under conditions minimizing the risk of any BSE/TSE carry over. Supplier statements confirming TSE/BSE safety for contact materials are also provided.

Testing is performed at appropriate stages during manufacture (IPC and/or release of active substance and finished product) for bioburden and endotoxin levels and for sterility.

The manufacture of finished product is performed under aseptic conditions in a controlled environment according to GMP. The risk of transmitting adventitious non-viral agents is considered negligible.

Viral agents and mycoplasma

As tebentafusp is manufactured in a prokaryotic recombinant *E. coli* cell line, the risk of propagating and transmitting adventitious viruses or mycoplasma to human beings from the product is negligible.

In conclusion, tebentafusp is considered safe for use with regards to lack of risk for transmission of adventitious agents.

2.4.3.6. GMO

N/A

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

The quality part of the dossier presented in support of the marketing authorisation application (MAA) for Kimmtrak finished product is of adequate quality. The control strategy for the tebentafusp active substance manufacturing process was established in line with ICH Q11 guidance. Overall, the manufacturing process is considered adequately described and the applied process parameters and IPCs, as well as their ranges, and the control of starting materials are considered adequate to control the process and ensure formation of active substance of adequate and consistent quality.

Overall, the approach taken to validate tebentafusp manufacturing process is considered adequate. The process is demonstrated to perform consistently and tebentafusp active substance meets all the biochemical, functional and microbiological acceptance criteria. The process development, including development of the control strategy, is overall considered adequately described and justified. A large number of thorough comparability studies have been made, confirming product comparability across sites, scales, and formulations.

Overall, the approach to setting the acceptance criteria for both active substance and finished product specifications is in line with ICH Q6B and the acceptance criteria are found appropriate.

The finished product manufacturing process is standard and consists of thawing of the active substance, pooling and mixing, sterile filtration, filling and capping, external washing of the vials, visual inspection and cold storage. Reprocessing is not performed. The description is comprehensive and acceptable. The submitted validation data demonstrate that the process is generally well controlled with little variation in the reported results. A shelf life of 36 months when stored at 2°C to 8°C is proposed for the finished product and this is supported by the data presented.

It is concluded that, from a quality point of view, Kimmtrak finished product can be approved.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The overall quality of Kimmtrak is considered acceptable when used in accordance with the conditions as defined in the SmPC.

The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The manufacturing process of the active substance is adequately described, controlled and validated. The active substance is well characterised and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated.

The quality of the finished product is controlled by adequate test methods and specifications. Adventitious agents' safety including TSE have been sufficiently assured.

2.4.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended some additional points for investigation.

2.5. Non-clinical aspects

2.5.1. Introduction

The TCR domain of tebentafusp recognises a glycoprotein 100 (gp100) peptide fragment (YLEPGPVTA), a melanocyte-lineage antigen expressed exclusively in normal melanocytes and overexpressed on melanocytic tumours, when presented by human leukocyte antigen (HLA)-A*02:01 on the cell surface. Therefore, the anti-tumour activity of tebentafusp is restricted to patients with the HLA-A*02:01 allele. An immune synapse is formed when the TCR targeting domain of tebentafusp binds to UM cells and the CD3 effector domain binds to polyclonal T cells. This immune synapse results in redirection, proliferation, and activation of polyclonal T cells regardless of their native TCR specificity. Tebentafusp-activated polyclonal T cells release inflammatory cytokines and cytolytic proteins, which result in direct lysis of UM tumour cells. In addition, tebentafusp-mediated lysis may prime an endogenous anti-tumour immune response via epitope spreading.

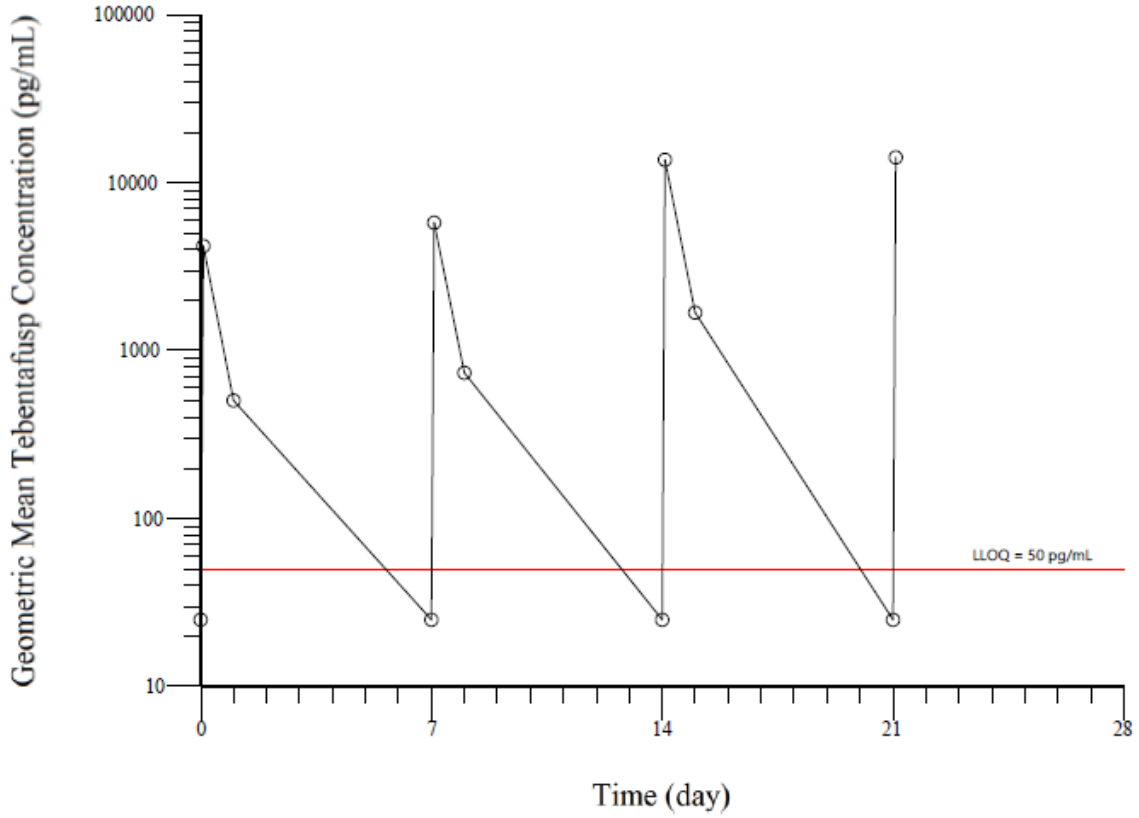
The tebentafusp soluble TCR targeting domain is highly specific for human gp100 peptide presented by human HLA-A*02:01. The tebentafusp anti-CD3 effector domain is specific for human CD3 and does not bind to or activate T cells from other species (Report IMC1029). Therefore, there are no relevant species in which tebentafusp pharmacology or toxicology can be tested, and the relevance of non-human pharmacokinetic (PK) studies is considered limited. Extensive *in vitro* analysis was thus performed to characterize the pharmacologic activity of tebentafusp and assess its potential for toxicity in patients. Only one Good Laboratory Practice (GLP)-compliant human tissue cross-reactivity study was included in the submission. Since safety is evaluated in clinical studies including the on-target adverse effects on normal melanocytes e.g. in skin, new *in vivo* non-clinical studies to look for off-target effects in animals not bearing the relevant targets appear redundant.

2.5.2. Pharmacology

Tebentafusp mode of action is well described and will be discussed further below. Tebentafusp demonstrates no reactivity against normal cells below 1 nM. This should be well above clinical exposure. However, towards normal melanocytes, tebentafusp show reactivity in the concentration range between 10 and 100 pM (0.01 -0.1 nM). In SmPC section 5.2, it is stated that C_{max} immediately after end of infusion is **4.2 – 13.7 ng/mL**, (below figure). Molecular weight is 77 kD. Hence, 1 nM corresponds to 77 ng/mL and e.g. 0.1 nM corresponds to 7.7 ng/mL providing a safety margin of 7.7/13.7 = 0.5. Therefore it is not surprising that the most common adverse drug reactions in patients treated with Kimmtrak were cytokine release syndrome (89 %) and rash (grouped term; 83 %), which included blister, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis bullous, dermatitis contact, dermatosis, drug eruption, eczema, eczema eyelids, erythema multiforme, exfoliative rash, interstitial granulomatous dermatitis, lichenification, lichenoid keratosis, palmar-plantar erythrodysaesthesia syndrome, papule, psoriasis, rash, rash erythematous, rash generalised, rash macular, rash maculo-papular, rash papular, rash pruritic, rash vesicular, seborrhoea, seborrhoeic

dermatitis, skin abrasion, skin erosion, skin exfoliation, skin irritation, skin plaque, solar dermatitis, toxic skin eruption, urticaria.

Figure 2 Tebentafusp Concentrations (Geometric Mean Profile Plot of Log Scale [Cycle 1])



Tebentafusp Concentrations (Geometric Mean Profile Plot of Log Scale [Cycle 1]). Noncompartmental PK parameters were not derived in study IMCgp100-202 due to the limited PK sample collections. However, serum tebentafusp concentrations were summarised after the first dose and third dose in Cycle 1. After dosing with 20 mcg on C1D1, geometric mean concentrations reached 4,200 pg/mL and were undetectable prior to the subsequent QW dose. After the first dose of 68 mcg on C1D15, the geometric mean tebentafusp concentrations reached 13700 pg/mL, were undetectable by pre-dose C2D1. Subsequent, Cmax mean concentrations ranged from 10000 to 20000 pg/mL indicating no further accumulation of tebentafusp after C1D15.

2.5.2.1. Primary pharmacodynamic studies

In vitro Pharmacology

By the use of surface plasmon resonance (BIAcore), it was shown that tebentafusp (also called IMCgp100) had very high affinity for the target gp100 on human leucocyte antigen (HLA-A*02:01). K_D was 24 pM and t½ 27 hours as determined from 5 different batches of tebentafusp (Report IMC1022). In a similar manner the K_D for CD3 was determined to 38 nM with a t½ of 8.4 minutes, a K_D three orders of magnitude lower than for gp100. The bifunctional assay showed KD of 37 nM and half-life of 11 minutes, hence the binding characteristics towards CD3 is the limiting factor of T-cell activation. Nevertheless, cellular functional assays show that tebentafusp activate T-cells at pM levels (IMC1014).

Tebentafusp selectivity towards other subtypes of gp100 was evaluated using the Octet biosensor system (Report IMC1040). While the half-life was highest for the target subtype, other subtypes showed half-life in a similar order of magnitude e.g. A*02:05 (71% of subtype 1) and A*02:02 (68% of subtype 1). *In vitro* cellular assay showed that tebentafusp was four times less potent in T-cell

activation through A*02:02 than A*02:01 (Report 1061). Other subtypes showed lower or no T-cell activation compared to A*02:01. The potential clinical relevance and implications of showing T-cell activation through A*02:02 is considered low as it is very rare in the Western population.

In functional cellular assays using CM, UM and artificially HLA-A*02:01 transduced cell lines, potent T-cell activation was shown with EC50s in the pM range. T cell activation was determined by measuring IFNγ release, while T cell killing was determined by GrB release. Effector cells used in these studies were either PBMCs or purified CD8+ positive T cells from normal healthy donors (IMC1014, IMC1015, and IMC1061).

Several studies evaluated mode of action of tebentafusp in cell based functional assays.

Study IMC1014 indicate that tebentafusp induces engagement of non-tumour specific T cells with the target melanoma cell lines through detection of the early release cytokine IFNγ. Moreover, re-direction of non-tumour specific T cell by the IMCgp100 to recognise gp100 expressing melanoma cells results in killing of these target cells as measured by the release of Lactate Dehydrogenase (LDH) and the release of granzyme B. Granzyme B is a member of the Granzyme family of serine proteases which are located in the cytotoxic granules of cytotoxic T lymphocytes (CTL). Granzyme B is crucial for the rapid induction of target cell death by apoptosis via the activation of several caspases such as caspase-3 and caspase-7. Granzyme B can be considered a more direct measure of CTL killing than IFNγ as IFNγ secretion is not limited to cytolytic cells and is a marker of T cell activation only.

Study IMC1015 show pM level potency of tebentafusp against several melanoma cell lines using LDH release as endpoint.

Study IMC1016 show that tebentafusp induces caspase-3/7 release in a dose dependent manner. Caspase activity can be observed as early as 4 hours after contact of tebentafusp with the melanoma cell line, Mel526. Caspases are proteolytic enzymes that become activated during the process of apoptosis.

Study IMC1061 indicate that tebentafusp may be more potent against uveal melanoma than cutaneous melanoma by comparing IFNγ-response of uveal and cutane melanoma cells presenting similar levels of HLA-A*02:01.

Finally, study IMC1020 show that PBMCs in presence of tebentafusp are activated to release IFNγ, TNF-α, IL-2, IL-6 and MIP1β, when they engage with the HLA-A2+/gp100+ melanoma cell line MEL526.

Similar experiments were performed using PBMCs from cancer patients.

Study IMC1017 showed that PBMCs from both melanoma (stage 4) cancer patients are redirected in the presence of tebentafusp and their resultant activation can be measured through IFNγ and Granzyme B release. Potency of tebentafusp appeared to be similar to when using PBMCs from healthy donors (pM range).

Study IMC1046 describes the use of PBMCs obtained from patients enrolled in cohort 6 of the Phase I study of IMCgp100/01. These PBMCs were used as effector cells within *in vitro* experiments to examine the kinetics of redirected killing of gp100+/HLA-A*0201+ melanoma cells (Mel624) using a clinically relevant dose of tebentafusp (81 pM). The results show that patient PBMCs can be efficiently redirected to kill melanoma tumour cells. However, one donor showed efficient killing of target cells within 12 hours and continued until the end of the assay at 60 hours, whereas the other donor plateaued at a low level of killing after 10 hours. Naturally, tebentafusp is only indicated in HLA-A*02:01 positive patients as specified in the SmPC.

Study IMC1018 show that hydrocortisone can inhibit the T cell activation induced by high concentrations of tebentafusp in a dose dependent manner.

Study IMC1019 evaluated the specificity of tebentafusp towards gp100 and CD3 using soluble proteins to inhibit synapse formation. Soluble gp100 could completely inhibit T cell activation at highest concentrations tested with an IC_{50} of 0.3 nM. Soluble CD3 showed only partially inhibited T cell activation at the highest concentration (0.5 µM). Nevertheless, evidence of relevant tumour-targeting effect is shown in clinical trials.

Study IMC1027 indicate that the terminally differentiated CD8+ effector memory and central memory cells were the major responders to tebentafusp in the presence of gp100 presenting target cells. Naïve T cells exhibited an insignificant response.

Study IMC1045 describes the kinetics of killing exerted by PBMC, CD8+ and CD4+ T cells subpopulations (Total, Tem, Tcm, Temra and naïve T cells) when redirected against melanoma cells using tebentafusp. The kinetics of killing appear to depend on the effector cells used. In this assay, PBMC killing kinetics show a lag of 22 hours before apoptotic events start to appear, reaching a maximum around 48 h. This correlates in broad terms with timing of cytokine release syndrome in patients.

Furthermore, tebentafusp redirects CD4+ T cells as well as CD8+ T cells to kill gp100+ melanoma cells. Killing by tebentafusp-redirected CD4+ T cells appear to be delayed compared to CD8+ T cells but was still very efficient and potent in this study.

The different CD4+ and CD8+ T cells subpopulations showed different kinetics and efficiency of killing. In both CD4+ and CD8+ T cells, T effector subsets were the most efficient and fast killers.

Study 1047 show that T regulatory cells, when co-incubated with CD8+ T cells have no impact on the efficacy of tebentafusp.

Hence, the efficiency and velocity of tebentafusp in redirecting T cells towards killing gp100 expressing tumour cells very much depend on the status and profile of the T cell population in each patient at the time of treatment, although it appears that the Treg cell have limited negative impact on the sought effects of tebentafusp.

Study IMC1030 suggests that tebentafusp mediated T cell activation is dependent on the level of gp100 presentation on the surface of target cells. Significant activation of CD8+ T cells was observed at a concentration of peptide used to pulse T2 cells of 10^{-9} M corresponding to approximately 18 epitopes per cell. At lower concentrations of peptide used to pulse T2 cells, the level of T cell activation was low indicating a minimum threshold of antigen presentation is needed for robust T cell activation. applicant states that the melanoma cell lines used for functional assays exceeds these requirements and clinical trials show that gp100 is targeted in both uveal melanoma tumours and normal melanocytes *in vivo*.

Study IMC-MED-201-03 indicate that tremelimumab (an immune checkpoint blocker) may enhance the redirecting effect on T-cells of tebentafusp, however no statistical evaluation was presented to support this.

In vivo **Pharmacology**

One *in vivo* pharmacology study was included in the submission. In this study Beige/SCID mice were inoculated with the cutaneous melanoma cell line Mel526 mixed with human PBMC from healthy donors. Mice in group 3, 4, 5 and 6 were treated for 5 days with tebentafusp at varying dose levels. Group 7 was administered a control protein not binding to CD3. Group 1 was inoculated only with the melanoma cell line and group 2 with both the cell line and PBMC. Delay in tumour take and tumour

growth was observed for group 4 (0.04 mg/kg/day) and 5 (0.01 mg/kg/day). Dose-response appear to be bell shaped, since the two mid doses showed the highest degree of delay in tumour take and tumour growth. The dose of 0.01 mg/kg/day corresponds to a human equivalent dose of 0.8 µg/kg/day for 5 days. This could be compared to the maintenance dose of 68 µg/week in patients (for a 50 kg patient = 1.36 µg/kg/week), which is not far off the dose in mice. However, it should be noted that, a single dose PK study in C57BL/6 or SCID mice show higher serum concentrations at this active dose in the *in vivo* pharmacology study (0.01 mg/kg/day) than patients (C_{max} 4.2 -13.7 ng/mL), see Table 3.3.3. It should be noted that serum concentrations in mice were comparable to patients at the dose 0.001 mg/kg, a dose lower than the lowest dose included in the *in vivo* study, which is not anticipated to show significant beneficial effect.

2.5.2.2. Secondary pharmacodynamic studies

Since, tebentafusp is specific for human gp100 and CD3 with no affinity to e.g. monkey, rat or mice, secondary and safety pharmacology was evaluated using *in vitro* methods on human tissues and cells.. The engineered T cell receptor on tebentafusp is highly specific for gp100, however at higher concentration this selectivity is lost. Evaluation of potential off target tissues was performed using the functional readouts IFNγ and Granzyme B. The applicant has chosen a panel of normal human tissue cells targeting the main organ functions, that cannot be assessed in animal toxicology studies, to determine the potential reactivity of tebentafusp with these selected normal tissues (Reports IMC1001 to IMC1013). A limit of clinical relevance was set at 1 nM. Only astrocytes and as expected epidermal melanocytes showed activity at tebentafusp concentrations below 1 nM.

With regard to normal astrocytes, 1 out of five lots showed functional activity in presence of tebentafusp (IMC1001).

Tebentafusp showed reactivity towards normal melanocytes expressing gp100 using readouts of INFγ and Granzyme B in 5 out of 5 lots. Study IMC1012 showed a generally lower reactivity of tebentafusp for normal melanocytes than for a melanoma cell line. Two of the normal epidermal melanocyte lots reacted even stronger than the melanoma cell line in the Granzyme B assay (N10 and N13). This is also the case in study IMC1055 for IFNγ for N10. These findings correlate with the high incidence of adverse reactions in the skin of patients (SmPC).

Tebentafusp is apparently not showing alloreactivity (IMC1021, IMC1057) as shown by testing an expanded alloreactivity panel of human Class 1 HLA genotypes expected to be HLA-A*02:01-positive.

Studies IMC1023 (whole blood) and IMC1024 (platelets) show that tebentafusp is not interfering with CD3+ T cells or platelets in whole blood in the absence of target cells in peripheral blood leading to release of cytokines.

The immune check point inhibitors tremelimumab and durvalumab appeared not to enhance the effect of tebentafusp on T-cell activation using IFNγ as endpoint against normal melanocytes (IMC-MED-201-02) including the most sensitive lot N13. Moreover, the two immune check point inhibitors did not enhance cytokine release in whole blood administered in combinations with tebentafusp at clinically relevant concentrations (IMC-MED-201-01), except slightly in a few cases, which are not expected to significantly increase the already known risk of cytokine release syndrome in patients during treatment with tebentafusp.

A thorough efficacy and safety assessment was performed in order to assure similarity of potency and specificity between 7 different batches of tebentafusp including GMP batches of drug product (IMC1055). The assessment was performed in line with previous functional assays using cell lines, human tissue cells and whole blood with cytokines as end-points. All 7 lots of tebentafusp reacted in a

similar manner in all assays. In this report a direct comparison between a cutane melanoma cell line Mel624 and the normal epidermal melanocyte lot N10 was performed. It appears, that this time, the normal melanocyte cells show higher/similar reactivity in the presence of tebentafusp as compared to the cutaneous melanoma cell line.

An impurity of tebentafusp with less specificity was qualified by comparing a spiked formulation of tebentafusp (6.7 % impurity) with one or two reference batches in functional cellular assays. Furthermore, representative analysis of several batches of tebentafusp showed that only one batch had above 1% of this impurity (1.1%). Hence, these data may prepare a basis for a specification for the specific impurity but not the overall total purity. This issue is discussed in Module 3.

2.5.2.3. Safety pharmacology programme

Safety pharmacology studies were not conducted for tebentafusp. Tebentafusp is a human specific protein and does not bind proteins from nonhuman species. Therefore, there are no relevant species in which tebentafusp pharmacology or toxicology can be tested.

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interaction studies of tebentafusp were not conducted. Tebentafusp is a human specific protein and does not bind proteins from nonhuman species. Therefore, there are no relevant species in which tebentafusp pharmacology or toxicology can be tested.

Pharmacodynamic drug interactions have been evaluated in functional cellular assays with hydrocortisone and immune check point inhibitors tremelimumab and durvalumab (previous section).

2.5.3. Pharmacokinetics

Methods of Analysis

No toxicokinetic studies were undertaken with tebentafusp. Hence, no bioanalytical studies had to be conducted to GLP. One explorative PK study of tebentafusp in C57BL/6 mice were conducted using a bioanalytical method employing the electro-chemiluminescens (ECL) immunoassay format, with biotinylated HLA-A*02-gp100 antigen used to capture tebentafusp in serum samples. After incubation with the analyte, a goat anti-scFv antibody was used followed by detection with a SULFO-TAG™ conjugated donkey anti-goat antibody in order to be selective for the intact tebentafusp protein. The unit for the immunoassay was ng/mL. Method development, partial validation and sample analysis were carried out at York Bioanalytical Solutions, York, UK. LLOQ of the immune assay was later changed to 200 pg/mL due to challenges of sensitivity (validated range: 200-10000 pg/mL).

The remainder of the pharmacokinetic studies were using ^{3}H-labeled and the biodistribution study ^{125}I-labeled tebentafusp. The unit for the PK studies using ^{3}H-labeled tebentafusp was ng equivalents/g and for the biodistribution study using ^{125}I ng equivalents/g. Hence, radiochemical methods were used and were therefore not selective for the intact protein, although bioanalysis was considered state of the art.

Absorption

The pharmacokinetics of tebentafusp after single dose intravenous administration was evaluated in male C57BL/6 mice. One study used un-labelled tebentafusp (C85954, YCZ006, Report IMC1028) and one study 3H-labeled tebentafusp (IMCgp100 or 3H-IMCgp100). Hence, immunoassay could be compared to radiochemical analysis. The immunoassay appeared not to be as sensitive as the radiochemical method. Therefore, tebentafusp could only be detected out to 12 hours after dosing

(LLOQ = 200 pg/mL), when using immunoassay, whereas the radiochemical analysis could follow tebentafusp related radioactivity at similar dose levels out to 72 hours after dosing, see Table 2. The reported terminal half-lives reflect this discrepancy as the immunoassay report half-lives of 1.7 to 2.4 hours, whereas the radiochemical analysis report half-lives of 65.6 to 92.6 hours. It should be noted that the ^{3}H-label of tebentafusp can undergo renal reuptake as small peptides after tebentafusp degradation and may not reflect true half-life of tebentafusp. However, it is reassuring to see that AUCs were in a similar range when comparing the use of the two bioanalytical methods. The terminal half-life of tebentafusp in patients is reported to be 6-8 hours (SmPC) using a similar assay format as for the mouse study of unlabelled tebentafusp, but with LLOQ of 25 pg/mL (Pop PK Report). ^{3}H-labelled tebentafusp was also administered subcutaneously and showed bioavailability of 40% compared to intravenous administration at the same dose level of 0.05 mg/kg. Time for maximal serum concentration was 2 hours Cmax was 93.6 ng/mL. Across the dose range of 0.001 to 0.1, C_0 and AUC were dose proportional after intravenous administration in the mouse.

Single and repeat -dose pharmacokinetics was also evaluated in the *in vivo* pharmacology model of the SCID mouse at 0.01 mg/kg, the dose of the optimal pharmacological effect. When comparing half-life to single dose PK studies of un-labelled and ^{3}H-labelled tebentafusp, half-life of tebentafusp in the unlabelled study fits with $t_{½\alpha}$ and $t_{½\beta}$ correlates with the half-life reported for the ^{3}H-labelled tebentafusp. Hence, PK of tebentafusp in female SCID mice appear to behave similarly to male C57BL/6 mice. It should be mentioned that clearance was higher and AUC was lower after 5 days of repeat dosing and this was by the applicant attributed to possibly be due to ADAs, which however was not analysed for in this study (IM-CH-01-10).

Table 2. Comparison of PK parameters when using un-labelled and ^{3}H-labeled tebentafusp (IMC1028 and IM-CH-01-09)

IMCgp100									
Dose (mg/kg)	Mouse Strain	Dose Route	T_{max} (h)	C_0 (ng/mL)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	$t_{1/2}$ (h)	Ext.$^{+}$ (%)
0.001	C57BL/6	i.v.	-	19.6	-	53	55	2.4	3.5
0.01	C57BL/6	i.v.	-	192.8	-	464	469	1.8	1.1
0.1	C57BL/6	i.v.	-	2155	-	4942	4978	1.7	0.7
^{3}H-IMCgp100									
Dose (mg/kg)	Mouse Strain	Dose Route	$T_{max}$$^{\$}$ (h)	C_0 (ng equiv/g)	C_{max} (ng equiv/g)	AUC_{0-t} (ng equiv.h/g)	$AUC_{0-\infty}$ (ng equiv.h/g)	$t_{1/2}$ (h)	Ext.$^{+}$ (%)
0.005	C57BL/6	i.v.	-	70.8	-	282	393	92.6	27.5
0.05	C57BL/6	i.v.	-	721.6	-	2834	3356	65.6	15.5
0.05	C57BL/6	s.c.*	2.0	-	93.6	892	1337	65.6	33.0
0.05	HDD	i.v.	-	550.7	-	2432	2708	35.9	9.7

\+ % of AUC extrapolated to infinity, calculated as $(AUC_{0-\infty} - AUC_{0-t}) / AUC_{0-\infty} \times 100$ (ideally ≤ 20 %).
$ Median values quoted.
* Bioavailability of s.c. dosing based on total radioactivity was *ca.* 40 % ($AUC_{0-\infty}$ s.c. / $AUC_{0-\infty}$ i.v. x 100).

Distribution

Preclinical biodistribution studies using ^{125}I-radiolabeled tebentafusp and a non-gp100 binding protein as negative control administered to tumour-bearing severe combined immune deficiency (SCID) mice were conducted to establish potential non-specific tissue toxicity risks and tumour targeting proof of concept, see Figure 3.4.1. The biodistribution was carried out as both single and repeat dose (daily, over 5 days) studies (IM-CH-01-09, single dose and IM-CH-01-10, repeat-dose, GLP).

Preclinical biodistribution studies demonstrated:

- Tebentafusp was retained in the melanoma tumour for a significantly longer timeframe with a half-life of binding the tumour of approximately 24 hours, see Figure 3.
- Tebentafusp did not accumulate in the brain.
- Tebentafusp accumulation in the highly vascular organs such as heart, lungs, liver and kidney was rapidly cleared between 8 and 24 hours. Furthermore, this may represent residual circulating ^{125}I-radiolabeled tebentafusp as there was no flush step after exsanguination prior to analysis.
- Accumulation was observed in the thyroid, peaking between the 24 and 72 hours, and likely represents an accumulation of free ^{125}I. A similar observation was noted for the digestive tract (stomach, small intestine and colon), although smaller in magnitude, peaking at 24 hours before clearance at 48 hours. The original report also suggested this as an elimination route, however, this is unclear since it is widely reported in literature that gastric mucosa is a site where iodide naturally accumulates.
- There was little difference for biodistribution of ^{125}I-radiolabeled tebentafusp between single and daily repeat doses.

Figure 3. Radioactive concentration (%ID/g) in organs/tissues sampled after injection of ^{125}I-mTCR1 (tebentafusp) fusion protein to xenograft SCID mice (IM-CH-01-10)

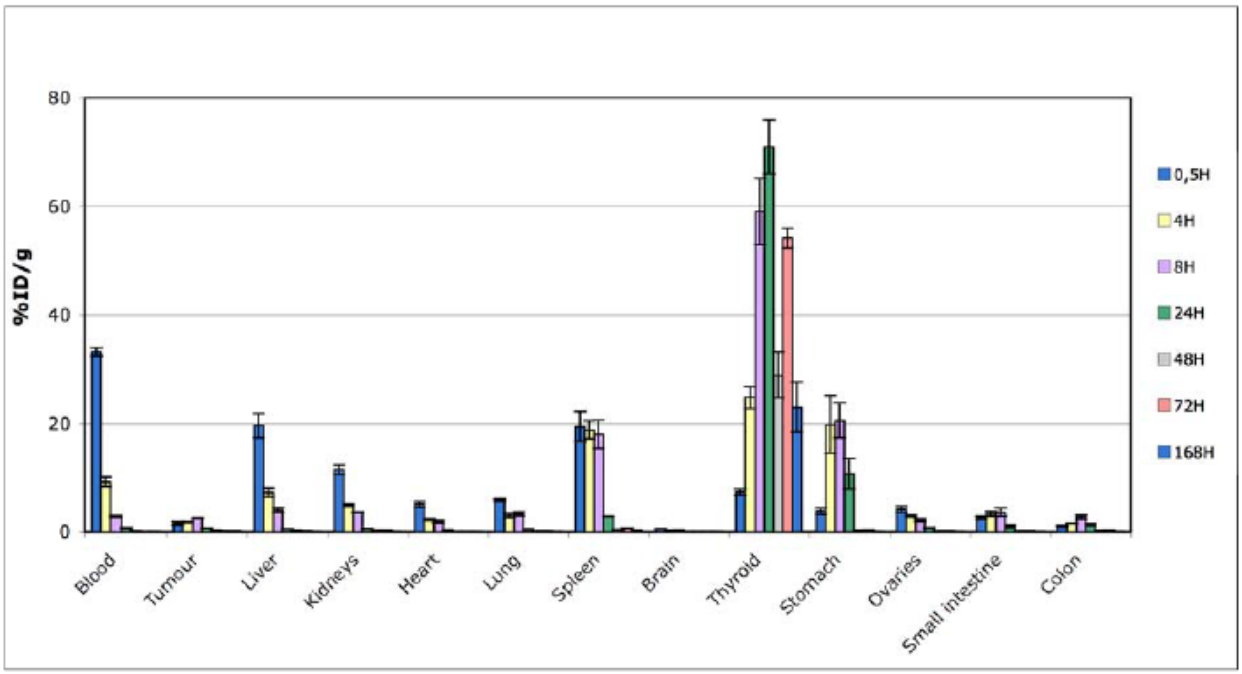


Figure 4. Radioactive concentration (%ID/g) in organs/tissues sampled after repeated injection of ^{125}I-tebentafusp fusion protein to xenograft SCID mice (IM-CH-01-10)

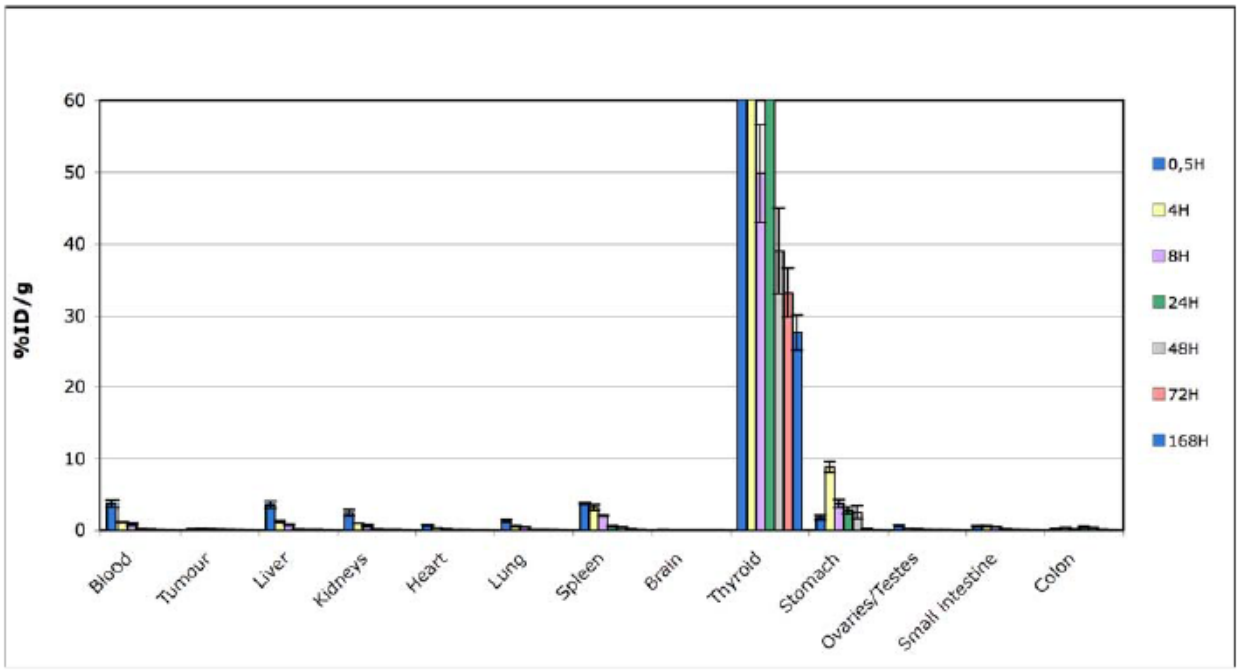


Table 3. Values of half-life for organs and tissues sampled following ^{125}I-tebentafusp injection (IM-CH-01-09)

Blood	Tumor	Liver	Kidney	Ovaries	Heart	Lungs	Spleen	Brain	Stomach	Small Intestine	Colon	Carcass
1.5h	20h	6h	9h	6h	11h	6h	9h	5.5h	22h	12h	14h	13h

Two distribution studies were conducted in tumour-bearing (Mel526) severe combined immune deficiency (SCID) mice. Mice were administered either ^{125}I-tebentafusp (^{125}I-mTCR1) or a non-gp100-binding fusion protein (^{125}I-mTCR2). Radioactivity was followed in blood, serum and a list of major organs including thyroid and brain for 168 hours. Radioactivity was similar between serum and blood indicating that tebentafusp is not binding to red cells. As expected, for both fusion proteins, ^{125}I accumulated in the thyroid. Unforeseen, tebentafusp accumulated in the intestinal system.

Metabolism

No specific studies were conducted to study tebentafusp metabolism as classical drug metabolic elimination does not represent an important clearance mechanism for large proteins (monoclonal antibodies (mAbs), fusion proteins, etc.).

Excretion

Tebentafusp biodistribution studies also looked for radioactivity in the urine and feces of the mice. Results indicated that there was less than 10% radioactivity of the injected dose found in feces over seven days, 8% of this found in the first 24 hours. Urine analysis showed approximately 90% radioactivity with most in the first 24 hours. The excreted material was not analyzed for the presence of intact tebentafusp or metabolites, and the radioactivity may represent elimination of liberated ^{125}I. It is widely reported that elimination of fusion proteins and mAbs occur via intracellular catabolism through receptor mediated endocytosis and subsequent degradation by lysosomes (Chen et al 2012, Ovacik and Lin 2018). Non-specific clearance through the liver via uptake by macrophages and endothelial cells and subsequent catabolism may also play a role, however this is not considered to be a significant elimination pathway for fusion proteins (Chen et al 2012).

Pharmacokinetic Drug Interactions

No specific drug–drug interactions studies were conducted for tebentafusp. Tebentafusp is a fusion protein and is not metabolised by Cytochrome P450 (CYP450) enzymes or transported by P-glycoprotein (Pgp) or related ABC membrane transporters. Cytokines produced by activated lymphocytes may impact the levels of Pgp and the activity of CYP450 enzymes (Harvey 2014).

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

No single dose toxicity studies were performed for tebentafusp. Tebentafusp is a human specific protein and does not bind proteins from nonhuman species. Therefore, there are no relevant species in which tebentafusp pharmacology or toxicology can be tested.

2.5.4.2. Repeat dose toxicity

No repeat dose toxicity studies were performed for tebentafusp. Tebentafusp is a human specific protein and does not bind proteins from nonhuman species. Therefore, there are no relevant species in which tebentafusp pharmacology or toxicology can be tested.

2.5.4.3. Genotoxicity

Genetic toxicology studies were not conducted for tebentafusp in accordance with the ICH S6 guidance.

2.5.4.4. Carcinogenicity

Carcinogenicity studies were not conducted for tebentafusp in accordance with ICH S6 and ICH S9 guidance.

2.5.4.5. Reproductive and developmental toxicity

No animal developmental and reproductive toxicity studies were performed for tebentafusp.

Due to the specificity for human targets, embryo-fetal development (EFD) studies cannot be conducted in nonclinical species. Therefore, a weight of evidence assessment was conducted to evaluate the risk of tebentafusp administration on pregnancy and embryo-fetal development. A literature search revealed that gp100 is expressed embryonically in melanocytes found in the skin, inner ear, and eyes by 7 weeks of gestation, and MHC Class I classical proteins (including HLA-A*02:01) and transporter-associated-with-antigen-processing (TAP) proteins required for presentation of antigen on the cell surface are expressed very early in embryonic development. In addition, CD3+T cells begin to populate the periphery and are capable of being activated by around 12 weeks of gestation.

2.5.4.6. Local Tolerance

Local tolerance studies were not conducted for tebentafusp. Tebentafusp is a human specific protein and does not bind proteins from nonhuman species. Therefore, there are no relevant species in which tebentafusp pharmacology or toxicology can be tested.

2.5.5. Ecotoxicity/environmental risk assessment

Tebentafusp is thought to undergo target-mediated clearance from the plasma via interaction with target HLA-A2/gp100 peptide on melanoma cells and CD3+ lymphocytes, followed by intracellular catabolism to its constituent amino acids. As such, elimination of intact biologically active protein is not expected. Under the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP) Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00 Corr 2) and the guidance in Questions and Answers on Guideline on the Environmental Risk Assessment for Human Use (EMA/CHMP/SWP/22609/2010), a fusion protein such as tebentafusp is unlikely to result in a significant risk to the environment and can be exempt from environmental fate and effects testing, as such biopharmaceuticals are considered unlikely to be released, or readily degrade resulting in minimal risk to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacology

Tebentafusp is specific for human targets on both ends (CD3 for the T cell and gp100, which is enriched in melanoma cells and normal melanocytes). Gp100 is presented by peptide–human leukocyte antigen (HLA) complexes. In this case HLA-A*02:01.

The pharmacology of tebentafusp appears to be well-understood. *In vitro* studies using cell lines of cutaneous melanomas and a few uveal melanomas were used along with typically PBMCs from healthy donors as a source of T cells show relevant effect at pM concentrations. However, tebentafusp also show reactivity towards normal melanocytes as clinical trials also show, adverse effects related to the skin occur in close to 90% of the patients. *In vitro* studies suggest some safety margin between the two cell types, however not convincing. When comparing serum concentrations in patients just after infusion with EC_{50} in normal melanocytes, the safety margin is below 1. All in all, *in vitro* proof of concept can be accepted. Specifically, this is by observing tebentafusp as a mediator of immune synapses and thereby by several immune cascade mechanisms inducing killing of gp100 presenting melanoma cell lines in the presence of PBMCs or isolated T cells from healthy human donors.

It is reassuring that it was possible to present a study of *in vivo* proof of concept although the cell line used is not a uveal melanoma cell line, but a cutaneous cell line.

Tebentafusp also show some T cell activation through the human leucocyte complex subtype A*02:02. The clinical relevance of this finding appears to be low.

The reactivity with astrocytes was deemed a low clinical risk because of i) lack of gp100 expression in these cell lots, ii) variable and infrequent nature of the reactivity observed in these studies, iii) the nM concentration at which reactivity was observed with this single astrocyte lot was above the anticipated clinical concentration range for tebentafusp, and iv) tebentafusp is a large biologic entity of approximately 76 kDa which might not be expected to penetrate the CNS. Dizziness and paresthesia was observed as adverse event in the clinical trials. However, these effects are not deemed related to CNS toxicity, but rather secondary to CRS and skin reactions.

Study IMC1018 showed that hydrocortisone can inhibit the T cell activation induced by high concentrations of tebentafusp in a dose dependent manner. Specific recommendations for corticosteroid rescue medication to relieve CRS and acute skin reactions are found in SmPC section 4.2.

PBMCs from two cancer patients were employed in a functional assay using a cutaneous melanoma cell line. In this study, the dynamics of the T cell activation was very different between the two patients.

Nevertheless, at least adverse effects of CRS and acute skin reactions occurred in approximately 90% of the patients. Hence, most patients can be expected to respond to the treatment. Studies of which types of T cells are capable of targeting the melanoma cells, indicated that the terminally differentiated $CD8^+$ effector memory and central memory cells were the major responders to tebentafusp in the presence of gp100 presenting target cells. Naïve T cells exhibited an insignificant response.

The applicant acknowledged that toxicities related to the skin are expected but stated that the data indicate that a therapeutic index of approximately 10 (1 versus 10 pM) was observed.

High incidence of AEs related to the skin is well documented in the clinical trials but appear to be manageable. The high incidence is therefore consistent with these *in vitro* data.

One *in vivo* animal (Beige/SCID) study was presented. Here, tebentafusp induced reduced tumour take and tumour growth compared to control, although by showing bell-shaped dose-response. Moreover, the exposure showing beneficial effects was higher as compared to patients. However, there is no doubt that effects (beneficial and adverse) are observed in clinical trials, hence the animal model (SCID mouse) is probably not predictive in terms of level of exposure providing reductions in tumour volume in patients.

Safety pharmacology was also evaluated in functional *in vitro* assays using cell types from different human tissues. The only tissues showing reactivity in the presence of tebentafusp was astrocytes and melanocytes. All 5 lots of melanocytes showed high reactivity as was expected, however one lot of astrocytes also showed some activity. This is not considered clinically relevant as no adverse effects were observed in the clinical trials, which could be related to CNS toxicity.

In the safety pharmacology studies using normal melanocytes, some lots appeared to induce even stronger reactivity of T cells in the presence of tebentafusp as compared to cutaneous melanoma cell lines. However, overall, *in vitro* data correlates with clinical data, as acute skin reactions are very common (>90%).

Pharmacokinetics

Single and repeat-dose pharmacokinetics was evaluated in both Beige/SCID mouse and two strains of normal mice using non-labelled and ^3H-labeled tebentafusp. It appears that the radiolabelled tebentafusp, by having lower LLOQ, show a very long terminal half-life. This could however be an artefact, since this is not observed in the clinical trials in which a more sensitive bioanalytical method was used.

Distribution studies were conducted in tumour bearing SCID mice using ^{125}I-tebentafusp. However, the distribution appeared to be more or less controlled by the ^{125}I-portion of the molecule. Therefore, these studies are considered of limited value. Unforeseen, tebentafusp accumulated in the intestinal system. However, this may be artifactual due to the iodine label, since iodine naturally accumulates here. With regard to accumulation in the tumour, this appeared not to be very much higher than in other organs at 72 hours, when the tumour/blood ratio is at its highest (2.762). Actually at 72 hours the highest concentrations were found in stomach and ratios above 1 was also found for liver, kidney, spleen and colon. Moreover, at 168 hours, radioactivity/g appear to be lower than in e.g. the spleen and less than double of the liver and blood. Hence, the wanted accumulation in the melanoma-tumour is not considered convincing from the data in these studies of ^{125}I-labelled tebentafusp. When reading through reports on the distribution studies, no clear comparison between the distribution data of the gp100 binding and the negative control fusion proteins could be found in terms of tumour take or major organs, except that it was stated that the negative control is cleared more slowly and that the amount in the tumour is half that of tebentafusp at 24 hours. A discussion of the differences and similarities between the tissue distribution of tebentafusp and the negative control protein not binding gp100 is therefore not considered fulfilling. All in all, the quantitative predictivity of the ^{125}I-labelled

proteins is questioned in these distribution studies, therefore these issues will not be further pursued. ^{125}I-labelling was used, since ^{14}C-labelling of tebentafusp was not considered feasible, as this would require that ^{14}C was supplied as nutrient (e.g. ^{14}C-glucose) during biosynthesis for the specific activity to become sufficiently high for use in distribution studies.

No specific studies were conducted to study tebentafusp metabolism as classical drug metabolic elimination does not represent an important clearance mechanism for large proteins. Since tebentafusp is a human fusion protein specific for human targets, classical drug metabolism studies are not deemed necessary. The following wording is presented in SmPC section 5.2: *The metabolic pathway of tebentafusp has not been characterised. Like other protein therapeutics, tebentafusp is expected to be degraded into small peptides and amino acids via catabolic pathways.*

Excretion of ^{125}I-labelled tebentafusp was evaluated in the biodistribution study (IM-CH-01-10). The value of the study in terms of excretion is considered limited as proteins are normally catabolised and it was not determined if the radioactivity represented intact, metabolised tebentafusp or free ^{125}iodine.

In SmPC section 5.2 Pharmacokinetics, the following wording is presented: *The excretion of tebentafusp is not fully characterised.* This is considered acceptable from a non-clinical point of view.

Cytokine release syndrome is the most important adverse reaction for tebentafusp. The following wording is presented in SmPC section 4.5:

No formal drug interaction studies have been performed with tebentafusp.

Initiation of KIMMTRAK treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug-drug interaction risk is during the first 24 hours of the first three doses of KIMMTRAK in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. In these patients, monitor for toxicity (e.g., warfarin) or drug concentrations (e.g., cyclosporine). Adjust the dose of the concomitant drug as needed.

Toxicology

A thorough weight of evidence evaluation of the of tebentafusp was presented. Tebentafusp's ability to directly affect embryo-fetal development requires that tebentafusp crosses the placenta and gains access to the fetus. The molecular weight of tebetafusp is 77 kDa, therefore, it is much too large to cross the placenta by diffusion. It also does not contain an Fc domain and, therefore, cannot bind to the neonatal Fc receptor (FcRn), which facilitates transfer of IgG molecules across the placenta, nor does it have domains that could bind to other placental transporters. Thus, tebentafusp would not be able to gain access to or elicit pharmacologic activity directly in the embryo/fetus. There is also no evidence that tebentafusp could interfere with implantation or the maintenance of pregnancy through its mechanism of action.

Based on the results of this weight of evidence assessment, tebentafusp would not be expected to adversely affect embryo-fetal development or the maintenance of pregnancy when administered during pregnancy. The reproductive toxicity potential is considered low, since tebentafusp is not likely to be able to cross the placenta. According to literature (Bowman, 2012) nonFc containing biopharmaceuticals can be secreted into breastmilk, however absorption over neonatal gut is considered unlikely due to proteolytic degradation.

An apparently well-designed tissue cross reactivity study was hampered by very poor sensitivity of the IHC method, which could not even detect gp100 in normal melanocytes. Therefore, this study unfortunately, is considered of limited value.

The active substance is a protein that undergoes catabolism to peptides and amino-acids in the body. Therefore, tebentafusp is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Tebentafusp is a bispecific fusion protein, comprised of a T cell receptor (TCR; targeting domain) fused to an antibody fragment targeting CD3 (cluster of differentiation 3; effector domain). The TCR end binds with high affinity to a gp100 peptide presented by human leukocyte antigen – A*02:01 (HLA-A*02:01) on the cell surface of uveal melanoma tumor cells, and the effector domain binds to the CD3 receptor on the polyclonal T cell. An immune synapse is formed when the TCR targeting domain of tebentafusp binds to uveal melanoma cells and the CD3 effector domain binds to polyclonal T cells. This immune synapse results in redirection and activation of polyclonal T cells regardless of their native TCR specificity. Tebentafusp-activated polyclonal T cells release inflammatory cytokines and cytolytic proteins, which result in direct lysis of uveal melanoma tumour cells. As tebentafusp is a human-specific protein, there are no relevant animal species in which non-clinical toxicology of tebentafusp could be tested. No carcinogenicity, genotoxicity, or developmental and reproductive toxicity studies have been conducted with tebentafusp. This is acceptable. In conclusion, from a non-clinical point of view, Kimmtrak is eligible for marketing authorisation.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

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

- **Tabular overview of clinical studies**

Study Number Study Status	Key Study Objectives	Study Design	Patient Population	Treatment Arm and Dosing Regimen	Patients Enrolled/ Treated (N)
IMCgp100-202 (Study 202) Enrollment completed, treatment and follow-up ongoing	Efficacy, safety, PK, and IM	Phase 3, open-label, randomized, controlled, multicenter	Previously untreated (1L) HLA-A*02:01-positive patients with advanced UM	Arm 1: Tebentafusp 20 mcg on C1D1, 30 mcg on C1D8, and 68 mcg on C1D15 and weekly thereafter Arm 2: Investigator's choice *Dacarbazine* (1000 mg/m^2 on D1 of each 21-day cycle) *Ipilimumab* (3 mg/kg on D1 of each 21-day cycle for maximum of 4 doses) *Pembrolizumab* (2 mg/kg up to maximum of 200 mg or 200 mg IV, where locally approved, on D1 of each 21-day cycle)	**252/245** **126/111** *7/7* *16/13* *103/91*
IMCgp100-102 (Study 102) Enrollment completed, treatment and follow-up ongoing	Safety, efficacy, PK, and IM	Phase 1/2, open-label, uncontrolled, multi-center	Previously treated (2L+) HLA-A*02:01-positive patients with advanced UM	Phase 1 dose-escalation cohorts Tebentafusp 20 mcg on C1D1, 30 mcg on C1D8, and the respective cohort dose below on C1D15 and weekly thereafter: *Cohort 1: 54 mcg* *Cohort 2: 64 mcg* *Cohort 3: 73 mcg* *Cohort 4: 68 mcg* Phase 2 dose-expansion cohort Tebentafusp 20 mcg on C1D1, 30 mcg on C1D8, and 68 mcg on C1D15 and weekly thereafter	**19/19** *3/3* *6/6* *4/4* *6/6* **127/127**
IMCgp100-01 (Study 01) Completed	Safety, PK, efficacy, and IM	Phase 1, FIH, open-label, uncontrolled, dose-finding	Previously treated HLA-A*02:01-positive patients with advanced melanoma	Arm 1 (weekly dosing) Tebentafusp by weight dose: *5 ng/kg* *15 ng/kg* *45 ng/kg* *135 ng/kg* *270 ng/kg* *405 ng/kg* *600 ng/kg* *900 ng/kg* Tebentafusp flat dose: *20 mcg intra-patient dose escalation* *30 mcg intra-patient dose escalation* *50 mcg*	**66/66** *3/3* *3/3* *3/3* *3/3* *3/3* *6/6* *20/20* *4/4* *7/7* *3/3* *11/11*

2.6.2. Clinical pharmacology

Tebentafusp (also known as IMCgp100) is a 77 kDa bispecific protein comprised of an affinity-enhanced soluble T cell receptor domain fused to an anti-cluster of differentiation 3 single-chain variable fragment for treatment of unresectable or metastatic uveal melanoma. The recommended dose administered to patients intravenously is 20 mcg on Day 1, 30 mcg on Day 8, and 68 mcg on Day 15 and weekly thereafter. In clinical studies, tebentafusp was being developed in two formulations with different concentrations, 0.5 mg/mL and 0.2 mg/mL.

2.6.2.1. Pharmacokinetics

Methods

The concentrations of tebentafusp in human serum were determined using an indirect sandwich immunoassay on the Meso Scale Discovery platform. Immunogenicity was tested using a homogenous

bridging electrochemiluminescence method and a tiered approach for screening, confirmation and titre determination of ADAs against tebentafusp.

Concentration data from three tebentafusp studies (Study IMCgp100-01, IMCgp100-102 and IMCgp100-202) in patients with melanoma were described by a 2-compartment population PK model with intravenous input and linear clearance. Renal function and high titre ADA's were identified as significant covariates for CL. The population PK dataset contained 5642 measurable PK samples from 587 patients (ITT population). The number of BLQ values were 3592 out of 9235 concentration records. The BLQ data were retained in the dataset but excluded from model development.

Table 4.Population Pharmacokinetic Parameters

Parameter	Units	Estimate	Standard Error
CL	L/day	4.33	2.8
V_1	L	5.25	0.5
Q	L/day	11.4	3.1
V_2	L	470	79.9
eGFR ~ CL	mL/min/1.73m^2	3.32	1.4
ADA Titer ≥ 8192 ~ CL	-	46.2	8.5
Interindividual Variability	CV%		
CL		78.5	46.9
V_1		32.5	10.1
Q		40.9	7.3
V_2		174.2	13.5
Residual Error			
Additive	ng/mL	0.24	0.081

ADA = anti-drug antibody; CL = clearance; CV = coefficient of variation; eGFR = estimated glomerular filtration rate; Q = inter-compartmental clearance; V_1 = volume of distribution in the central compartment; V_2 = volume of distribution in the peripheral compartment

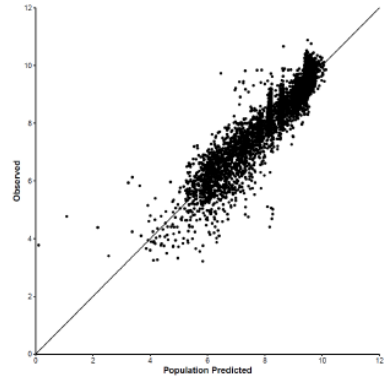
Clearance is estimated by the following equation: $CL = 4.33 * (EGFR/120)^{3.32} * 46.2^{ADA}$

Source: 515.lst

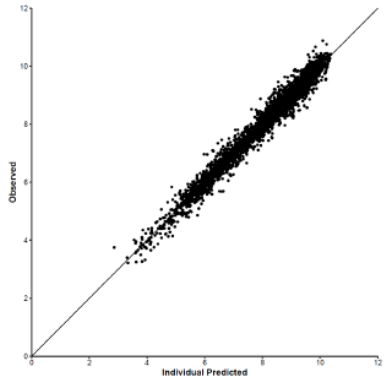
RSEs of the parameter estimates for the final model (Run #515) were low <10% except for V2 (79.9%). The IIV had CV% <15% for all parameters except for CL (46.9%). Eta Shrinkage was not given. The distribution (CIs) of parameter estimates were not given and the model was not validated e.g. by bootstrap. The final model showed large distributions of CWRES vs PRED.

Figure 5. Standard Goodness – of-Fit Plots of Final PK Model (Run #515)

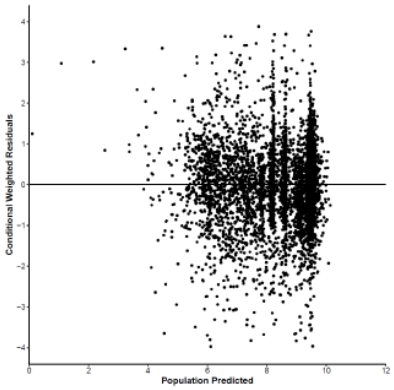
Population Predicted v Observed Concentration



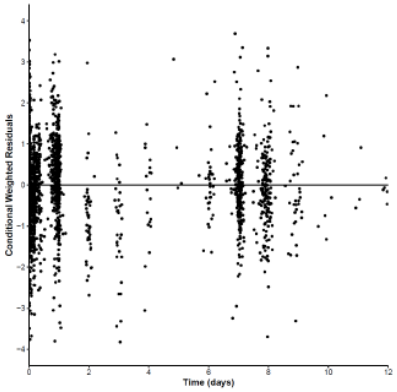
Individual Predicted v Observed Concentration



Conditional Weighted Residual v Population Predicted Concentration



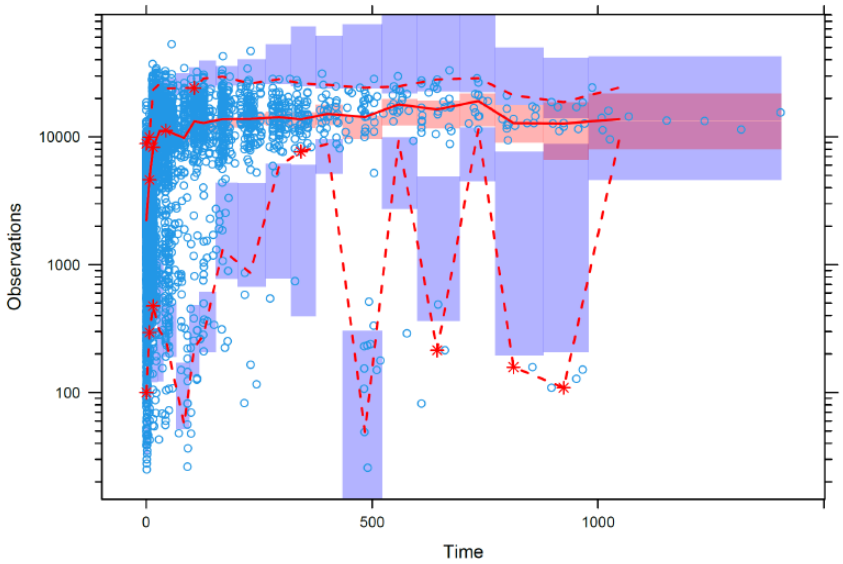
Conditional Weighted Residual v Time



"Observations" are tebentafusp concentrations. "Population predictions" are the concentrations predicted for individual's observations based on typical (population) values of the pharmacokinetic parameters, whereas "Individual predictions" are the concentrations predicted for individual's observations based on individual values of pharmacokinetic parameters. All the concentrations are in pg/mL unit and have been log-transformed. The circles are the pairs of observations and predictions or weighted residuals.

Source: IMCgp100_IntegratedPK_BasicGOF_515.pdf

Figure 6. Visual Predictive Check (Log Scale [Run # 515])



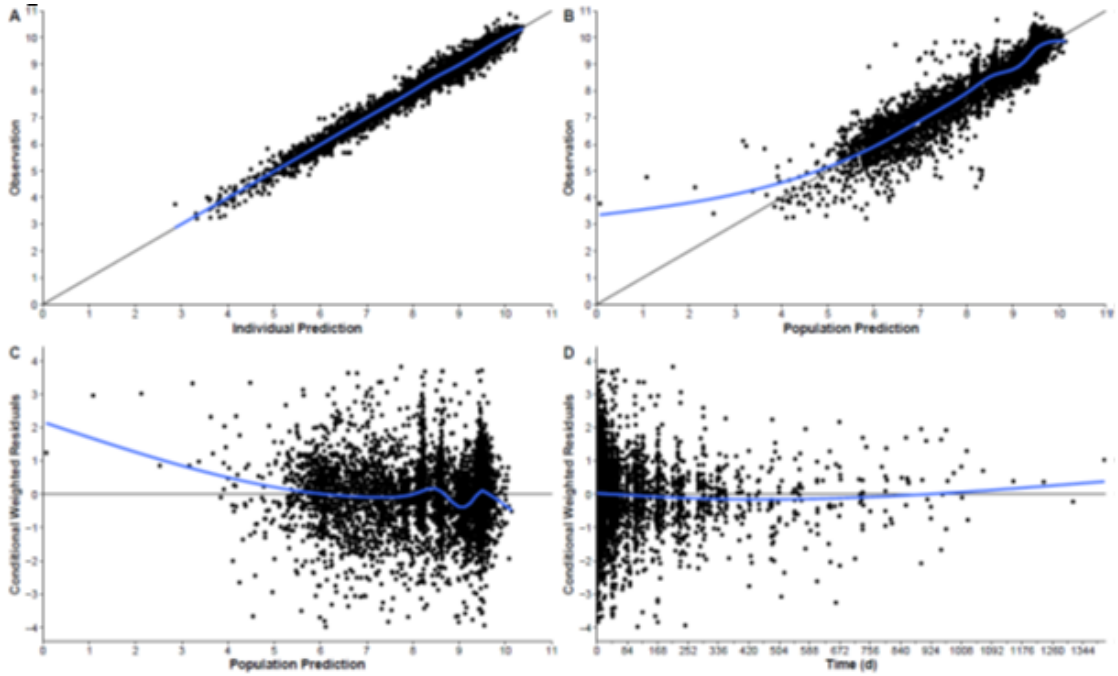
The blue circle represents the observed concentration. The solid and dashed lines represent the median and 2.5th and 97.5th percentiles of the observations. The shaded red and blue areas represent the 95% CI of the median and 2.5th and 97.5th percentiles predicted by the model, respectively.
Source: PsN_vpc_plots_515.pdf

The final PK model was updated by adding a temporal effect of ADA titre >8192 as a categorical variable to further explore the effect of ADA on clearance. High titre ADA was retained as a significant covariate in the updated model (run 618.lst). Parameter estimates and GoF plots were provided (See below table and Figures). Shrinkage was rather high for V2 and CL, 34.3% and 47.1%, respectively.

Parameter	Final Parameter Estimate	Bootstrap mean (95% CI)
CL	4.29	4.26 (4.23-4.29)
V_1	5.24	5.25 (5.24-5.25)
Q	11.4	11.41 (11.38-11.44)
V_2	477	499 (493-505)
GFR	3.46	3.52 (3.48-3.57)
ADA	32.9	41.1 (38.6-43.6)

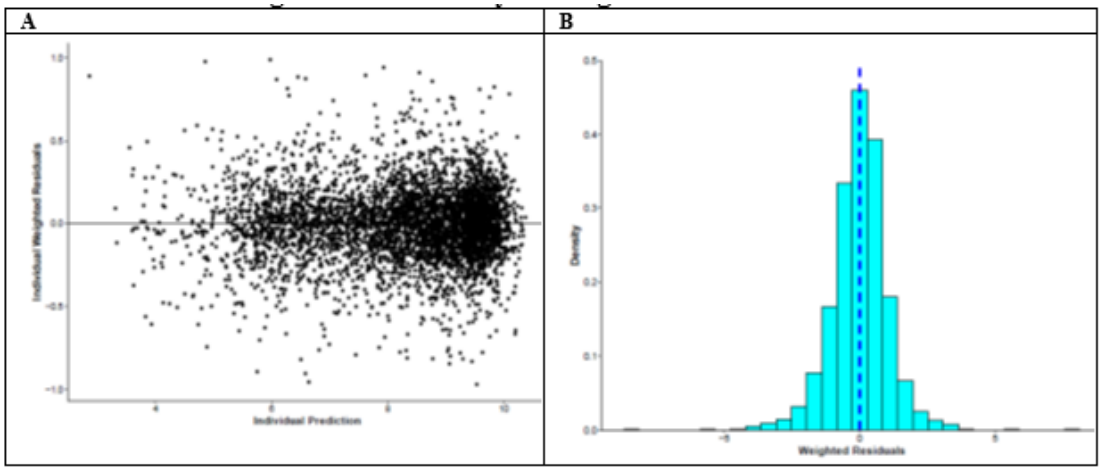
Parameter	η-Shrinkage
CL	47.1%
V_1	5.98%
Q	17.3%
V_2	34.3 %

Figure 7. Goodness -of-fit Plots for Final PK Model 618



CWRES = conditional weighted residual; DV = dependent variable; IPRED = individual prediction; PK = pharmacokinetics; PRED = population prediction.
Goodness-of-fit plots for final PK model 618 with [A] DV versus IPRED, [B] DV versus PRED, [C] CWRES versus PRED, and [D] CWRES versus time.

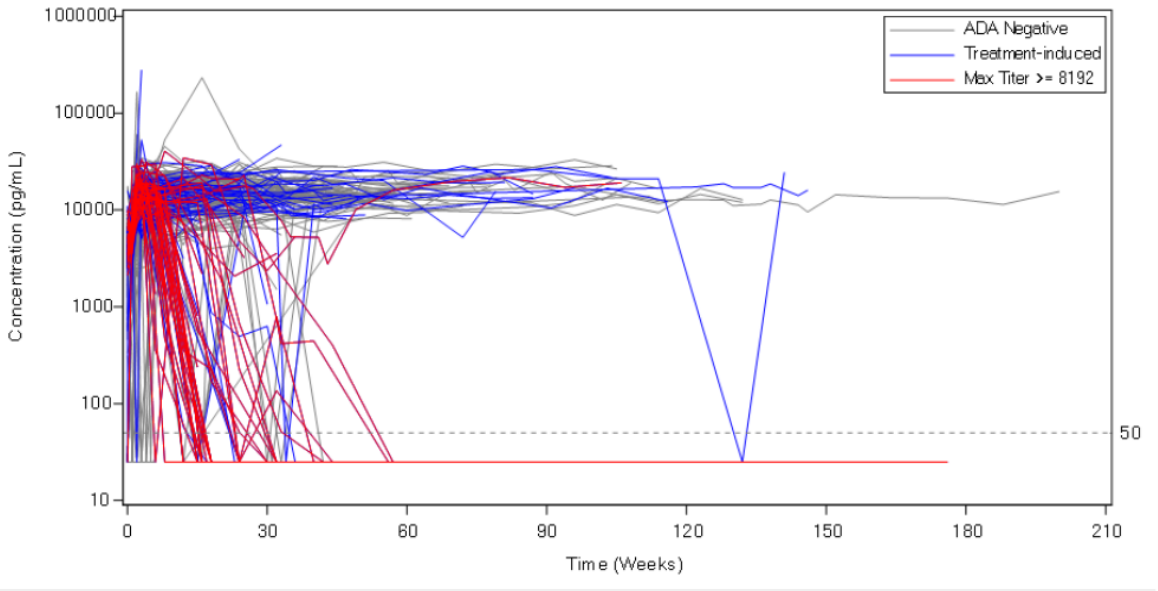
Figure 8. Goodness – of – fit Plots for Individual Weighted Residuals Versus Individual Predictions and Histogram of the Density of Weighted Residuals



Using the updated model (Run #618), additional VPCs stratified by study with expanded view of the first 60 days of treatment were provided to emphasize the intra-patient dose escalation and expected steady-state at the target dose (68 mcg) over the first several weeks of treatment (data not shown).

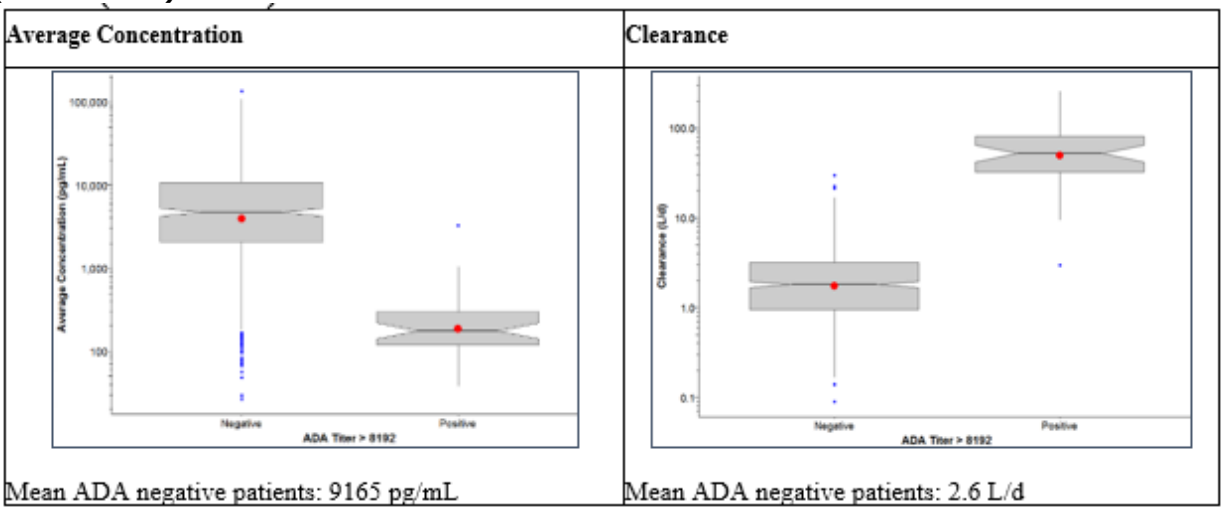
Analysis of tebentafusp Cmax stratified by ADA titre quartiles revealed that patients with ADA titre >1:8192 demonstrated persistent reduced peak concentrations of tebentafusp across studies 102 and 202 (Figures 39 and 6).

Figure 9. Maximum Serum Tebentafusp Concentration Stratified by ADA Status



ADA = anti-drug antibody; Max = maximum
Output File Ref: F_01; Source Listings: IADPC, IADIS

Figure 10. PopPK Model Simulations of Tebentafusp PK Parameters Stratified by ADA Status (Titre >8192)



There was no formal E-R modelling. The exposure response relations were evaluated by graphical analyses using Kaplan-Meier curves, box plots or scatter plots. Exposure expressed as Cmax and Cavg after the first (20 mcg) and third (50-68 mcg) doses in Cycle 1 were derived using the final Pop PK model. The effect of tebentafusp exposure were evaluated against Cmax and Cavg values or against exposure quartiles.

Absorption

Maximum plasma concentrations (Cmax) reached 4.2 ng/mL - 13.7 ng/mL immediately at the end of infusion (T = 0.5 hours) in study 202. The product is intended for intravenous administration and the bioavailability is therefore 100%.

Distribution

The estimated central volume of distribution of tebentafusp in melanoma patients was 5.25 L. This is derived from the Pop PK model as no dedicated clinical pharmacology studies were conducted.

Elimination

The excretion of tebentafusp is not fully characterised. It is expected tebentafusp as fusion protein to be degraded through receptor mediated endocytosis and subsequent degradation by lysosomes (Chen et al 2012, Ovacik and Lin 2018). The size-selective cut-off for glomerular filtration is approximately 60 kDa (Meibohm and Zhou 2012). While intact tebentafusp is not likely to be efficiently eliminated via renal CL given its size of 77 kDa, PK model covariate assessment demonstrated slightly reduced CL in the presence of reduced eGFR. This suggests passive glomerular filtration may also play a minor role in the elimination of tebentafusp.

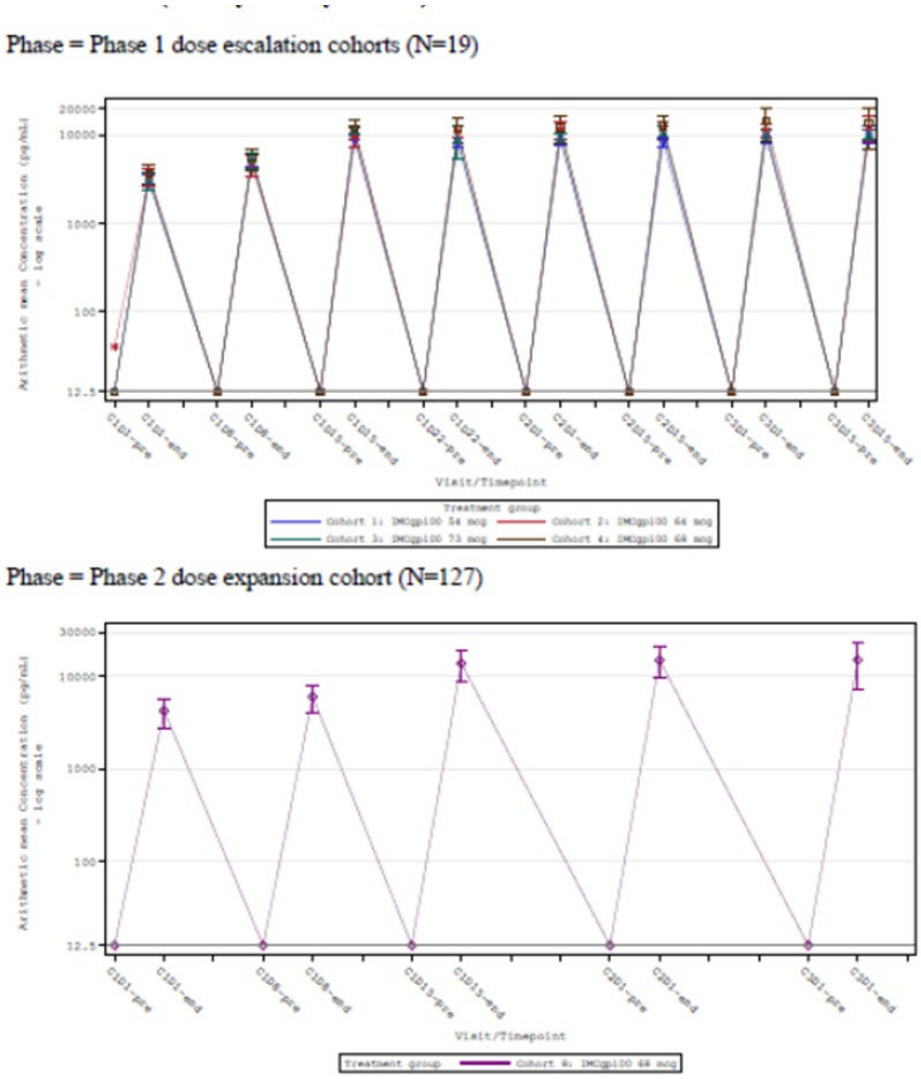
Following administration of tebentafusp in metastatic uveal melanoma patients, the estimated systemic clearance was 4.33 L/d, with a terminal half-life of 6-8 hours.

The metabolic pathway of tebentafusp has not been characterised. Protein (monoclonal antibodies (mAbs), fusion proteins, etc.) metabolic elimination does not represent an important clearance mechanism.

Dose proportionality and time dependencies

In study 102 the increase in geometric mean PK exposure (Cmax) of tebentafusp was approximately dose proportional between the 20mcg dose administered on C1D1 and the 68mcg dose administered on C1D15. From the dose escalation data, the observed terminal t1/2 was 6.8 to 7.5 hours. Subsequent mean Cmax values after C1D15 ranged from 10000 to 20000 pg/mL, and mean pre-dose concentrations were undetectable, indicating no accumulation with QW dosing at the 68mcg dose ***(Figure 11).***

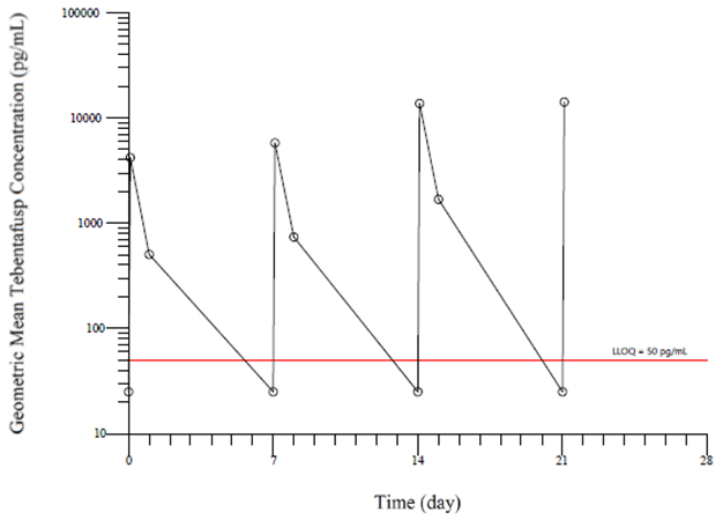
Figure 11. Tebentafusp Mean Concentration Versus Time Profile Cycle 1 Day 15 (Safety Analysis Set)



Top Panel: Phase 1 dose escalation cohorts (N=19)
Bottom Panel: Phase 2 dose expansion cohort (N=127)
Lower limit of quantification (LLOQ) = 25 pg/mL
Concentrations below the LLOQ were plotted as 12.5 pg/mL (half the LLOQ)
Source: IMCgp100-102 Clinical Study Report Figure 17

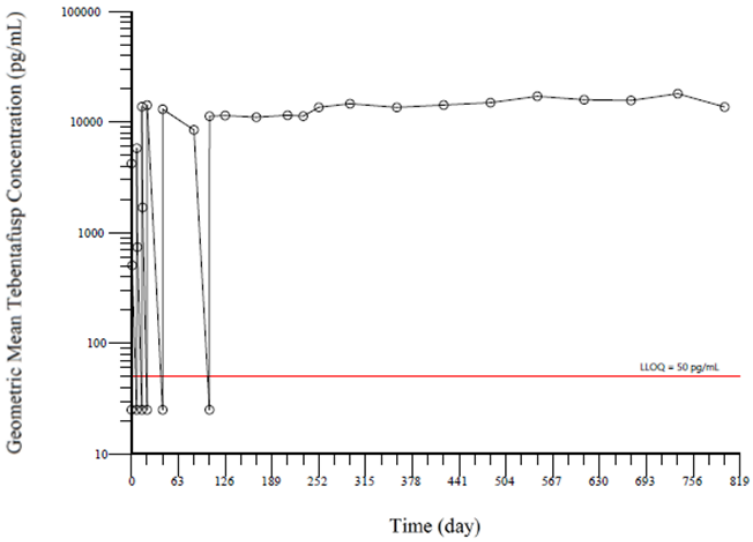
In study 202, after dosing with 20 mcg on C1D1, geometric mean concentrations reached 4,200 pg/mL and were undetectable prior to the subsequent QW dose. After the first dose of 68 mcg on C1D15, the geometric mean tebentafusp concentrations reached 13700 pg/mL but tebentafusp were undetectable by pre-dose C2D1. Subsequent, Cmax mean concentrations ranged from 10000 to 20000 pg/mL indicating no further accumulation of tebentafusp after C1D15 (**Figure *12*** and **Figure *13***).

Figure 12. Tebentafusp Concentrations (Geometric Mean Profile Plot of Log Scale [Cycle 1])



LLOQ = lower limit of quantification (50 pg/mL)
The nominal time values were set to the visit and time points to generate the x-axis time values. For time points where the geometric mean was not calculated due to a minimum value of 0, a value of half the LLOQ (25 pg/mL) was used for display purposes.
Source: IMCgp100-202 Clinical Study Report; Figure 11

Figure 13. Tebentafusp Concentrations (Geometric Mean Profile Plot of Log Scale [All Cycles])



LLOQ = lower limit of quantification (50 pg/mL)
The nominal time values were set to the visit and time points to generate the x-axis time values. For time points where the geometric mean was not calculated due to a minimum value of 0, a value of half the LLOQ (25 pg/mL) was used for display purposes.
Source: IMCgp100-202 Clinical Study Report; Figure 12.

The inter-individual variation in CL and Vd is around 80 and 30%, respectively. Intra-patient variability in tebentafusp Cmax values for patients who received at least 2 IV infusions at the 68 mcg target dose in Studies 102 and 202 was a mean %CV of 63.5% and 62.6% for all patients in Studies 102 and 202, respectively. Excluding patients with ADA titre >8192, the %CV was 45.5% across both studies while in patients with ADA titre >8192, the %CV for Cmax was 160% because high titre ADA contributed to higher clearance and therefore contributed to greater Cmax variability.

Special populations

No studies in special populations were conducted. A population PK analysis was used to identify potential significant covariates affecting tebentafusp PK. Only body weight and eGFR were identified as significant covariate on tebentafusp clearance in the presented final model.

Estimated tebentafusp CL slightly decreased (3.32 L/d) in patients with moderate renal impairment (eGFR ranging from 30 to 59 mL/min). High interpatient variability was observed (78 %CV) and CL values in renal impaired patients were essentially within the range observed in patients with normal renal function. No impact on safety or efficacy parameters was identified in patients with mild to moderate renal impairment and no dose adjustments are recommended. There is no information available in patients with severe renal impairment (eGFR less than 30 mL/min).

Tebentafusp is 77 kDa protein. The size cut-off for glomerular filtration being comprised between 60-70 kDa, tebentafusp renal excretion by glomerular filtration cannot be excluded which is in line with the pop PK model. Based on POP PK simulations showing tebentafusp exposure increased by roughly ten-fold, even larger increase in patients with severe renal impairment. Monitoring of AEs in patients with severe renal impairment should thus be included as part of the first PSUR.

Tebentafusp PK in subject with impaired hepatic function was not formally investigated in a study, nor in the population PK analysis. AST and ALT enzymes level did not modify tebentafusp average concentration or maximum concentration and this is adequately reflected in the SmPC. Population pharmacokinetic analysis indicated that there was no significant effect of race, weight (43 to 163 kg) and age (23 to 91 years) on tebentafusp clearance.

All assumptions on the pharmacokinetics in special populations are derived from the PopPK model.

Pharmacokinetic interaction studies

No drug interaction study was conducted and no information was presented other than the statement that risk of drug-drug-interactions is highest during the first 24 hours for patients receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index. The sponsor conducted a review of Studies 102 and 202 (in which CRS data were more comprehensively identified) and evaluated the potential impact of elevated cytokines on concomitant medications that are substrates for CYP enzymes reported to be suppressed by elevated cytokines (ie, CYP3A4, CYP2C9, and CYP1A2) using the rates of Grade 3 or 4 TEAEs, QTcF prolongation >500 msec and TEAEs leading to discontinuation and death. Twenty (5.1%) tebentafusp-treated mUM patients were identified as having received concomitant medications with narrow therapeutic index within a 2-week period of a CRS episode and there was no evidence of a cytokine-induced DDI interaction in these patients.

2.6.2.2. Pharmacodynamics

Mechanism of action

Tebentafusp is a bispecific monoclonal antibody recognizing a gp100-derived peptide target to redirect local T lymphocytes to kill gp100-positive target cells (e.g., melanoma tumour cells). The gp100-derived peptide is presented by a subset of the population that express a specific variant of the major histocompatibility complex class I known as HLA-A2. Glycoprotein 100 is only expressed in non-vital normal cells (melanocytes) and in tumours derived from these melanocytes.

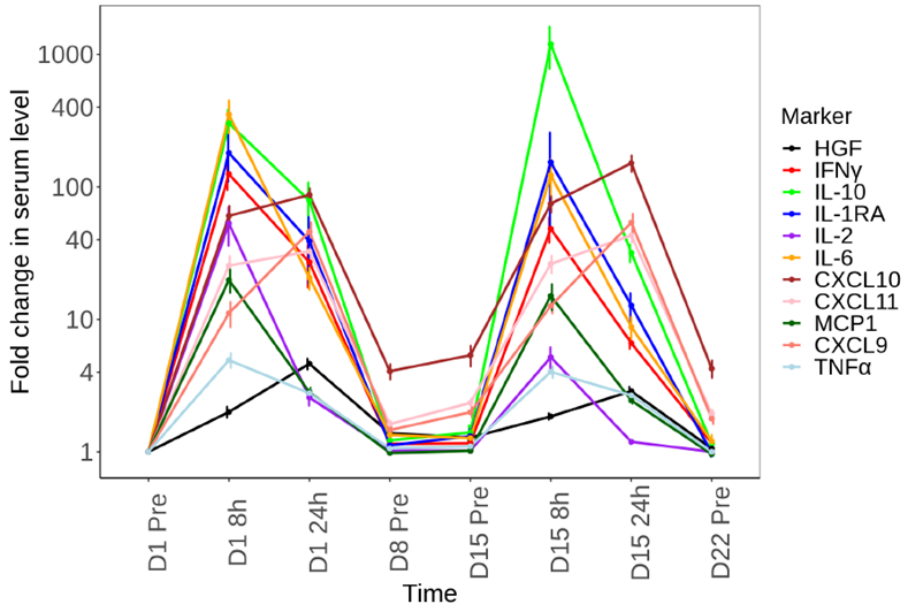
Tebentafusp is comprised of an affinity-enhanced soluble TCR domain fused to an anti-CD3 single-chain variable fragment. The TCR domain targets the gp100 peptide fragment (YLEPGPVTA) when presented by HLA-A*02:01 on the cell surface. An immune synapse is formed when the TCR targeting domain of tebentafusp binds to UM cells and the CD3 effector domain binds to polyclonal T cells. This

immune synapse results in redirection, proliferation, and activation of polyclonal T cells regardless of their native TCR specificity. Tebentafusp-activated polyclonal T cells release inflammatory cytokines and cytolytic proteins, which result in direct killing of UM tumour cells. In addition, tebentafusp-mediated killing may prime an endogenous anti-tumour immune response via epitope spreading.

Primary and Secondary pharmacology

Levels of 11 serum immune markers associated with inflammatory responses (IFN-γ, tumour necrosis factor [TNF]-α, IL-2, and IL-6), immune modulation (IL-10 and IL-1RA), and chemotaxis (C-X-C motif ligand [CXCL]9[MIG], CXCL10 [IP-10], CXCL11[I-TAC], hepatocyte growth factor (HGF), and monocyte chemoattractant protein-1 [MCP-1]) increased transiently, peaking at 8 to 24 hours post treatment. Biomarkers returned to baseline levels as measured in samples collected at Day 8, prior to patients receiving the second dose. The treatment-induced increase was seen again after the third dose, where the magnitude of increase was higher for certain markers, notably IL-10 and CXCL10 (**Figure *14***).

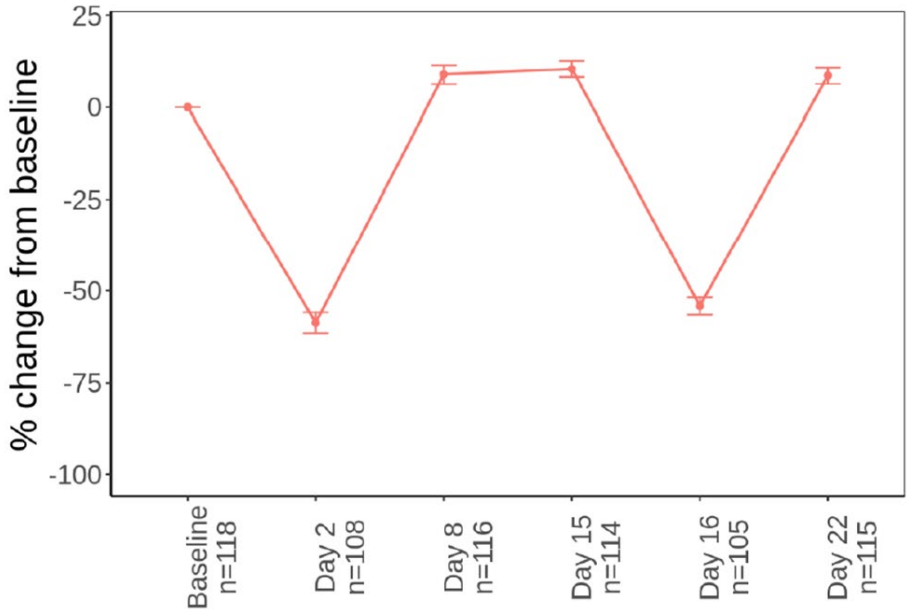
Figure 14. Change in Serum Cytokine Levels Over Time



CXCL = C-X-C motif Ligand; D = Day; HGF = hepatocyte growth factor; IL = interleukin; MCP = monocyte chemoattractant protein; TNF – tumor necrosis factor

Blood lymphocyte levels decreased by 60% within 24 hours of the first dose of tebentafusp and returned to baseline by Day 8 after the first dose (**Figure *15***). This pattern was repeated after the third dose of tebentafusp on Day 15.

Figure 15. Change in Blood Lymphocytes Over Time



In study 102, tebentafusp increased CD3 (3.2-fold), CD4 (2.1-fold), and CD8 (2.3-fold) T cell levels in the tumour by Day 16, consistent with T cell trafficking into the tumour microenvironment. The majority of biopsies (68%) had a ⩾ 1.5-fold increase in T cells by Day 16, after 3 doses of tebentafusp.

In gene expression analyses of paired baseline and on-treatment tumour biopsies collected at Day 16 the following messenger RNA (mRNA) levels increased after 3 doses of tebentafusp:

• Interferon alpha (type 1 IFN) and gamma (type 2 IFN) pathway genes (2- and 3-fold respectively)

• HLA class 1, transporter associated with antigen processing (TAP)1, TAP2 and Proteasome 20S Subunit Beta 8 (PSMB8) (2-fold).

• Cytotoxic CD8 genes, granzyme B and perforin, that are required for tumour cell killing (2- to 3-fold).

Expression levels of the following genes were reduced after 3 doses of tebentafusp:

• Tumour-specific melanoma markers GP100 and tyrosine related protein 1 (TYRP1),

• Tumour proliferation genes including marker of proliferation Ki67 (MKI67), Baculoviral IAP Repeat Containing 5 (BIRC5) and cyclin dependent kinase2 (CDK2).

Dose justification

Justification for the Phase 3 tebentafusp dose and regimen is based on clinical data from the dose escalation phases of study IMCgp100-01 and study IMCgp100-102 with supporting data from the expansion phase of study IMCgp100-102.

During Part 1 of study 01 the maximum tolerated dose (MTD) or recommended Phase 2 dose (RP2D) of tebentafusp when given weekly (QW) or daily was to be established. During Part 2, the MTD or RP2D for each regimen were then tested further in expanded patient groups. PK data gathered in Arm 1 indicated that the tebentafusp Cmax was directly proportional to absolute dose within a cohort. Heavier patients tended to have higher serum tebentafusp concentrations and a higher frequency of AEs. Flat doses, rather than weight-based doses, were incorporated for Arm 2 and during the dose-expansion phase. The 4-week treatment break for the QW dosing regimen was removed from Arm 1 as all key toxicities generally occurred within the first 3 QW doses and then decreased in both frequency

and severity over time. Given no clinically meaningful differences in safety or efficacy were identified between the QW and daily dosing regimens, and in light of the easier utility of a QW regimen, subsequent evaluation focused on weekly dosing. The emerging safety profile of tebentafusp suggested that CRS (and associated hypotension) was more likely to occur during the first 2 weeks, after which tachyphylaxis occurred. Therefore, as has been used for other T cell-engaging bispecifics, an intra-patient escalation regimen (IE; Arm 1) during Weeks 1 and 2 (i.e., 20 and 30 mcg, respectively) prior to dosing 50 mcg was selected as the preferred regimen to evaluate further in the subsequent development.

In phase 1 part of study 102 the MTD and/or the RP2D of tebentafusp in the QW RP2D-IE was to be identified, where part 2 then should estimate ORR, OS and PFS with this RP2D of tebentafusp in the RP2D-IE. During the Phase 1 portion of the study, the IE regimen, identified in study IMCgp100-01, was further optimised using a standard 3+3 dose-escalation design and evaluating higher Week 3 doses (54 to 73 mcg). Thus, all patients received fixed low doses of tebentafusp at C1D1 (20 mcg) and C1D8 (30 mcg) followed by an escalated cohort-specific QW dose administered at C1D15 and beyond. Dose escalation identified the following RP2D-IE: 20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter for further evaluation during the Phase 2 dose expansion.

Antidrug Antibody (ADA)

In IMCgp100-01, 3 of 78 patients (3.8%) developed ADA to tebentafusp. All 3 ADA-positive patients demonstrated a de novo treatment-induced ADA response. The onset times ranged from 58 to 218 days (median time to onset 15 weeks), and there was no specific association with dose level or dosing regimen. The 3 patients demonstrated persistent ADA responses that were apparent through the end of treatment.

In IMCgp100-102, 48 of 144 patients (33.3%) developed ADA to tebentafusp. Of the 48 patients with positive ADA responses, 40 patients (83.3%) had de novo treatment-induced ADA responses, with a median titre of 1:8192 (range, 1:4 to 1:4100000). Eight of 48 patients had treatment-boosted pre-existing ADA (median titre-fold change of 10-fold and range of 4- to 32768-fold). The median time to onset of detectable treatment-induced ADA responses was 9 weeks. After initial onset, treatment-induced ADA responses remained persistent in 87.5% of patients.

In IMCgp100-202, 63 of 220 evaluable patients (28.6%) developed ADA to tebentafusp. Of the 63 ADA-positive patients, 61 patients had treatment-induced ADA responses with a median titre of 1:2050 (range, 1:4 to 1:1048576). The median time to onset of detectable treatment-induced ADA responses was 6.3 weeks. The majority of patients (95.1%) demonstrated persistent ADA responses after onset.

Patients with low to moderate ADA titres had no meaningful change in tebentafusp Cavg or clearance. In IMCgp100-102 and IMCgp100-202, patients with an ADA titre > 1:8192 demonstrated reduced peak concentrations of tebentafusp and moderately increased clearance. The frequency and grade of hypersensitivity AEs in IMCgp100-102 and IMCgp100-202 did not increase with onset of ADA or magnitude of ADA titre. There was no association between ADA status and OS in IMCgp100-01, IMCgp100-102, and IMCgp100-202. High ADA titres (study IMCgp100-102: > 81920; study IMCgp100-202: > 24584) did not appear to impact OS. There was no meaningful association between tumour shrinkage and ADA status or titre.

Exposure-response analysis was conducted based on the pop PK model.

There was no clinically significant trend between PK exposure and overall survival (OS) or maximal change in tumour size from baseline, a surrogate of OS identified in Phase 2.

There was no association between PK exposure and toxicities including: acute skin reactions, rash, hypo/hyper-pigmentation or hepatoxicity.

There was no association between PK exposure and cytokine release syndrome or either baseline or on-treatment lymphocyte counts.

2.6.3. Discussion on clinical pharmacology

A validated indirect sandwich immunoassay method was used for determination of tebentafusp in human serum. Antibodies to tebentafusp in human serum samples were tested by a homogenous bridging electrochemiluminescence method using a tiered approach. A lack of parallelism was identified in undiluted ISR samples from Study 102. Additional dilution was applied during sample analysis to overcome this issue. The report for results of binding and neutralising ADA assessment in Study 202 should be provided post-authorisation as a recommendation (REC). A final NAb report will be submitted upon finalisation by end of March 2022.

The Pop PK of tebentafusp could be described by a 2-compartment model with linear elimination, interindividual variability on all structural terms and an additive error model to describe the residual variability. A high number of samples were BLQ (33%) and excluded from model development. The main PK parameters reported in the SmPC such as volume of distribution, clearance, exposures in special populations, exposures in populations with high ADA titre were all derived from the final Pop PK model.

No impact on safety or efficacy parameters were identified in patients with mild to moderate renal impairment and no dose adjustments are recommended. However, there are limited data from patients with moderate renal impairment and no available information from patients with severe renal impairment, so therefore it is recommended in the SmPC section 4.2 that dosing in patients with severe renal impairment should be done with caution and careful monitoring.

Tebentafusp PK in patients with hepatic impairment was not formally investigated due to lack of data completeness to comply with hepatic impairment Child Pugh classification (EMA guideline CPMP/EWP/2339/02). In place, the impact of AST/ALT levels on tebentafusp PK were assessed. The results showed no significant impact.

The exposure response relations were evaluated by graphical analyses using Kaplan-Meier curves, box plots or scatter plots.

Even though excretion and metabolic pathway of tebentafusp have not been characterised, the nature of the product allows some assumptions and makes this acceptable. It is widely reported that elimination of fusion proteins and mAbs occur via intracellular catabolism through receptor mediated endocytosis and subsequent degradation by lysosomes. Non-specific clearance through the liver via uptake by macrophages and endothelial cells and subsequent catabolism may also play a role, however this is not considered to be a significant elimination pathway for fusion proteins. Classical drug metabolic elimination does not represent an important clearance mechanism for large proteins (monoclonal antibodies (mAbs), fusion proteins, etc.).

The increase in geometric mean PK exposure (Cmax) of tebentafusp was approximately dose proportional between the 20mcg dose administered on C1D1 and the 68mcg dose administered on C1D15. Repeat-dose data from study the first in human study support dose proportionality. No Accumulation was observed thus not indicating time-dependency.

Studies 102 and 202 were conducted in the target population uveal melanoma patients. Study 01 was conducted in malignant melanoma patients, of whom ~20% were UM, thus there is no reason to assume there should be different PK described in this report compared to the target population although no specific clinical pharmacology studies were conducted. As no studies in special populations exist, all information is derived from the pop PK model. Based on these findings, only renal function

and the presence of high titre ADA were identified as relevant PK covariates. Patients with high titre ADA appear to have persistently diminished tebentafusp Cmax compared to patients with low titre ADA or ADA-negative status. Because ADA status or tebentafusp exposure were not associated with safety or efficacy of tebentafusp, there is no need to recommend monitoring of ADA or dose adjustment based on renal function. The lack of information on severe renal impairment is adequately reflected in the SmPC as well as the fact that no clinical study has been conducted on the topic. Age, weight, and race had no impact on the clearance of tebentafusp in patients with melanoma (see SmPC for more details).

Unlike many therapeutic small molecules, antibodies are not subject to metabolic drug-drug interactions and are not substrates of the multi-drug resistance (MDR) efflux pumps. Tebentafusp is a fusion protein and is not metabolised by Cytochrome P450 (CYP450) enzymes or transported by P-glycoprotein (Pgp) or related ABC membrane transporters. Thus, it is generally acceptable that no drug-drug-interaction studies are performed. However, cytokines produced by activated lymphocytes may impact the levels of Pgp and the activity of CYP450 enzymes, even though there was no evidence of a cytokine-induced DDI interaction in the studies conducted. The SmPC holds a precautionary statement, which is acceptable, stating that initiation of tebentafusp treatment causes transient release of cytokines that may suppress CYP450 enzymes. The highest drug-drug interaction risk is during the first 24 hours of the first three doses of tebentafusp in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index (see section 4.5 of the SmPC).

Tebentafusp mechanism of action is induction of cytokines due to T cell activation through T cell re-direction into tumours. As there were no PD studies, PD markers were assessed from study 102. Increase in cytokines and chemokines used as biomarkers, decrease in blood lymphocyte levels, increase in T cells and downregulation of melanoma genes in tumour biopsies support the proposed mechanism of action for tebentafusp.

Toxicity in study 01 led to the intra-patient escalation regimen. QW and IE is considered substantiated. The 73mcg in study 102 coursed liver enzyme elevations and 68mcg were identified as the MTD and was then chosen for maintenance dose for study 202. In light of the non-existent exposure-response relationship it is possible that a different dose would have achieved similar efficacy, but the dose finding is overall acceptable.

ADA frequencies in studies IMCgp100-102 (33%) and IMCgp100-202 (29%) were substantial with around one third of patients forming anti-drug-antibodies. The impact of ADA formation on the PK, safety and efficacy of tebentafusp was evaluated across studies IMCgp100-01, IMCgp100-102, and IMCgp100-202. There was reduced tebentafusp concentrations in patients with very high ADA titre, but no impact of ADA status or titre on either safety or efficacy has been reported.

2.6.4. Conclusions on clinical pharmacology

There were no dedicated pharmacology studies conducted, PK data are sparse, but obtained from the target population and thus representative for the patients to be treated. No exposure-response relationship could be identified. The pharmacokinetics of tebentafusp appear linear and dose-proportional over a dose range of 20 mcg to 68 mcg. Following weekly intravenous infusion in metastatic uveal melanoma patients, the maximum plasma concentrations (C_{max}) reached 4.2 ng/mL - 13.7 ng/mL immediately at the end of infusion (T = 0.5 hours). No accumulation was observed with a weekly dosing regimen at the target therapeutic doses. Tebentafusp displayed a volume of distribution comparable to blood volume (5.25 L). The excretion of tebentafusp is not fully characterised. Based on its molecular size that is close to the glomerular filtration size exclusion threshold, small amounts of tebentafusp may be excreted in the urine. Following administration of tebentafusp in metastatic uveal

melanoma patients the estimated systemic clearance was 4.29 L/d, with a terminal half-life of 6 to 8 hours. PopPK analysis indicated that there was no significant effect of weight, gender, race, and age on clearance. No impact on safety or efficacy parameters was identified in patients with mild to moderate renal impairment and no dose adjustments are recommended. There are limited data from patients with moderate renal impairment and there is no information available from patients with severe renal impairment. Population PK analyses demonstrated that baseline and on treatment ALT/AST elevations did not impact tebentafusp pharmacokinetics. No dose adjustments based on ALT/AST levels are recommended.

The report for results of binding and neutralising ADA assessment in Study 202 should be provided post-authorisation as a recommendation.

2.6.5. Clinical efficacy

Table 5. Overview of the Tebentafusp Clinical Development Program

Study Number Study Status	Study Design	Patient Population	Treatment	Patient Sample Size	Analysis Cutoff Dates
Pivotal Efficacy and Safety Study					
IMCgp100-202 (Study 202) Enrollment completed, treatment and follow-up ongoing	Phase 3, open-label, randomised, controlled, multi-centre	HLA-A*02:01-positive advanced UM previously untreated in the metastatic setting (1L)	Tebentafusp monotherapy Investigator's choice (ipilimumab, pembrolizumab, dacarbazine)	252/245 [a] 126/111 [a]	Interim/primary DCO date: 13Oct2020 Interim/primary CSR date: 13 April 2021 BLA DCO date: 13Oct2020
Supportive Efficacy and Safety Study					
IMCgp100-102 (Study 102) Enrollment completed, treatment and follow-up ongoing	Phase 1/2, open-label, uncontrolled, multi-centre	Previously treated (2L+) HLA-A*02:01-positive advanced UM	Tebentafusp monotherapy, dose escalation (Phase 1) Tebentafusp monotherapy, dose expansion (Phase 2)	19 127	Primary DCO date: 20Mar2020 Primary CSR date: 08Feb2021 BLA DCO date: 20Mar2020
Other Supportive Studies					
IMCgp100-01 (Study 01) Completed	Phase 1, FIH, open-label, uncontrolled, dose-finding	Previously treated HLA-A*02:01-positive advanced melanoma	Tebentafusp monotherapy	84 (n=19 with mUM)	Final DBL date: 11Aug2017 Final CSR date: 09Feb2018 BLA DCO date: 11Aug2017

Table 5. Overview of the Tebentafusp Clinical Development Program

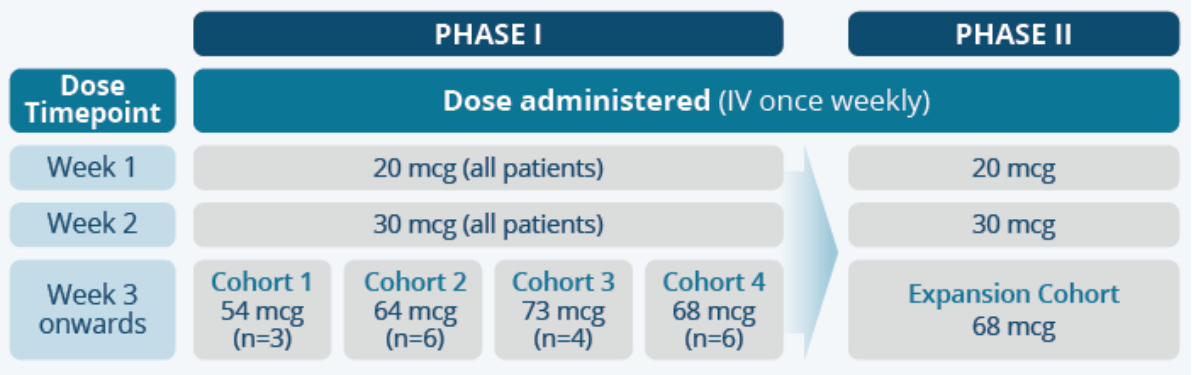
Study Number Study Status	Study Design	Patient Population	Treatment	Patient Sample Size	Analysis Cutoff Dates
IMCgp100-401 (Study 401) Completed	Phase 2, open-label, multi-centre, rollover	Previously treated HLA-A*02:01-positive advanced melanoma	Tebentafusp monotherapy	3	Final DBL date: 14May2019 Final CSR date: 13Nov2019 BLA DCO date: 14May2019
IMCgp100-201 (Study 201) Enrollment completed, treatment and follow-up ongoing	Phase 1b/2, open-label, uncontrolled, multi-centre	Previously treated unresectable stage III or metastatic stage IV CM	Tebentafusp monotherapy Tebentafusp + immunotherapy	27 85	No CSR BLA DCO date: 13Oct2020

1L = first line; 2L+ = second line and greater; BLA = Biologics License Application; CM = cutaneous melanoma; CSR = clinical study report; DBL = database lock; DCO = data cutoff; FIH = first-in-human; HLA = human leukocyte antigen; mUM = metastatic uveal melanoma; UM = uveal melanoma.

[a] Patients randomised/treated.

2.6.5.1. Dose response study

Figure 16. Study 102 Design



IV = intravenous(ly). Source: Module 5.3.5.2, Study 102 CSR, Figure 1.

Study 102 is an ongoing Phase 1/2, open-label study evaluating the safety and efficacy of tebentafusp using an intra-patient dose-escalation regimen in HLA-A*02:01-positive patients with previously treated mUM. The Phase 1 dose-escalation portion of the study further optimised the intra-patient escalation regimen from the first-in-human study (Study 01) to achieve greater exposure closer to those doses where PRs were observed in UM in Study 01. The recommended Phase 2 dose identified was 20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter. This regimen was used in Study 102 Phase 2 expansion and in the Phase 3 Study 202 and is the proposed dosing regimen.

The Phase 2 expansion portion evaluated the activity of tebentafusp in 127 patients with previously treated mUM (DCO date of 20 March 2020).

The majority of patients were white (99.3%) and approximately half were male (49.6%), with a mean age of 61.0 years (range, 25 to 88 years). More than half of patients (58.3%) had LDH>ULN. All

patients had received prior anticancer therapies (range 1-5) in the metastatic setting; approximately one-third of patients received ≥ 2 prior lines of therapy.

Table 6. Comparison of Key Efficacy Outcomes Between Study 202 (ITT Analysis Set) and Study 102 Phase 2 Expansion (FAS)

Parameter	Study 202 (1L)		Study 102 (2L+)
	Tebentafusp (N = 252)	Investigator's Choice (N = 126)	Tebentafusp (N = 127)
Overall survival			
Median (95% CI), months	21.7 (18.6, 28.6)	16.0 (9.7, 18.4)	16.8 (12.9, 21.3)
Hazard ratio (95% CI) – stratified	0.51 (0.37, 0.71)	--	NA
p value	< 0.0001	--	NA
Progression-free survival			
Median (95% CI), months	3.3 (3.0, 5.0)	2.9 (2.8, 3.0)	2.8 (2.0, 3.7)
Hazard ratio (95% CI) – stratified	0.73 (0.58, 0.94)	--	NA
p value	0.0139	--	NA
Best overall response, n (%)			
Complete response	1 (0.4)	0	0
Partial response	22 (7.9)	6 (4.8)	6 (4.7)
Stable disease	92 (36.5)	28 (22.2)	57 (44.9)
Progressive disease	131 (52.0)	78 (61.9)	60 (47.2)
Not evaluable	6 (2.4)	14 (11.1)	4 (3.1)
Objective response rate (CR + PR)			
n (%)	23 (9.1)	6 (4.8)	6 (4.7)
95% CI [a]	5.9, 13.4	1.8, 10.1	1.8, 10.0
Disease control rate (CR + PR + SD) [a]			
n (%)	115 (45.6)	34 (27.0)	29 (22.8)
95% CI [b]	39.4, 52.0	19.5, 35.6	15.9, 31.1
Duration of response			
Median (95% CI), months	9.9 (5.4, --)	9.7 (2.7, --)	8.7 (5.6, 24.5)

Table 6. Comparison of Key Efficacy Outcomes Between Study 202 (ITT Analysis Set) and Study 102 Phase 2 Expansion (FAS)

Parameter	Study 202 (1L)		Study 102 (2L+)
	Tebentafusp (N = 252)	Investigator's Choice (N = 126)	Tebentafusp (N = 127)

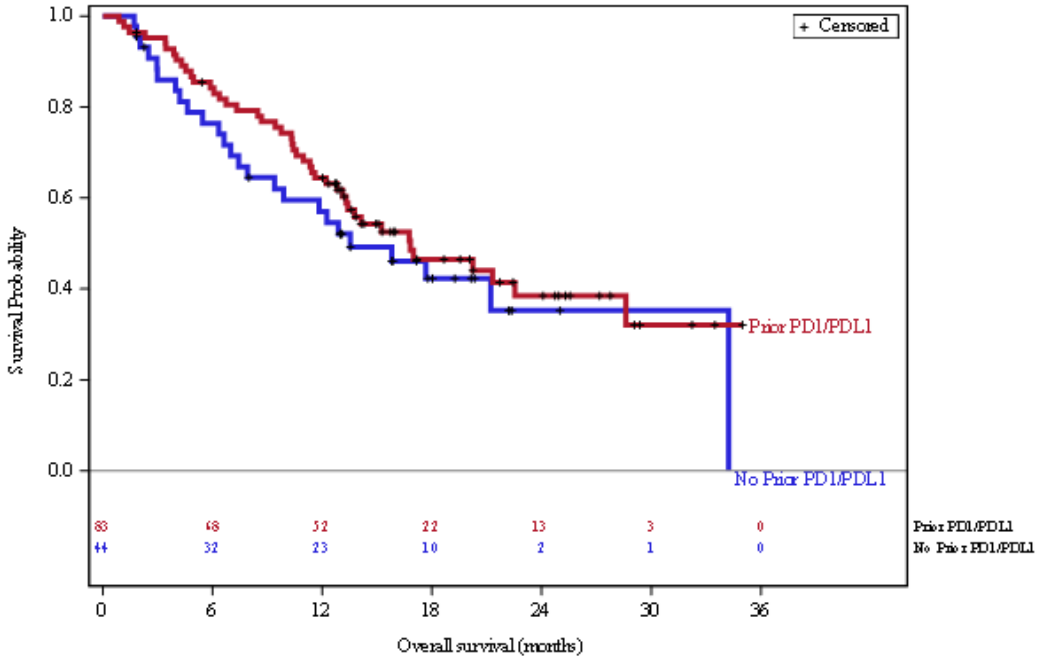
-- = missing; 1L = first line; 2L+ = second line and greater; CI = confidence interval; CR = complete response; FAS = Full Analysis Set; ITT = Intent-to-treat; NA = not applicable; PR = partial response; SD = stable disease.
a SD ≥ 12 weeks for Study 202 and ≥ 24 weeks for Study 102.
b 95% CIs are calculated for the rate using the exact Clopper-Pearson method.
Source: Module 2.7.3, Table 9, Table 10, and Table 11.

The dose-response study (phase 1 part) of study 102 provided information to support the dose selection, please also refer to section of clinical pharmacology).

Regarding efficacy, results from 127 pre-treated patients showed an encouraging improvement of OS 16.8 months (95%CI: 12.9, 21.3) compared to historical controls with a median survival of ≤12 months (Rantala, 2019; Khoja, 2019). The ORR is low (as in the pivotal study), but if patients with stable disease ≥24 weeks were included, the clinical benefit rate (CBR) reached 22.8%. For the few responders, the DOR was promising with 8.7 months (95%CI: 5.6, 24.5).

Moreover, metastatic uveal melanoma has been very difficult to treat, with no systemic or local treatment advances in the metastatic setting for decades with any effect on OS. Considering this context, the results from study 102 of clinical efficacy is considered clinically relevant and supportive of the line-agnostic indication sought.

Figure 17. Study 102 (Phase 2 Expansion): Overall Survival by Prior PDx Use

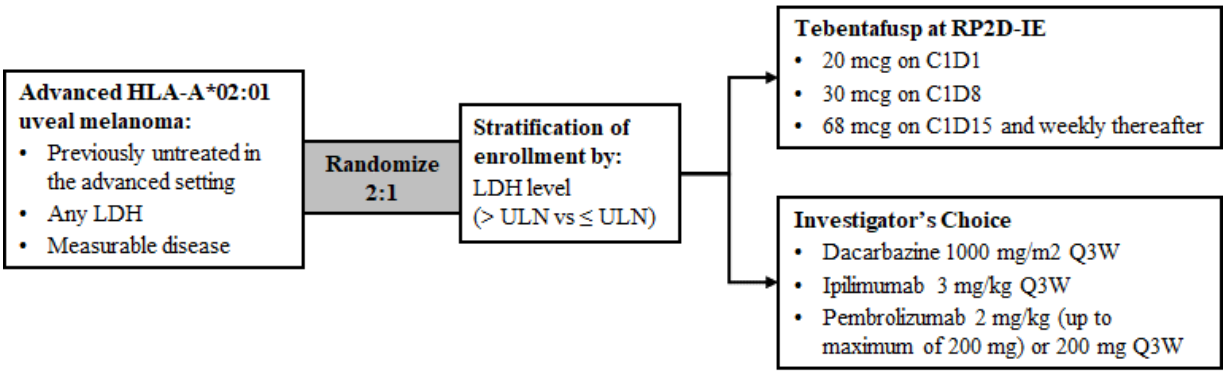


2.6.5.2. Main study

IMCgp100-202 (study 202): A randomised, open-label, multicentre study to assess efficacy and safety of IMCgp100 versus investigator choice in HLA-A*02:01 positive patients with previously untreated advanced uveal melanoma

Methods

Figure 18. Study 202 Design



C#D# = Cycle # Day #; HLA = human leukocyte antigen; LDH = lactate dehydrogenase; Q3W = every 3 weeks; RP2D-IE = recommended Phase 2 dose intrapatient escalation regimen; ULN = upper limit of normal. Source: Module 5.3.5.1, Study 202 CSR, Figure 1.

Methods

Study Participants

Inclusion Criteria

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

1. Male or female patients aged ≥ 18 years of age at the time of informed consent.

2. Ability to provide and understand written informed consent prior to any study procedures.

3. Histologically or cytologically confirmed mUM.

4. Had to meet the following criteria related to prior treatment:

- No prior systemic therapy in the metastatic or advanced setting including chemotherapy, immunotherapy, or targeted therapy.
- No prior regional liver-directed therapy, including chemotherapy, radiotherapy, or embolisation.
- Prior surgical resection of oligometastatic disease was allowed.
- Prior neoadjuvant or adjuvant therapy was allowed provided administered in the curative setting in patients with localised disease. Patients must not have been retreated with an investigator's choice therapy that was administered as adjuvant or neoadjuvant treatment. Additionally, patients who received nivolumab as prior adjuvant/neoadjuvant treatment should not have received pembrolizumab as investigator's choice therapy.

5. HLA-A*02:01 positive by central assay.

6. Life expectancy of > 3 months as estimated by the investigator.

7. Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1 at screening.

8. Patients had measurable or non-measurable disease according to RECIST v1.1.

9. All other relevant medical conditions had to be well-managed and stable, in the opinion of the investigator, for at least 28 days prior to first administration of study drug.

Exclusion Criteria

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

1. Patient with any out-of-range laboratory values defined as:

- Serum creatinine > 1.5 × ULN and/or creatinine clearance (calculated using Cockcroft-Gault formula or measured) < 50 mL/minute.
- Total bilirubin > 1.5 × ULN, except for patients with Gilbert's syndrome who were excluded if total bilirubin > 3.0 × ULN or direct bilirubin > 1.5 × ULN.
- Alanine aminotransferase (ALT) > 3 × ULN.
- Aspartate aminotransferase (AST) > 3 × ULN.
- Absolute neutrophil count < 1.0 × 109/L.
- Absolute lymphocyte count < 0.5 × 109/L.
- Platelet count < 75 × 109/L.
- Haemoglobin < 8 g/dL.

2. History of severe hypersensitivity reactions (eg, anaphylaxis) to other biologic drugs or monoclonal antibodies.

3. Clinically significant cardiac disease or impaired cardiac function, including any of the following:

- Clinically significant and/or uncontrolled heart disease such as congestive heart failure (New York Heart Association Grade ≥ 2), uncontrolled hypertension, or clinically significant arrhythmia that required medical treatment.
- QTc corrected by Fridericia's formula (QTcF) > 470 msec on screening electrocardiogram (ECG) or congenital long QT syndrome. NOTE: If the initial automated QTcF interval was > 470 msec at screening, for the purpose of determining eligibility, the mean QTcF, based on at least 3 ECGs obtained over a brief time interval (ie, within 30 minutes), had to be manually determined by a medically qualified person.
- Acute myocardial infarction or unstable angina pectoris < 6 months prior to screening.

4. Presence of symptomatic or untreated central nervous system (CNS) metastases, or CNS metastases that required doses of corticosteroids within the prior 3 weeks to study Day 1. Patients with brain metastases were eligible if lesions had been treated with localised therapy and there was no evidence of progression for at least 4 weeks by magnetic resonance imaging (MRI) prior to the first dose of study drug.

5. Active infection that required systemic antibiotic therapy. Patients who required systemic antibiotics for infection must have completed therapy at least 1 week prior to the first dose of study drug.

6. Known history of human immunodeficiency virus (HIV) infection. Testing for HIV status was not necessary unless clinically indicated.

7. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection per institutional protocol. Testing for HBV or HCV status was not necessary unless clinically indicated or the patient had a history of HBV or HCV infection.

8. Malignant disease, other than that being treated in this study. Exceptions to this exclusion included the following: malignancies that were treated curatively and had not recurred within 2 years prior to study treatment; completely resected basal cell and squamous cell skin cancers; any malignancy considered to be indolent and that had never required therapy; and completely resected carcinoma in situ of any type.

9. Any medical condition that, in the investigator's or Sponsor's judgment, prevented the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures, or interpretation of study results.

10. Patients who received systemic steroid therapy or any other immunosuppressive medication at any dose level, as these might have interfered with the mechanism of action of study treatment. Local steroid therapies (eg, otic, ophthalmic, intra-articular or inhaled medications) were acceptable.

11. History of adrenal insufficiency.

12. History of interstitial lung disease.

13. History of pneumonitis that required corticosteroid treatment or current pneumonitis.

14. History of colitis or inflammatory bowel disease.

15. Major surgery within 2 weeks of the first dose of study drug (minimally invasive procedures such as bronchoscopy, tumour biopsy, insertion of a central venous access device, and insertion of a feeding tube were not considered major surgery and were not exclusionary).

16. Radiotherapy within 2 weeks of the first dose of study drug, with the exception of palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumour mass.

17. Use of haematopoietic colony-stimulating growth factors (eg, granulocyte colonystimulating factor, granulocyte-macrophage colony-stimulating factor, macrophage colony-stimulating factor) ≤ 2 weeks prior to start of study drug. An erythroidstimulating agent was allowed as long as it was initiated at least 2 weeks prior to the first dose of study treatment and the patient was not red blood cell transfusion dependent.

18. Pregnant, likely to become pregnant, or lactating women (where pregnancy was defined as the state of a female after conception and until the termination of gestation).

19. Women of childbearing potential who were sexually active with a non-sterilised male partner, defined as all women physiologically capable of becoming pregnant, unless they were using highly effective contraception during study treatment, and must have agreed to continue using such precautions for 6 months after the final dose of investigational product; cessation of birth control after this point had to be discussed with a responsible physician.

20. Male patients had to be surgically sterile or used double barrier contraception methods from enrolment through treatment and for 6 months following administration of the last dose of study drug.

21. Patients who were in an institution due to official or judicial order.

22. Patients who were related to the investigator or any sub-investigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in the conduct of the study.

23. Contraindication for treatment with investigator's choice alternatives (dacarbazine, ipilimumab and pembrolizumab) as per applicable labelling. Patient may have had a contraindication to 1 or 2 of the choices if he/she was a candidate for dosing with at least 1 investigator's choice and met all other study eligibility criteria.

Treatments

Table 7. Treatments Administered

Study Treatment	Dose	Schedule	Route of Administration
Tebentafusp	20 mcg C1D1; 30 mcg C1D8; 68 mcg C1D15 and 68 mcg at subsequent doses	QW: Days 1, 8, and 15 of 21-day cycle	Intravenous
Dacarbazine	1000 mg/m^2	Q3W: Day 1 of every 21-day cycle	Intravenous
Ipilimumab	3 mg/kg	Q3W for total of 4 doses: Day 1 of every 21-day cycle	Intravenous
Pembrolizumab	2 mg/kg up to a maximum of 200 mg OR 200 mg fixed dose, where approved locally	Q3W: Day 1 of every 21-day cycle	Intravenous

C#D# = Cycle # Day #; Q3W = every 3 weeks; QW = weekly.

Objectives and endpoints

Table 8. Primary Objectives and Endpoints

Objective	Endpoint
The dual primary objectives are: • To compare the OS in all patients randomized to tebentafusp monotherapy versus all patients randomized to investigator's choice monotherapy • To compare the OS in all patients randomized to tebentafusp monotherapy who develop a rash within the first week of treatment versus all patients randomized to investigator's choice monotherapy Both objectives relate to HLA-A*02:01-positive patients with advanced UM with no prior treatment in the metastatic setting.	OS, defined as the time from randomization until death by any cause

HLA = human leukocyte antigen; OS = overall survival; UM = urothelial melanoma.

Table 9. Secondary Objectives and Endpoints

Objective	Endpoint
To characterize the safety and tolerability of tebentafusp monotherapy in the intra-patient dose-escalation regimen relative to investigator's choice	Safety and tolerability: Incidence and severity of AEs and SAEs; changes in safety laboratory parameters, vital signs, and electrocardiogram (QT interval corrected by Fridericia's formula); dose interruptions, reductions, discontinuations, and dose intensity of all administered agents
To characterize the PK profile of tebentafusp monotherapy in the intra-patient dose-escalation regimen	Mean serum concentrations over time
To assess the antitumor efficacy of tebentafusp versus investigator's choice with the parameters of PFS, BOR, DOR, TTR, and DCR using RECIST v1.1	• PFS • BOR • DOR • TTR • DCR (defined as CR or PR, or SD ≥ 24 weeks) [a]
To evaluate the treatment and disease impact to HRQoL in patients treated with tebentafusp versus investigator's choice. HRQoL will be assessed by the EQ-5D,5L and the EORTC QLQ-C30	EQ-5D,5L and EORTC QLQ-C30 change from baseline over time and between treatment strategies
To evaluate the incidence of anti-tebentafusp antibody formation following multiple infusions of tebentafusp in the intra-patient dose-escalation regimen	Assessments of anti-tebentafusp antibody formation

AE = adverse event; BOR = best overall response; C_{max} = maximum observed concentration; C_{min} = minimum observed concentration; CR = complete response; C_{trough} = drug concentration at X days after dosing; DCR = disease control rate; DOR = duration of response; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer quality of life questionnaire; EQ-5D,5L = EuroQoL-5 Dimensions – 5 levels of disease severity scale; HRQoL = health-related quality of life; PFS = progression-free survival; PK = pharmacokinetic(s); PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; SD = stable disease; TTR = time to response.

[a] For this primary analysis, DCR is based on SD ≥ 12 weeks.

PFS is defined as the time from randomisation to the date of progression or death due to any cause.

ORR is defined as the proportion of patients achieving an objective response.

DOR is defined as the time from first documented objective response until the date of documented disease progression.

TTR is defined as the time from the start of treatment to objective response.

DCR is defined as the proportion of patients with either an objective response or stable disease.

Outcomes/endpoints

Please refer to the section above on objectives, as the corresponding endpoint is also reported and assessed there.

Sample size

ITT Analysis

Overall survival was the primary endpoint for this study. Assuming a 2:1 randomisation ratio of tebentafusp versus investigator's choice, 250 events (deaths) were needed in the randomised trial to provide 89% power to detect a difference of survival distribution that could be characterised by a 0.645 HR for OS with a 2-sided significance level of 0.045. Assuming OS was exponentially distributed, this may have translated to a median OS of 18.6 months in the tebentafusp arm and 12 months in the

investigator's choice arm. Considering a non-uniform recruitment of about 33 months and 10% annual drop-out rate, 369 patients needed to be randomised in a 2:1 ratio to the 2 arms in order to observe 250 events after 51 months as follows:

• 246 patients to Arm 1 (tebentafusp)

• 123 patients to Arm 2 (investigator's choice)

Three analyses of OS were planned: 2 formal interim analyses and the final analysis. To randomize 369 patients (assuming a 10% screen failure rate), 410 patients were needed to be enrolled. To enrol 410 patients, approximately 900 patients were needed to be pre-screened (allowing for a 5% attrition rate and assuming 48% of patients are HLA-A*02:01 positive). The prevalence of HLA-A*02:01 varied depending on the region, so additional patients may be needed to be pre-screened to enrol 410 patients.

Rash Analysis Set (RAS)

The study was also powered for the analysis of OS in the RAS. Assuming 50% of the tebentafusp-treated patients developed a rash within the first week of treatment, there would be an approximate 1:1 ratio between patients in the tebentafusp arm and the investigator's choice control arm. One hundred sixty-four (164) events (deaths) were needed to provide 89% power to detect a difference in survival distributions that could be characterised by a 0.531 HR for OS with a 2-sided significance level of 0.005. Assuming OS was exponentially distributed, this may have translated to a median OS of 22.6 months in the tebentafusp arm and 12 months in the investigator's choice arm.

The size of the study was changed while the study was ongoing. The number of required OS events in protocol version 1, 2, 3, and 4 was 219, which required 327 patients to be randomised. A sample size re-estimation was also planned. In protocol version 5 (31 March 2020) the sample size was increased to 369 subjects and the planned sample size re-estimation was removed. The Applicant claims that the sample size was increased since an additional primary objective was added (OS comparison in the rash group) and the power of OS was increased to 89%.

The most important objective of the study is to show that treatment with tebentafusp provides longer survival than investigator's choice of treatment. The Applicant aimed to show a median OS of at least 18.6 months with tebentafusp, which is longer than the median OS obtained with any of the comparator treatments (approximately 12 months). The median OS target for tebentafusp is concordant with the results of the supportive study 102 (median OS 16.8 months). Observational studies reported a median survival of ≤12 months for patients who received the treatment options included in the investigator's choice (Rantala, 2019; Khoja, 2019). An improvement in median survival of approximately 5 months is considered clinically relevant in the targeted disease, so the assumptions made about the sample size calculations are considered reasonable.

Randomisation and blinding (masking)

Patients were randomised in a 2:1 ratio to either Arm 1 (tebentafusp) or Arm 2 (investigator's choice). Assignment to the treatment arms was determined by the Interactive Response Technology (IRT).

Randomisation to 1 of the 2 treatment arms was stratified by LDH levels. The 2 strata used were: (1) baseline LDH below or equal to the ULN, and (2) baseline LDH above the ULN. LDH levels utilised for stratification were assessed centrally during the screening period. Recent evidence suggests that the LDH level at the time of diagnosis has a significant impact on prognosis in metastatic UM. In the PUMMA study, a multivariate analysis of potential prognostic factors identified LDH above the upper

limit of normal (ULN) as associated with shortened OS (multivariate hazard ratio [HR] 1.88, p < 0.0001) (Nicholas, 2016; Khoja, 2019). Similar findings were obtained in an independent UM dataset, confirming that an LDH level above the ULN is associated with shortened OS (multivariate HR 1.6; p = 0.014; Valpione, 2015). With the strong prognostic value of LDH level, stratified randomisation would protect imbalance in the 2 arms for overall prognosis.

Given the distinct toxicity patterns at the first infusion of the agents being studied (tebentafusp versus investigator's choice), the open-label design was chosen because the treatment assignment could not be blinded.

Table 10. Baseline LDH at Local and Central Labs Versus Randomisation Strata in Study 202 (ITT Population)

	Randomised Strata in Study 202					
	Tebentafusp		Investigator's Choice		Total	
Result	≤ULN (N=162) n (%)	>ULN (N=90) n (%)	≤ULN (N=80) n (%)	>ULN (N=46) n (%)	≤ULN (N=242) n (%)	>ULN (N=136) n (%)
Local LDH						
≤ULN	121 (74.7)	8 (8.9)	62 (77.5)	2 (4.3)	183 (75.6)	10 (7.4)
>ULN	41 (25.3)	81 (90.0)	18 (22.5)	43 (93.5)	59 (24.4)	124 (91.2)
Missing	0	1 (1.1)	0	1 (2.2)	0	2 (1.5)
Overall concordance (%)	80.2		83.3		81.2	
Central LDH						
≤ULN	147 (90.7)	5 (5.6)	73 (91.3)	2 (4.3)	220 (90.9)	7 (5.1)
>ULN	1 (0.6)	81 (90.0)	1 (1.3)	41 (89.1)	2 (0.8)	122 (89.7)
Missing	14 (8.6)	4 (4.4)	6 (7.5)	3 (6.5)	20 (8.3)	7 (5.1)
Overall concordance (%)	90.5		90.5		90.5	

ITT = Intent-to-treat; LDH = lactate dehydrogenase; ULN = upper limit of normal.

Statistical methods

Analysis populations

Table 11. Definitions of Analysis Sets

Analysis Set	Definition
ITT Analysis Set	The ITT Analysis Set comprised all patients assigned to treatment analyzed by the treatment assignment whether or not the patient received the assigned treatment. All patients randomized in the study were analyzed in the ITT population. The ITT Analysis Set was used for all summaries and analyses of demography, baseline characteristics, disposition, medical history, prior anticancer therapy, and efficacy data summaries and analyses.
RAS	The RAS comprised all patients assigned to tebentafusp who developed a rash within the first week of treatment (ie, Study Days 1 to 7 and prior to the second dose in case the second dose was received early) and all patients randomized to investigator's choice regardless of rash. If the analysis for the RAS crossed the pre-specified stopping boundaries and stopping boundaries for the ITT Analysis Set at the same planned analysis were not crossed, then this analysis set was also to be used for demography, baseline characteristics, efficacy, and safety data summaries and analyses. If the stopping boundaries for the RAS OS analysis were crossed, then summaries of demographics, baseline characteristics, and safety were also to be run on this analysis set.
Safety Analysis Set	The Safety Analysis Set included all randomized patients who received at least 1 full or partial dose of tebentafusp or investigator's choice. Patients were classified in this set according to initial treatment received. The Safety Analysis Set was used for all safety summaries.
PK Analysis Set	The PK Analysis Set included patients in the Safety Analysis Set who had at least 1 measurable PK concentration and who had the relevant date, time, and dosing data for the sample.

ITT = Intent-to-treat; OS = overall survival; PK = pharmacokinetics; RAS = Rash Analysis Set.

There are two main analysis populations: ITT and RASH. ITT is defined as all randomised patients regardless of received treatment. The RASH population only included patients assigned to tebentafusp, who experienced a rash within the first treatment week. The ITT will be used for all efficacy endpoints.

The RASH population is used for the OS comparison between the RASH patients and all patients assigned to the comparator arm. The definition of the RASH population is understood. However, the RASH population is defined by a post-randomisation event and therefore the results of such analysis cannot be interpreted as a causal effect of treatment. All the analyses performed in the RASH are thus considered explorative and prone to bias.

Primary endpoint OS

The primary analysis of OS in all randomised patients will be analysed using a 2-sided log rank test stratified by LDH status for generation of the p-value. The HR will be estimated using a stratified Cox-proportional hazards model using the Efron approach for handling ties, together with the associated profile likelihood 95% Cis for the HR. Kaplan-Meier plots of OS will be presented by treatment group. Median OS with 95%CIs will be presented. In addition, landmark survival estimates with corresponding 95% CIs will also be presented using Kaplan-Meier methodology.

Sensitivity analysis for OS

OS will also be analysed based on an unstratified log rank test as a supportive analysis. An additional sensitivity analysis will evaluate OS in the Safety Population.

Censoring rules for OS

For patients without documentation of death, OS will be censored at the last date the patient was known to be alive and will be followed continuously while patients are treated on trial and every 3 months in the follow-up phase.

Secondary endpoint PFS

The PFS analysis will include all randomised patients and will be conducted using a 2-sided log-rank test stratified by LDH status (LDH above the ULN versus LDH below or equal to the ULN; measured centrally) for generation of the p-value. Formal testing of PFS in the RAS will not be conducted. The HR will be estimated using a stratified Cox-proportional hazards model using the Efron approach for handling ties, together with the associated profile likelihood 95% CIs for the HR. Kaplan-Meier plots of PFS will be presented by treatment arm. Summaries of PFS will be provided, including median PFS for each treatment and landmark estimates at specific time points with corresponding CIs.

Censoring rules for PFS

Patients who have not progressed or died at the time of the analysis will be censored at the time of the last evaluable tumour assessment. Patients with 2 or more missed tumour assessments will be censored at the time of the last tumour assessment prior to the missed assessments. If the patient has no evaluable visits or does not have baseline data, they will be censored at 0 days unless they die within 2 planned radiological assessment visits of Baseline (ie, within 26 weeks). Patients who withdraw from randomised therapy or receives another anti-cancer therapy prior to PD will be followed for PFS.

Sensitivity analyses for PFS

Table 4-2

Analysis	Situation	Situation –sub	Date of Event or Censor	Event / Censor
1		a) Progression occurred at a scan performed outside of the protocol-scheduled	The midpoint between the time of progression and the previous	event

Analysis	Situation	Situation –sub	Date of Event or Censor	Event / Censor
	Evaluation-time bias	time points (i.e PD occurred outside of Day 77-91(week 12), 161-175 (week 24), 245-259 (week 36) etc)	evaluable tumor assessment	
			Actual PD date, if PD within correct scan window	event
		b) PD on first scan and first scan outside of correct time windows	Midpoint between the PD date and randomization date	event
		c) death report without PD	Date of Death	Event
2	**Attrition bias**	a) PD regardless of missed scan visits	Actual progression time (i.e. ignore the 2 missed visit rule)	Event
		b) Died without PD and no subsequent therapy	Date of Death	Event
		c) Received a subsequent therapy prior to PD/death	Last evaluable tumor assessment prior to start date of first subsequent therapy	censor
		d) No PD/death and received a subsequent therapy	Last evaluable tumor assessment prior to start date of first subsequent therapy	censor

Secondary endpoints ORR and BOR

Objective response rate was compared between treatment arms using a stratified Cochran Mantel-Haenszel (CMH) test adjusting for baseline LDH status. The results of the analysis were presented in terms of an odds ratio together with its associated 95% CI. A summary of BOR and ORR was also presented by treatment arm. The BOR was to occur after all patients had the opportunity to be evaluated for 3 planned assessments or approximately 36 weeks. Any CRs or PRs that occur after a further anti-cancer therapy was received will not be included in the numerator for the ORR calculation by RECIST v1.1.

OS will be tested using a stratified log-rank test with LDH as a stratification factor. Patients will be followed regardless treatment discontinuation. An unstratified analysis was planned as sensitivity analysis.

PFS will be tested with the same methods as described for OS. Patients will be followed for PFS regardless treatment discontinuation. In the primary analysis for PFS, patients will be censored if they not progressed or died at the time of the analysis at the time of the last evaluable tumour assessment. Patients with 2 or more missed tumour assessments will be censored at the time of the last tumour assessment prior to the missed assessments. If the patient has no evaluable visits or does not have baseline data, they will be censored at 0 days unless they die within 2 planned radiological assessment visits of Baseline. Several sensitivity analyses testing the impact of the censoring rules were performed.

The overall response rate (unconfirmed) between the arms will be compared using a stratified Cochran Mantel-Haenszel test adjusting for baseline LDH status. Patients who switched to another anti-cancer therapy and were responders will not be considered as responder in the analysis.

Interim analysis and type I error control

Interim analyses

Two interim analyses will be performed using a 3-stage group sequential design. The first interim analysis will be based on approximately 60% of the events (150 events) and the second interim analysis will be based on approximately 80% of the events (200 events). Analyses of OS will be based on O'Brien- Fleming boundaries (O'Brien and Fleming, 1979). The Lan-DeMets approach (Lan and DeMets, 1983) that approximates the O'Brien-Fleming spending function will be used to adjust for situations where the actual number of events up to the data cut-off date for a given interim analysis does not match the planned number.

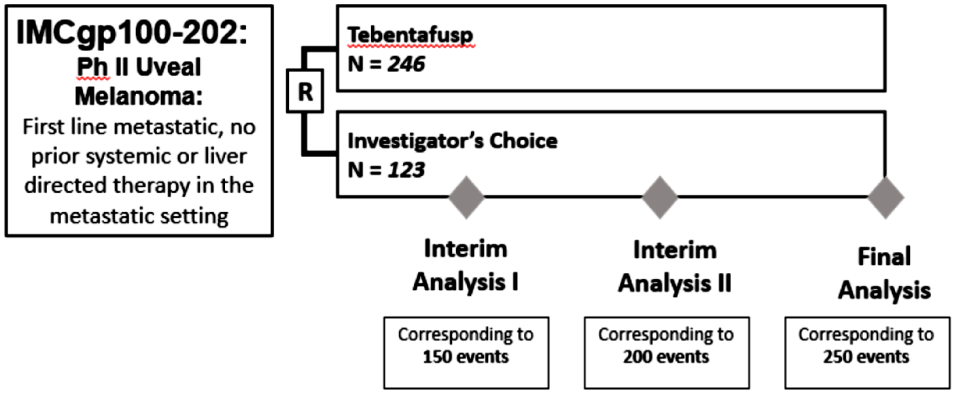


Figure 5.1. Study Design and Interim Analyses for the ITT Population

Multiple testing strategy

There are 2 analyses of the primary endpoint of OS, relating to the 2 objectives of the study. The overall study 2-sided α-level of 5% will be split between these objectives. Ten percent of the study's overall Type I error rate will be allocated to the OS analysis in the RAS (α= 0.5%). Ninety percent of the study's overall Type I error rate will be allocated to the OS analysis in the ITT (α= 4.5%). However, if the first interim OS analysis in the RAS group crosses the pre-specified stopping boundary, then the α from that analysis will be carried over to this ITT analysis and the overall α-level for that analysis will therefore be 5%. Otherwise, an overall α-level of 4.5% will be applied to the ITT OS analyses. The analysis of PFS will follow the ITT analysis of OS in a hierarchical manner. PFS will not be formally tested unless the null hypothesis for the OS endpoint is rejected, using the α level that is used for the ITT OS analysis. The analysis of ORR will follow the ITT analyses for OS and PFS in a hierarchical manner. ORR will not be formally tested unless the null hypotheses for OS and PFS are rejected. ORR will not be formally tested in the RAS.

Since neither PFS nor BOR will be tested on an interim basis, both endpoints will be tested at an overall alpha level of 0.045 (two-sided) or 0.05 if the alpha from the RAS analysis is transferred to the ITT analyses.

Changes to the SAP and to the Planned Analyses

Changes to the SAP

DOCUMENT REVISON HISTORY

VERSION	DATE	AUTHOR/ UPDATED BY	COMMENTS
0.1	10MAR2017	Xiaohua Sheng	Initial draft
0.2	28MAR2017	Xiaohua Sheng	Comments for V0.1 addressed
1.0	19APRIL2017	Nicola Little	Comments for V0.2 addressed
2.0	12JUN2020	Jie Tang	Further clarification of endpoints and analysis methods to following the protocol amendment
3.0	27OCT2020	Susan Wu (Note: CRO company name change from FMD K&L to ClinChoice)	• Remove PK parameter from secondary endpoint (Section 2.1). • Deleted subgroup "Prior surgery for management of oligometastatic disease (Yes/No)" (Section 2.6) • Add post treatment anti-cancer therapy start date imputation rule (Section 3.5). • Add death date imputation rule (Section 3.5). • Change ORR/DCR analysis method from logistic regression to CMH test (Section 4.2.1.2). • Add time to QLQ-C30 sustained deterioration censoring rule. • Add time to onset of each AESI, and time to resolution of each AESI summaries/analysis. • Add additional lab CTCAE shift summaries. • Add vital sign shift from pre-dose to post dose at each dosing schedule.

The final SAP (Version 3.0), dated 28 October 2020, described the planned analyses.

Table 12. Summary of Changes to Planned Analyses

Analysis Planned in SAP or Protocol	Key Details of Change (CSR Section Affected by the Change)	Rationale for Change
DCR defined as CR + PR + SD ≥ 24 weeks	DCR was programmed based on SD ≥ 12 weeks (Section 11.4.1.2.2)	Due to inconsistency in the SAP
TEAEs with missing relationship to study drug were counted as 'missing'	TEAEs with missing relationship to study drug were counted as 'related' (this applied to 3 PTs in the dataset) (Section 12.2.3.3)	Accidental oversight

CR = complete response; CSR = clinical study report; DCR = disease control rate; PR = partial response; PT = preferred term SAP = statistical analysis plan; SD = stable disease; TEAE = treatment-emergent adverse event.

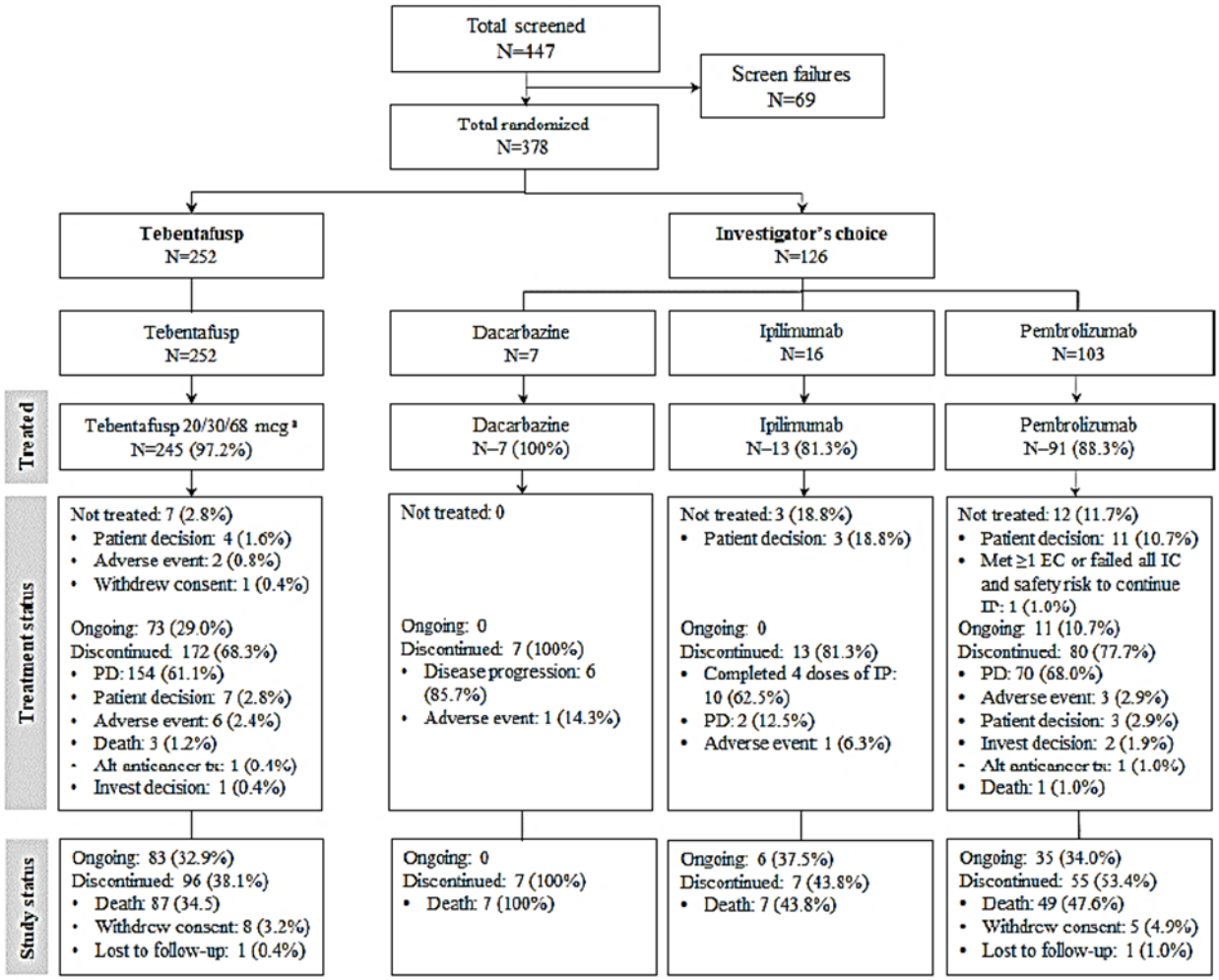
In addition to the analyses described in the SAP, the Sponsor conducted additional exploratory, post-hoc analyses to further elucidate the safety and efficacy of tebentafusp. SAS software Version 9.4 was used.

Two interim analyses for OS are planned (60% of information fraction and 80% of information fraction). The O'Brien-Fleming spending function will be used to calculate the stooping boundaries. To keep the type I error at 5% the alpha is split between ITT-OS (0.045) and RASH-OS (0.005), with a possible alpha transfer from RASH-OS to ITT-OS. A hierarchical approach was used to control for multiplicity across the secondary endpoints.

Results

- **Participant flow**

Figure 19. Patient Disposition (ITT Analysis Set)



Alt = alternative; Invest = investigator; IP = investigational product; ITT = Intent-to-treat; PD = progressive disease; tx = therapy.

[a] 20/30/68 mcg refers to the dosing regimen applied throughout the study. The proposed dosing regimen is 20 mcg at Cycle 1 Day 1, 30 mcg at Cycle 1 Day 8, and 68 mcg at Cycle 1 Day 15 and weekly thereafter.

Source: Table 14.1.1 and Table 14.1.2.

- **Recruitment**

From 04 October 2017 to 18 June 2020, 447 HLA-A*02:01-positive patients were screened, of whom 378 patients were randomly assigned (2:1) to tebentafusp (n=252) or investigator's choice (n=126) at 58 sites in 14 countries (US, Germany, France, United Kingdom, Poland, Canada, Australia, Belgium, Spain, Switzerland, Ukraine, Russia, Italy, and the Netherlands). Treatment choices available in the investigator's choice arm were pembrolizumab (n=103; 81.8%), ipilimumab (n=16; 12.7%), and dacarbazine (n=7; 5.6%).

As of 13 October 2020, the DCO date of the primary analysis, the median duration of follow-up for all patients was 14.1 months (range, 12.7 to 15.6 months).

- **Conduct of the study**

Table 13. Summary of Global Protocol Amendments

Amendment Number, Version Number (Date of Approval)	Key Details of Amendment	Rationale for Amendment
Amendment 1, Version 2 (28 March 2017)	Detailed the statistical methods for the primary analysis of OS.	To provide additional detail to statistical methods section.
	Removed extent of liver metastatic disease as a prespecified covariate. Added a multiple testing strategy to provide strong control of the type I error rate.	
	Added exclusion criteria for patients with autoimmunity including pneumonitis, interstitial lung disease, and inflammatory bowel disease.	To limit the risk of immune-related AEs associated with study drug.
	Explained that corticosteroids prior to the start of treatment were exclusionary.	Corticosteroids prior to the start of treatment may interfere with the mechanism of action of study drug.
Amendment 2, Version 3 (11 April2017)	Throughout the protocol, revised the target tebentafusp dose at C1D15 and beyond from 75 to 68 mcg.	Given information indicating that the actual dose administered and defined as the RP2D in the Phase I study (IMCgp100-102) was 68 mcg.
Amendment 3, Version 4 (20 December 2018)	Revised the single-agent dosing regimen of tebentafusp.	Given data from a Phase I study (IMCgp100-102) identifying an escalated dose and regimen.
	Revised dosing of pembrolizumab in the investigator's choice arm.	To be consistent with approved dosing for treatment of advanced melanoma.
	Updated guidance on dose modifications and follow-up for toxicities to include additional guidance on management of hypotension and CRS events, including a CRS grading scale.	To provide clarification to the recommended toxicity and dose modification guidance for tebentafusp based on investigator notification letter for hypotension and CRS.
	Updated prohibited concomitant medications section to permit treatments for hypotension and CRS.	To provide additional guidance for patient management.
	Revised the requirements for reporting of irAEs to include hypotension and CRS events. In addition, revised the guidelines for management of irAEs to include events of hypotension and CRS.	Given that these events are included in the Reference Safety Information for tebentafusp as expected events.

Amendment Number, Version Number (Date of Approval)	Key Details of Amendment	Rationale for Amendment
	Made the following changes to the statistical analysis section: removed the Per-protocol Set analysis; corrected PFS definition regarding subsequent therapy; removed confirmation of response and clarified analyses of ORR; added secondary endpoints to the multiple testing strategy and clarified the definition of exploratory efficacy endpoints.	To reflect the statistical analysis plan.
	Updated prohibited medications to allow treatment with denosumab, tocilizumab, or bisphosphonates during the study if required.	To provide additional guidance for patient management.
	Described the 0.2 mg/mL formulation of tebentafusp.	To introduce a new formulation of tebentafusp for use in clinical development.
	Updated exclusion criteria to clarify that a patient may have had a contraindication to 1 or 2 of the investigator's choices if he/she was a candidate for dosing with at least 1 investigator's choice and met all other study eligibility criteria. Patients who were institutionalized due to official or judicial order were excluded. Additionally, patients who were related to the investigator or any sub-investigator, research assistant, pharmacist, study coordinator, or other staff thereof, directly involved in the conduct of the study were excluded.	To ensure that appropriate patients are included in the study.
	Removed 1-hour post-dose serum blood sample at C1D1, C1D8, and C1D15, and refined PK and ADA sampling time points after 3 months of treatment.	Based on review of PK and biomarker data collected to date in tebentafusp program.
	Indicated that all cytokine assessments, including those done in the event of suspected CRS, would be assessed centrally. Removed local cytokine assessment and replaced with additional, as needed, pharmacodynamic assessment of cytokines.	To allow a better understanding of the cytokine response with treatment.
	Added reference to a sub-study that would be introduced via a separate protocol at select sites to evaluate ECGs, PK, and biomarkers.	To further supplement existing safety, PK, and pharmacodynamic assessments.
Amendment 4, Version 5 (31 March 2020)	Removed sample size re-estimation planned to occur at 55 events. Increased target sample size to N = 369 based on new assumptions and without a formal sample size re-estimation.	Given the limited information that would have been available at the time of the sample size re-estimation.

Amendment Number, Version Number (Date of Approval)	Key Details of Amendment	Rationale for Amendment
	Added an additional primary objective: comparison of OS among patients randomized to tebentafusp monotherapy who developed a rash within the first week of treatment versus all patients randomized to investigator's choice monotherapy.	Given data from a Phase I study (IMCgp100-102) that confirmed an association between rash, an early and on-target pharmacodynamic biomarker, and tebentafusp activity (as demonstrated by tumor shrinkage, PFS, and OS).
	Increased overall power of the study for the primary endpoint of OS.	Given the addition of another primary endpoint (see above).
	Permitted enrolled patients at a given site who had been receiving at least 2 months of tebentafusp to switch between tebentafusp formulations.	To allow for greater operational flexibility, while maintaining safe conduct of the study.
	Allowed patients who received pembrolizumab on the investigator's choice arm to switch from weight-based to flat dosing where locally approved.	
	Revised Inclusion Criterion 4 to allow prior surgical resection of oligometastatic disease outside liver.	To better reflect standard of care for patients with oligometastatic disease.
	Updated Exclusion Criterion 1 to redefine out-of-range value for absolute lymphocyte count from 1.0 x 10^9/L to < 0.5 x 10^9/L.	Based on emerging data suggesting no adverse impact on treatment in either arm.
	Revised wording around the mandatory hold of antihypertensive drugs 24 hours before and after the tebentafusp administration during at least the first 3 weeks of treatment.	To allow greater flexibility by the treating investigators to adjust medications safely based on clinical context.
	Adjusted hypotension and CRS management guidelines to allow the earlier use of steroids and/or tocilizumab in the stetting of either prolonged Grade 2 events (ie, hypotension) despite the initial interventions or in response to initial onset of Grade 3 or 4 events.	To institute a more proactive approach to AE mitigation before allowing further worsening in patient's condition.
	Removed the option to conduct an ECG sub-study at select sites. Instead, indicated that all participating sites may have been asked to provide ECGs already being collected as part of the current study to a central ECG vendor for storage.	To allow for prospective central collection within the primary study.

ADA = anti-drug antibody; AE = adverse event; C#D# = Cycle# Day #; CRS = cytokine release syndrome; ECG = electrocardiogram; irAE = immune-related adverse event; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; RP2D = recommended Phase II dose.

Table 14. Important Protocol Deviations (ITT Analysis Set)

Category	Tebentafusp (N=252) n (%)	Investigator's Choice (N=126) n (%)	Overall (N=378) n (%)
Patients with ≥1 type of important protocol deviation	99 (39.3)	36 (28.6)	135 (35.7)
Trial procedures	57 (22.6)	14 (11.1)	71 (18.8)
Informed consent/HIPAA	18 (7.1)	12 (9.5)	30 (7.9)
SAE reporting	15 (6.0)	7 (5.6)	22 (5.8)
Inclusion/exclusion criteria	11 (4.4)	4 (3.2)	15 (4.0)
IP intervention	15 (6.0)	0	15 (4.0)
Discontinuation criteria	6 (2.4)	3 (2.4)	9 (2.4)
Prohibited medications	1 (0.4)	0	1 (0.3)

HIPAA = Health Insurance Portability and Accountability Act; IP = investigational product; ITT = Intent-to-treat; SAE = serious adverse event.
Source: Table 14.1.3.

Table 15. Summary of Trial Procedure Protocol Deviations by Treatment in Study 202 (ITT Population)

Category/ Sub-category	Number (%) of Patients	
	Tebentafusp (N=252)	**Investigator's Choice (N=126)**
Delayed SAE reporting	**1 (0.4)**	**0**
Delayed SAE reporting	1 (0.4)	0
Imaging assessment	**4 (1.6)**	**1 (0.8)**
Out-of-window assessment	3 (1.2)	1 (0.8)
Incorrect imaging modality used for follow-up	1 (0.4)	0
Inclusion/exclusion criteria	**1 (0.4)**	**0**
Inclusion criteria	1 (0.4)	0
Informed consent form	**1 (0.4)**	**0**
Pre-screening/screening procedure complete before consent	1 (0.4)	0
Miscellaneous	**1 (0.4)**	**2 (1.6)**
Delay in treatment discontinuation	1 (0.4)	0
Local LDH testing used for stratification	0	2 (1.6)
Missed dose	**11 (4.4)**	**0**
Site closed	2 (0.8)	0
Transportation issue	1 (0.4)	0
Vacation/patient decision	9 (3.6)	0
Missed safety assessment	**40 (15.9)**	**8 (6.3)**
ECG	2 (0.8)	0
Laboratory	21 (8.3)	8 (6.3)
Physical examination	2 (0.8)	0
Vital signs	19 (7.5)	0
Weight	1 (0.4)	0
Missed or incorrect pharmacodynamic assessment	**1 (0.4)**	**0**
Biomarkers	1 (0.4)	0
Safety assessment at incorrect time point	**5 (2.0)**	**0**
ECG	5 (2.0)	0
Safety reporting	**0**	**1 (0.8)**

Category/ Sub-category	Number (%) of Patients	
	Tebentafusp (N=252)	Investigator's Choice (N=126)
Delay in safety reporting	0	1 (0.8)
Survival follow-up	**2 (0.8)**	**2 (1.6)**
Delay in survival follow-up	2 (0.8)	2 (1.6)

ECG = electrocardiogram; ITT = Intent-to-treat; LDH = lactate dehydrogenase; SAE = serious adverse event.

Important protocol deviations are summarised in Table 10. The Applicant provided an overview of the Protocol deviations relating to trial procedures in Study 202 in Table 15.

- **Baseline data**

Table 16. Demographic and Baseline Characteristics of Patients in Study 202 (ITT Analysis Set) and Study 102 Phase 2 Expansion (FAS)

Characteristic	Study 202 (1L)		Study 102 (2L+)
	Tebentafusp (N = 252)	Investigator's Choice (N = 126)	Tebentafusp (N = 127)
Age, years			
n	252	126	127
Mean (Std)	61.3 (11.9)	63.6 (10.7)	61.0 (10.9)
Median (Min, Max)	63.5 (23, 92)	65.5 (25, 88)	61.0 (25, 88)
Gender, n (%)			
Female	124 (49.2)	64 (50.8)	64 (50.4)
Male	128 (50.8)	62 (49.2)	63 (49.6)
Race, n (%)			
American Indian/Alaska Native	0	1 (0.8)	0
White	222 (88.1)	107 (84.9)	126 (99.2)
Not reported	23 (9.1)	14 (11.1)	0
Not allowed as per local regulatory	5 (2.0)	3 (2.4)	0
Unknown	1 (0.4)	1 (0.8)	0
Other	1 (0.4)	0	1 (0.8)
Stage at initial diagnosis, n (%)			
I	48 (19.0)	14 (11.1)	11 (8.7)
II	89 (35.3)	40 (31.7)	41 (32.3)
III	56 (22.2)	34 (27.0)	28 (22.0)
IV	23 (9.1)	7 (5.6)	21 (1.5)
Missing	36 (14.3)	31 (24.6)	26 (20.5)
ECOG performance status, n (%)			
0	192 (76.2)	85 (67.5)	89 (70.1)
1	49 (19.4)	31 (24.6)	38 (29.9)

Table 16. Demographic and Baseline Characteristics of Patients in Study 202 (ITT Analysis Set) and Study 102 Phase 2 Expansion (FAS)

Characteristic	Study 202 (1L)		Study 102 (2L+)
	Tebentafusp (N = 252)	Investigator's Choice (N = 126)	Tebentafusp (N = 127)
2	0	1 (0.8)	0
Missing	11 (4.4)	9 (7.1)	0
Baseline LDH status, n (%) [a]			
≤ ULN	162 (64.3)	80 (63.5)	53 (41.7)
> ULN	90 (35.7)	46 (36.5)	74 (58.3)
Number of prior anti-cancer therapy regimens in the metastatic setting, n (%)			
0	252 (100.0%)	126 (100.0%)	0
1	0	0	84 (66.1)
2	0	0	36 (28.3)
3	0	0	2 (1.6)
4	0	0	4 (3.1)
5	0	0	1 (0.8)
n	NA	NA	127
Mean (Std)	NA	NA	1.4 (0.8)
Median (Min, Max)	NA	NA	1.0 (1, 5)

1L = first line; 2L+ = second line and greater; ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; IRT = interactive response technology; ITT = Intent-to-treat; LDH = lactate dehydrogenase; IRT = Interactive Response Technology; Max = maximum; Min = minimum; NA = not applicable; Std = standard deviation; ULN = upper limit of normal.

[a] LDH value is based on IRT result provided by statistician from the original randomisation scheme.

Source: Module 5.3.5.1, Study 202 CSR, Table 14.1.4, Table 14.1.5; Module 5.3.5.2, Study 102 CSR, Table 14.1.4, Table 14.1.5, Table 14.1.6.

Table 17. Baseline Disease Characteristics (ITT Analysis Set)

Characteristic	Tebentafusp (N=252)	Investigator's Choice (N=126)	Overall (N=378)
Site of initial uveal melanoma, n (%)			
Iris	3 (1.2)	5 (4.0)	8 (2.1)
Ciliary body	25 (9.9)	13 (10.3)	38 (10.1)
Choroid	193 (76.6)	93 (73.8)	286 (75.7)
Unknown	30 (11.9)	14 (11.1)	44 (11.6)
Missing	1 (0.4)	1 (0.8)	2 (0.5)
Stage of initial diagnosis, n (%)			
I	48 (19.0)	14 (11.1)	62 (16.4)
II	89 (35.3)	40 (31.7)	129 (34.1)
III	56 (22.2)	34 (27.0)	90 (23.8)
IV	23 (9.1)	7 (5.6)	30 (7.9)
Missing	36 (14.3)	31 (24.6)	67 (17.7)
Was metastasis observed at initial diagnosis, n (%)			
Yes	17 (6.7)	10 (7.9)	27 (7.1)
No	234 (92.9)	115 (91.3)	349 (92.3)
Missing	1 (0.4)	1 (0.8)	2 (0.5)
Baseline LDH, U/L [a]			
n	234	117	351
Mean (Std)	361.9 (476.2)	281.2 (187.5)	335.0 (405.1)
Median (Min, Max)	207.0 (119, 5572)	204.0 (133, 1199)	207.0 (119, 5572)
Randomization stratum, n (%)			
LDH ≤ULN 250 U/L	162 (64.3)	80 (63.5)	242 (64.0)
LDH >ULN 250 U/L	90 (35.7)	46 (36.5)	136 (36.0)
Largest metastatic lesion at baseline, n (%)			
≤3 cm	139 (55.2)	70 (55.6)	209 (55.3)
3.1-8.0 cm	92 (36.5)	46 (36.5)	138 (36.5)
≥8.1 cm	21 (8.3)	10 (7.9)	31 (8.2)
Pre-randomization choice of treatment, n (%)			
Pembrolizumab	199 (79.0)	103 (81.7)	302 (79.9)
Ipilimumab	40 (15.9)	16 (12.7)	56 (14.8)
Dacarbazine	13 (5.2)	7 (5.6)	20 (5.3)
Prior surgery for metastatic disease [b]			
Yes	24 (9.5)	9 (7.1)	33 (8.7)
No	228 (90.5)	117 (92.9)	345 (91.3)

ITT = Intent-to-treat; LDH = lactate dehydrogenase; Max = maximum; Min = minimum; Std = standard deviation; ULN = upper limit of normal.

[a] LDH value is based on central laboratory.

[b] Prior surgery for metastatic disease is based on a medical review.

Source: Table 14.1.5.

Table 18. Prior Anticancer Systemic Medication by Drug Class and Base Substance (ITT Analysis Set)

Drug Class Base Substance	Tebentafusp (N=252) n (%)	Investigator's Choice (N=126) n (%)	Overall (N=378) n (%)
Patients with at least 1 prior anticancer systemic medication	14 (5.6)	4 (3.2)	18 (4.8)
Antineoplastic agents	**11 (4.4)**	**3 (2.4)**	**14 (3.7)**
Sunitinib malate	6 (2.4)	2 (1.6)	8 (2.1)
Sunitinib	3 (1.2)	0	3 (0.8)
Investigational antineoplastic drugs	1 (0.4)	0	1 (0.3)
Nivolumab	1 (0.4)	0	1 (0.3)
Fotemustine	0	1 (0.8)	1 (0.3)
Antiepileptics	**1 (0.4)**	**0**	**1 (0.3)**
Valproic acid	1 (0.4)	0	1 (0.3)
Immunostimulants	**1 (0.4)**	**1 (0.8)**	**2 (0.5)**
Interferon	1 (0.4)	1 (0.8)	2 (0.5)
Ophthalmologicals	**1 (0.4)**	**0**	**1 (0.3)**
Bevacizumab [a]	1 (0.4)	0	1 (0.3)

ITT = Intent-to-treat.
[a] Used as a treatment for ocular issues or complications after local oncologic treatment but not as an anticancer therapy.
Source: Table 14.1.6.1.

Since mUM was an inclusion criterion, all of the included patients had metastatic disease. Hence, no subgroup analyses are presented of patients with localised vs metastatic disease.

- **Numbers analysed**

The Applicant presents pivotal data from 378 mUM patients from the pivotal study 202 (252 patients were randomised to tebentafusp) and supportive data from 127 patients from the phase 1-2 Study 102, who were treated with the proposed dosing regimen.

Exposure

A total of 109 patients (43.3%) in the tebentafusp arm and 18 patients (14.3%) in the investigator's choice arm were treated beyond RECIST progression.

Table 19. Treatment Beyond Progression (ITT Analysis Set)

Parameter	Tebentafusp (N=252)	Investigator's Choice (N=126)
Treatment duration, months [a]		
n (%)	109 (43.3)	18 (14.3)
Mean (Std)	3.5 (4.6)	2.3 (3.2)
Median (Min, Max)	1.9 (0.1, 28.8)	1.1 (0.1, 13.0)
<12 weeks	70 (27.8)	15 (11.9)
12-24 weeks	25 (9.9)	1 (0.8)
>24 weeks	14 (5.6)	2 (1.6)

ITT = Intent-to-treat; Max = maximum; Min = minimum; RECIST = Response Evaluation Criteria in Solid Tumors; Std = standard deviation.

[a] Duration of treatment beyond RECIST v1.1 progression is the time from RECIST v1.1 progression to the date of last dosing recorded at the time of the data cutoff.

Source: Table 14.2.5.2.

Table 20. Anti-neoplastic therapies since discontinuation (ITT Analysis Set)

		Investigator's Choice			
Therapy Class / Characteristic[1]	IMCgp100 (N=252) n (%)	Dacarbazine (N=7) n (%)	Ipilimumab (N=16) n (%)	Pembrolizumab (N=103) n (%)	Overall (N=378) n (%)
Systemic therapy	109 (43.3)	3 (42.9)	6 (37.5)	46 (44.7)	164 (43.4)
Chemotherapy	26 (10.3)	2 (28.6)	2 (12.5)	12 (11.7)	42 (11.1)
Immunotherapy	99 (39.3)	3 (42.9)	3 (18.8)	33 (32.0)	138 (36.5)
CTLA4	64 (25.4)	0	2 (12.5)	23 (22.3)	89 (23.5)
Other	7 (2.8)	0	0	4 (3.9)	11 (2.9)
PD1	88 (34.9)	3 (42.9)	2 (12.5)	24 (23.3)	117 (31.0)
PD1/other	1 (0.4)	0	0	0	1 (0.3)
Other	0	0	0	0	0
Targeted therapy	6 (2.4)	2 (28.6)	1 (6.3)	5 (4.9)	14 (3.7)
Local therapy other than radiotherapy	15 (6.0)	0	7 (43.8)	9 (8.7)	31 (8.2)
Radiotherapy	18 (7.1)	1 (14.3)	1 (6.3)	14 (13.6)	34 (9.0)
Surgery	1 (0.4)	0	0	2 (1.9)	3 (0.8)
Other	2 (0.8)	0	0	2 (1.9)	4 (1.1)
Best response on					
Any systemic therapy (n=164)[2]	109	3	6	46	164
Complete response	1 (0.9)	0	0	0	1 (0.6)
Partial response	0	0	0	0	0
Stable disease	17 (15.6)	1 (33.3)	2 (33.3)	5 (10.9)	25 (15.2)
Progressive disease	53 (48.6)	3 (100.0)	1 (16.7)	19 (41.3)	76 (46.3)
Non-evaluable/not applicable	55 (50.5)	1 (33.3)	2 (33.3)	22 (47.8)	80 (48.8)
CTLA4 systemic therapy (n=89)[2]	64	0	2	23	89
Complete response	1 (1.6)	0	0	0	1 (1.1)
Partial response	0	0	0	0	0
Stable disease	9 (14.1)	0	1 (50.0)	4 (17.4)	14 (15.7)
Progressive disease	21 (32.8)	0	0	8 (34.8)	29 (32.6)
Non-evaluable/not applicable	30 (46.9)	0	1 (50.0)	10 (43.5)	41 (46.1)

PD1 systemic therapy (n=117) [2]	88		3		2		24		117	
Complete response	1	(1.1)	0		0		0		1	(0.9)
Partial response	0		0		0		0		0	
Stable disease	12	(13.6)	0		1	(50.0)	2	(8.3)	15	(12.8)
Progressive disease	38	(43.2)	3	(100.0)	1	(50.0)	9	(37.5)	51	(43.6)
Non-evaluable/not applicable	41	(46.6)	0		0		12	(50.0)	53	(45.3)
PD1/other systemic therapy (n=1) [2]	1		0		0		0		1	
Complete response	0		0		0		0		0	
Partial response	0		0		0		0		0	
Stable disease	0		0		0		0		0	
Progressive disease	1	(100.0)	0		0		0		1	(100.0)
Non-evaluable/not applicable	0		0		0		0		0	
Other systemic therapy (n=11) [2]			7		0		0		4		11	
Complete response			0		0		0		0		0	
Partial response			0		0		0		0		0	
Stable disease			0		0		0		0		0	
Progressive disease			4	(57.1)	0		0		1	(25.0)	5	(45.5)
Non-evaluable/not applicable			3	(42.9)	0		0		2	(50.0)	5	(45.5)
Reason for discontinuation of systemic therapy (n=164) [3]			109		3		6		46		164	
Progressive disease			44	(40.4)	3	(100.0)	2	(33.3)	16	(34.8)	65	(39.6)
AE/toxicity			24	(22.0)	1	(33.3)	2	(33.3)	8	(17.4)	35	(21.3)
Withdrew consent			1	(0.9)	0		0		1	(2.2)	2	(1.2)
Completed regimen			13	(11.9)	0		0		2	(4.3)	15	(9.1)
Death			10	(9.2)	0		1	(16.7)	7	(15.2)	18	(11.0)
Other			6	(5.5)	0		1	(16.7)	3	(6.5)	10	(6.1)

[1] Therapy class is based on medical review.
[2] The percentage is based on the n who ever received such therapy.
[3] This would be for each systemic therapy and therefore percents will not add to 100.
Source: Listing 16.2.4.5, Output: t-14-01-09-01-anti-neo.
Program: t01090anti0neo.sas Cutoff Date: 13OCT2020 05MAR2021 01:53

Regarding the recommended duration of tebentafusp: 43% of patients continued treatment with tebentafusp post-progression and the median duration was 1.7 months. The short median duration might give the impression that a large proportion of the treated patients did not appear to benefit from the extended therapy. The Applicant has provided the duration of post-progression tebentafusp therapy in time intervals, and of the 109 patients who received treatment beyond progression, 48.6% had therapy for >2 months, 23.9% for >4 months, and 12.8% for >6 months. Very few had a treatment duration post-progression for more than 8 months (8.3%), >12 months (5.5%), >18 months (2.8%), while 1 patient was treated for more than 24 months.

- **Outcomes and estimation**

Primary endpoint - overall survival

Table 21. Summary of Overall Survival in Study 202 (ITT Analysis Set) and Study 102 Phase 2 Expansion (FAS)

Parameter	Study 202 (1L)		Study 102 (2L+)
	Tebentafusp (N = 252)	Investigator's Choice (N = 126)	Tebentafusp (N = 127)
Patients with events, n (%)	87 (34.5)	63 (50.0)	69 (54.3)
Survival			

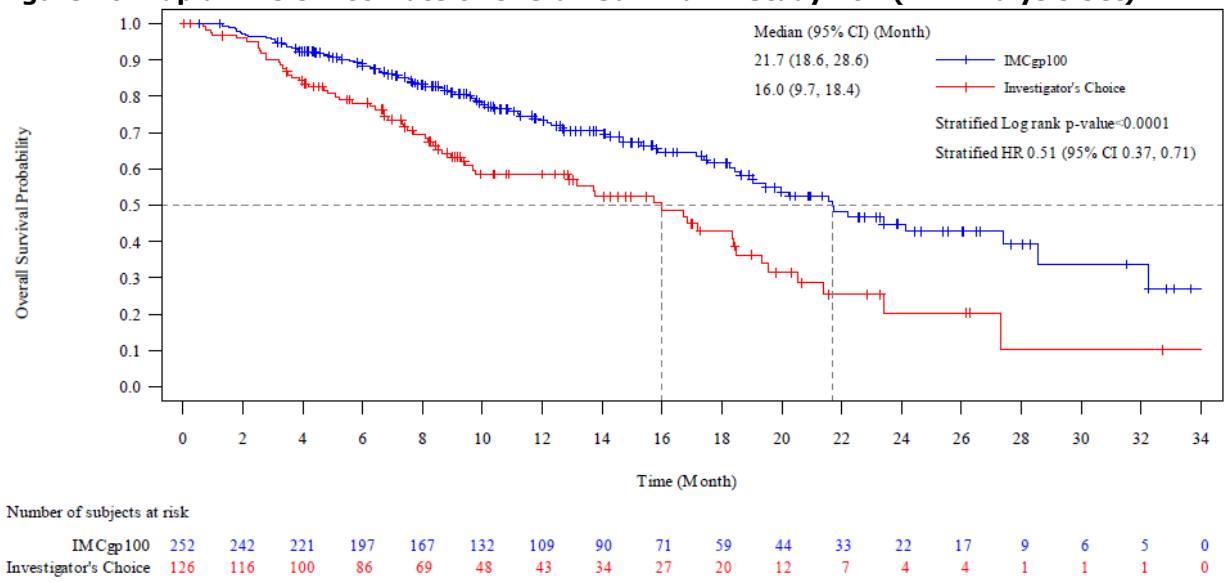
Table 21. Summary of Overall Survival in Study 202 (ITT Analysis Set) and Study 102 Phase 2 Expansion (FAS)

Parameter	Study 202 (1L)		Study 102 (2L+)
	Tebentafusp (N = 252)	Investigator's Choice (N = 126)	Tebentafusp (N = 127)
Median (95% CI), months	21.7 (18.6, 28.6)	16.0 (9.7, 18.4)	16.8 (12.9, 21.3)
Hazard ratio (95% CI) – stratified	0.51 (0.37, 0.71)	--	NA
p value	<0.0001	--	NA
Survival probability, % (95% CI)			
6 months	88.8 (84.1, 92.2)	78.1 (69.6, 84.6)	81.5 (73.5, 87.3)
9 months	81.1 (75.3, 85.7)	63.2 (53.4, 71.5)	72.5 (63.8, 79.5)
12 months	73.2 (66.4, 78.8)	58.5 (48.3, 67.3)	61.8 (52.6, 69.8)
18 months	61.5 (5.3, 68.7)	42.9 (31.5, 53.8)	44.9 (35.2, 54.2)
24 months	44.8 (34.9, 54.2)	20.3 (9.1, 34.7)	37.0 (26.5, 47.5)
30 months	33.6 (20.2, 47.6)	10.2 (1.1, 31.1)	31.7 (19.2, 45.0)
Median follow-up time, months (95% CI)	14.1 (12.5, 16.1)	14.3 (10.9, 17.0)	19.6 (16.0, 22.2)
Combined median follow-up time, months (95% CI)	14.1 (12.7, 15.6)		NA

1L = first line; 2L+ = second line and greater; CI = confidence interval; FAS = Full Analysis Set; ITT = Intent-to-treat; NA = not applicable.

Source: Module 5.3.5.1, Study 202 CSR, Table 14.2.1.1; Module 5.3.5.2, Study 102 CSR, Table 14.2.3.1.

Figure 20. Kaplan-Meier Estimate of Overall Survival in Study 202 (ITT Analysis Set)



CI = confidence interval; HR = hazard ratio; IMCgp100 = tebentafusp; ITT = Intent-to-treat.

Source: Module 5.3.5.1, Study 202 CSR, Figure 14.2.1.1.

Table 22. Summary of Overall Survival (RAS)

Parameter	Tebentafusp (N=149)	Investigator's Choice (N=126)
Patients with events, n (%)		
Deaths	43 (28.9)	63 (50.0)
Survival, months		
Median (95% CI), months	27.4 (20.2, --)	16.0 (9.7, 18.4)
Survival probability, % (95% CI)		
6 months	95.8 (90.8, 98.1)	78.1 (69.6, 84.6)
9 months	92.5 (86.5, 95.9)	63.2 (53.4, 71.5)
12 months	82.9 (74.6, 88.7)	58.5 (48.3, 67.3)
18 months	69.1 (58.5, 77.5)	42.9 (31.5, 53.8)
24 months	54.7 (42.3, 65.5)	20.3 (9.1, 34.7)
30 months	40.9 (24.0, 57.2)	10.2 (1.1, 31.1)
Median follow-up time, months (95% CI) [a]	16.1 (14.1, 18.2)	14.3 (10.9, 17.0)
Combined median follow-up time, months (95% CI) [a]	15.2 (13.3, 17.0)	
Stratified analysis		
Hazard ratio (95% CI) [b]	0.38 (0.25, 0.56)	NA
p value [c]	<0.0001	NA

-- = missing; CI = confidence interval; ITT = Intent-to-treat; LDH = lactate dehydrogenase; NA = not applicable; RAS = Rash Analysis Set.

[a] Reverse Kaplan-Meier estimate.

[b] Hazard ratio is from a stratified proportional hazards model stratified by LDH status. A hazard ratio < 1 favors tebentafusp.

[c] P value is from a stratified log-rank test stratified by LDH status.

[d] Hazard ratio is from an unstratified proportional hazards model. A hazard ratio < 1 favors tebentafusp.

[e] P value is from an unstratified log-rank test.

Source: Table 14.2.1.2.

In the pivotal 202 study, the primary endpoint of OS was met and clinically and statistically

significantly improved with tebentafusp, as the median OS was prolonged by 5.7 months from 16 months (95%CI: 9.7, 18.4) to 21.7 months (95%CI: 18.6, 28.6), HR 0.51 (95%CI: 0.37, 0.71). The OS data is considered rather mature as ~60% of the expected events were observed, with 34.5% events in the tebentafusp arm versus 50% events for the control arm after a median follow-up of ~14 months. Moreover, the KM curves clearly separate after approximately 3 months of therapy and stay separated.

Table 23. Summary of Overall Survival (Primary and Updated Analyses) – ITT Population

	Primary OS Analysis (DCO: 13 October 2020)		**Updated OS Analysis (DCO: 12 August 2021)**	
Statistic	**Tebentafusp (N=252)**	**Investigator's Choice (N=126)**	**Tebentafusp (N=252)**	**Investigator's Choice (N=126)**
Subjects with events, n (%)	87 (34.5)	63 (50.0)	127 (50.4)	79 (62.7)
Subjects with events censored, n (%)	165 (65.5)	63 (50.0)	125 (49.6)	47 (37.3)
Overall survival				
Median (95% CI), months	21.7 (18.6, 28.6)	16.0 (9.7, 18.4)	21.7 (19.1, 26.0)	16.7 (11.8, 19.3)
Stratified HR (95% CI) [a]	0.51 (0.37, 0.71)		0.58 (0.44, 0.77)	
P value [b]	< 0.0001		NA	
Median duration of follow-up [c]	14.1 (12.7, 15.6)		22.4 (20.7, 24.0)	

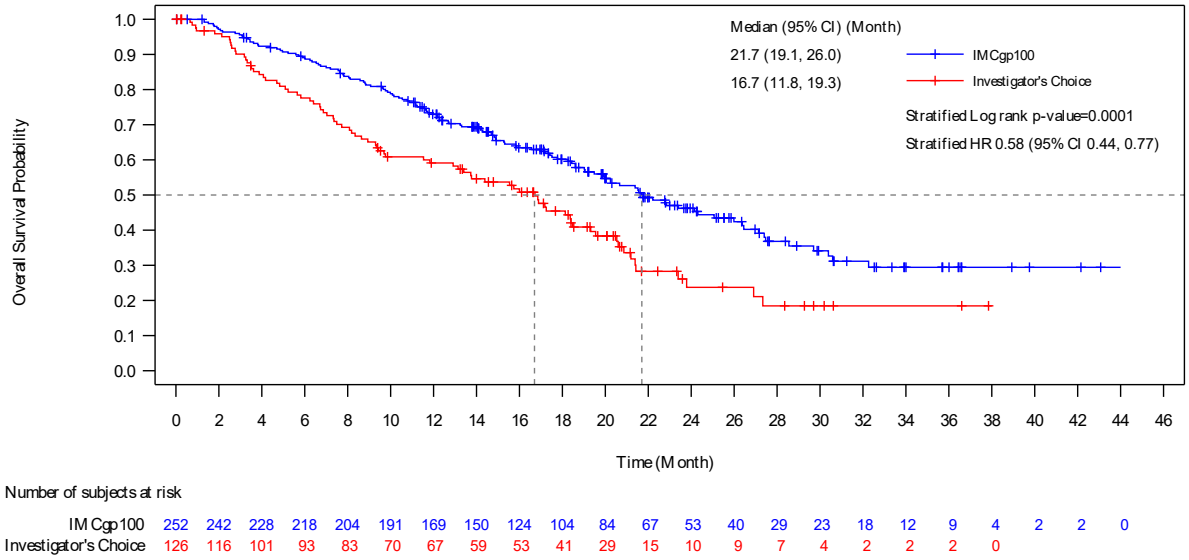
[a] Hazard ratio is from a stratified proportional hazards model stratified by LDH status. A hazard ratio < 1 favours tebentafusp.

[b] P value is from a stratified log-rank test stratified by LDH status.

[c] Reverse Kaplan-Meier estimate.

CI = confidence interval; DCO = data cutoff; ITT = intent-to-treat; LDH = lactate dehydrogenase; NA = not applicable; OS = overall survival.

Figure 21. Kaplan-Meier Estimate of Overall Survival (Updated Analysis) – ITT Population



CI = confidence interval; HR = hazard ratio; IMCgp100 = tebentafusp; ITT = Intent-to-treat.

The applicant has provided updated OS data (Table 8), with the DCO of 12 August 2021 and a median duration of follow-up of 22.4 months (~ 8 months longer follow-up) and ~54% events. The updated OS continued to favour the tebentafusp arm (HR=0.58; 95%CI 0.44, 0.77). However, this updated analysis occurred after patients on therapy of investigator's choice started to cross-over to tebentafusp. It is noted that cross-over was allowed, although data from the primary endpoint of OS was not considered fully mature and this hampers the updated and future results of the primary endpoint of the pivotal trial, which was also the main endpoint that was clinically meaningfully improved. The applicant's arguments for allowing cross-over are mainly due to ethical considerations, which is acknowledged. Moreover, according to the prespecified statistical analysis plan for this Phase 3 trial, the OS benefit of HR 0.51 was the final analysis that provided full control of the overall 5% type I error rate. Hence, all subsequent OS analyses are exploratory in nature and no longer statistically controlled.

Table 24. Listing of Crossover Patients and Their Overall Survival Status

Subject ID	Start of Crossover (Months)	Overall Survival (Months)	Status
1401005	36.14	36.60	Alive
1401008	28.25	29.70	Alive
8706002	27.89	29.27	Alive
8704003	20.86	25.46	Alive
8201008	20.76	23.59	Alive
1401016	18.89	19.15	Alive
8702006	18.83	20.76	Alive
5002002	17.81	20.07	Alive

Subject ID	Start of Crossover (Months)	Overall Survival (Months)	Status
1201008	17.08	19.65	Alive
8702008	15.61	18.27	Alive
6401020	14.75	16.62	Alive
8708007	14.23	16.10	Alive
1201010	13.17	14.55	Alive
8715005	13.17	9.40[a]	Alive
8704007	12.91	17.25	Death
6102006	12.71	15.54	Death

[a] The last known alive date is prior to the date of cross-over due to delayed data entry relative to the date of cross-over. For some patients, the date of cross-over was provided external to the case report forms.

From Table 23, it is evident that 16 patients, who were originally randomised to investigator's choice, had been allowed to cross-over to receive tebentafusp after PD. The timing of the crossover and their OS as of 12 August 2021 is shown, and only 2 patients had died at DCO.

Secondary endpoint – Progression-free survival (PFS)

Table 25. Summary of Progression-free Survival in Study 202 (ITT Analysis Set) and Study 102 Phase 2 Expansion (FAS)

Parameter	Study 202 (1L)		Study 102 (2L+)
	Tebentafusp (N = 252)	Investigator's Choice (N = 126)	Tebentafusp (N = 127)
Patients with PFS events, n (%)	198 (78.6)	97 (77.0)	117 (92.1)
PFS			
Median (95% CI), months	3.3 (3.0, 5.0)	2.9 (2.8, 3.0)	2.8 (2.0, 3.7)
Hazard ratio (95% CI) – stratified	0.73 (0.58, 0.94)	--	NA
p value	0.0139	--	NA
PFS probability, % (95% CI)			
3 months	54.8 (48.3, 60.9)	42.3 (32.9, 51.3)	47.6 (38.6, 56.0)
6 months	30.9 (25.0, 37.0)	18.9 (12.0, 27.2)	25.0 (17.8, 32.9)
9 months	19.8 (1.7, 25.5)	11.7 (6.1, 19.2)	16.8 (10.8, 23.9)
12 months	14.1 (9.5, 19.5)	6.2 (2.3, 13.0)	10.9 (6.2, 17.2)
Median follow-up time, months	13.8 (10.9, 16.8)	11.3 (8.3, 16.9)	25.8 (12.4, NC)

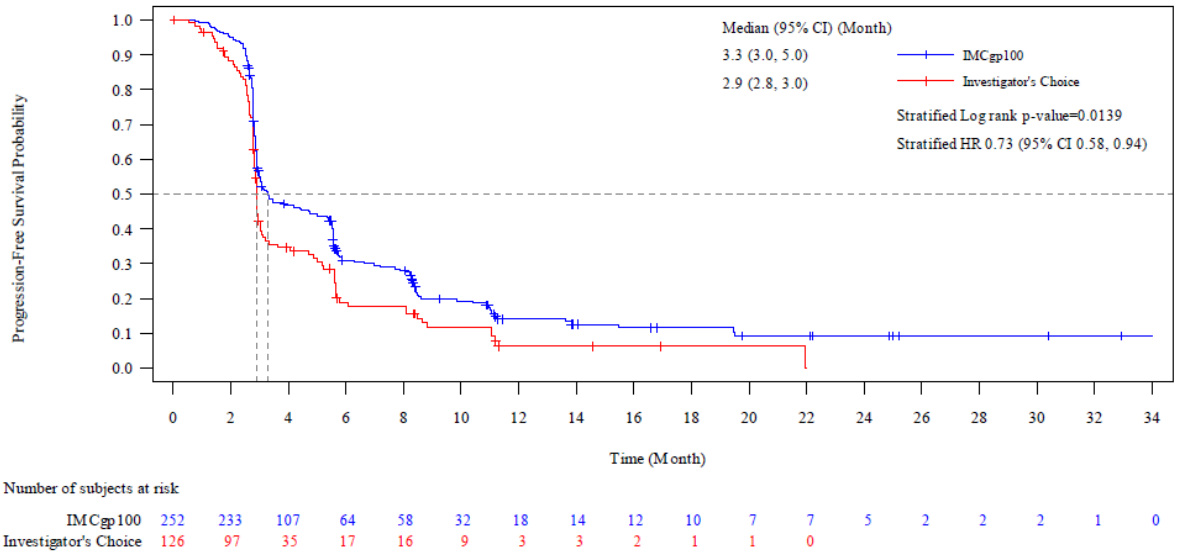
Table 25. Summary of Progression-free Survival in Study 202 (ITT Analysis Set) and Study 102 Phase 2 Expansion (FAS)

Parameter	Study 202 (1L)		Study 102 (2L+)
	Tebentafusp (N = 252)	Investigator's Choice (N = 126)	Tebentafusp (N = 127)
(95% CI)			
Combined median follow-up time, months (95% CI)	11.4 (11.1, 1.6)		NA

1L = first line; 2L+ = second line and greater; CI = confidence interval; FAS = Full Analysis Set; ITT = Intent-to-treat; NA = not applicable; NC = not calculable; PFS = progression-free survival.

Source: Module 5.3.5.1, Study 202 CSR, Table 14.2.2.1; Module 5.3.5.2, Study 102 CSR, Table 14.2.2.2.

Figure 22. Kaplan-Meier Estimate of Progression-free Survival in Study 202 (ITT Analysis Set)



CI = confidence interval; HR = hazard ratio; IMCgp100 = tebentafusp; ITT = Intent-to-treat.

Source: Module 5.3.5.1, Study 202 CSR, Figure 14.2.2.1.

Table 26. Sensitivity analyses of PFS

Sensitivity Analyses [1] of Progression-Free Survival (PFS) by Treatment, Assess Evaluation-Time Bias
Intent to Treat Analysis Set

	IMCgp100 (N=252)	Investigator's Choice (N=126)
Subjects with events n (%)		
PFS events	200 (79.4)	101 (80.2)
Death	17 (6.7)	18 (14.3)
Progressive disease	135 (53.6)	53 (42.1)
PD on first scan and first scan outside of correct time windows	30 (11.9)	19 (15.1)
Progression occurred at a scan performed outside of at the protocol-scheduled time points	18 (7.1)	11 (8.7)
Censored	52 (20.6)	25 (19.8)
No baseline assessment and no death	1 (0.4)	2 (1.6)
No post-baseline tumor assessment and no death	5 (2.0)	9 (7.1)
Patient on study and no progression or death reported	46 (18.3)	14 (11.1)
Progression-free survival (months)		
25 th percentile (95% CI)	2.7 (2.6, 2.8)	2.6 (1.5, 2.8)
Median (95% CI)	3.0 (2.9, 4.4)	2.9 (2.8, 2.9)
Stratified analysis:		
Hazard ratio (95% CI) [3]	0.77 (0.60, 0.98)	
P-value [4]	0.0308	
Unstratified analysis:		
Hazard ratio (95% CI) [5]	0.75 (0.59, 0.95)	
P-value [6]	0.0170	

[1] In order to assess possible evaluation-time bias, which could occur if scans are not performed at the protocol-scheduled time points, the midpoint between the time of progression and the previous evaluable tumor assessment may be analyzed using a stratified log rank test. Note: midpoint is for progression events only. PFS events of death will remain as the date of death.
[2] Reverse kaplan meier estimate.
[3] Hazard ratio is from a stratified proportional hazards model stratified by LDH status. A hazard ratio < 1 favors IMCgp100.
[4] P-value is from a stratified log-rank test stratified by LDH status.
[5] Hazard ratio is from an un-stratified proportional hazards model. A hazard ratio < 1 favors IMCgp100.
[6] P-value is from an un-stratified log-rank test.
Progression-free survival (PFS) is defined as the time from randomization to the date of first documented progression (per RECIST v 1.1) as determined by investigator assessment or death due to any cause, whichever occurs first, regardless of whether the patient withdraws from randomized therapy or receives another anti-cancer therapy prior to progression.
"-" means missing.
Source: Listing 16.2.6.3, Output: t-14-02-02-02-pfs-eva.
Program: t02020pfs0eva.sas Cutoff Date: 13OCT2020 05MAR2021 01:56

The assessment of response and progressive disease was done according to RECIST 1.1, but since tebentafusp is an immunotherapy, results according to immune-mediated response criteria (irRECIST) are also relevant to perform, due to the different mode of action of immunotherapies and the unusual patterns of response that include tumour flare and pseudoprogression (Seymour et al. Lancet Oncol 2017; 18: e143-52).

The Applicant conducted an exploratory analysis of ORR according to irRECIST: 9.9% (25/252) irRECIST vs 9% (22/252) RECIST. 11% (28/252) of patients on tebentafusp were 'upgraded' from RECIST PD to a better irRECIST outcome; 25 patients were 'upgraded' from RECIST PD to irSD, 1 patient was 'upgraded' from RECIST SD to irPR, and 2 RECIST PDs were upgraded to *irPR (*

Table 27*).*

Table 27. BOR per Modified irRECIST as Assessed by Investigator in Tebentafusp Arm (N=252)

RECIST 1.1 BOR Derived from TL, NTL, and NL Data	irRECIST BOR Derived from Investigator-assessed Overall Response (CRF Data)						
Frequency	irCR	irPR	irSD	irPD (uncon-firmed)	PD (confirmed)	NE	Total
CR	1	0	0	0	0	0	1
PR	0	21	0	0	0	1	22
SD ≥12 weeks	0	**1**	91	0	0	0	92
PD	0	**2**	**25**	90	11	3	131
NE	0	0	0	0	0	6	6
Total	1	24	116	90	11	10	252

BOR = best overall response; CR = complete response; CRF = case report form; ir = immune-related; NE = not evaluable; NL = new lesion; NTL = non-target lesion; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumours; SD = stable disease; TL = target lesion.

Secondary endpoints – Best overall response, ORR and DCR

Table 28. Summary of Best Overall Response, Objective Response Rate and Disease Control Rate (ITT Analysis Set)

Parameter	Tebentafusp (N=252)	Investigator's Choice (N=126)
Best overall response, n (%)		
Complete response	1 (0.4)	0
Partial response	22 (8.7)	6 (4.8)
Stable disease	92 (36.5)	28 (22.2)
Progression of disease	131 (52.0)	78 (61.9)
Not evaluable	6 (2.4)	14 (11.1)
Not evaluable post-baseline tumor assessments and no death recorded	6 (2.4)	10 (7.9)
All post-baseline assessments have an overall response of not evaluable	0	1 (0.8)
SD recorded prior to Week 12 [a] from randomization	0	3 (2.4)
Objective response rate (CR/PR)		
n (%)	23 (9.1)	6 (4.8)
95% CI [b]	5.9, 13.4	1.8, 10.1
Stratified odds ratio (tebentafusp/investigator's choice)	1.98	NA
95% CI of odds ratio [c]	0.79, 4.97	NA
Disease control rate (CR/PR/SD ≥12 weeks)		

n (%)	115 (45.6)	34 (27.0)
95% CI [b]	39.4, 52.0	19.5, 35.6
Stratified odds ratio (tebentafusp/investigator's choice)	2.33	NA
95% CI of odds ratio [c]	1.45, 3.75	NA

CI = confidence interval; CMH = Cochran-Mantel-Haenszel; CR = complete response; ITT = Intent-to-treat; LDH = lactate dehydrogenase; PR = partial response; SD = stable disease.
[a] Defined as disease assessment conducted prior to Day 77.
[b] 95% CIs are calculated for the rate using the exact Clopper-Pearson method.
[c] Stratified CMH test stratified by LDH status.
Source: Table 14.2.3.

Table 29. Summary of Best Overall Response and Objective Response Rate in Study 202 (ITT Analysis Set)

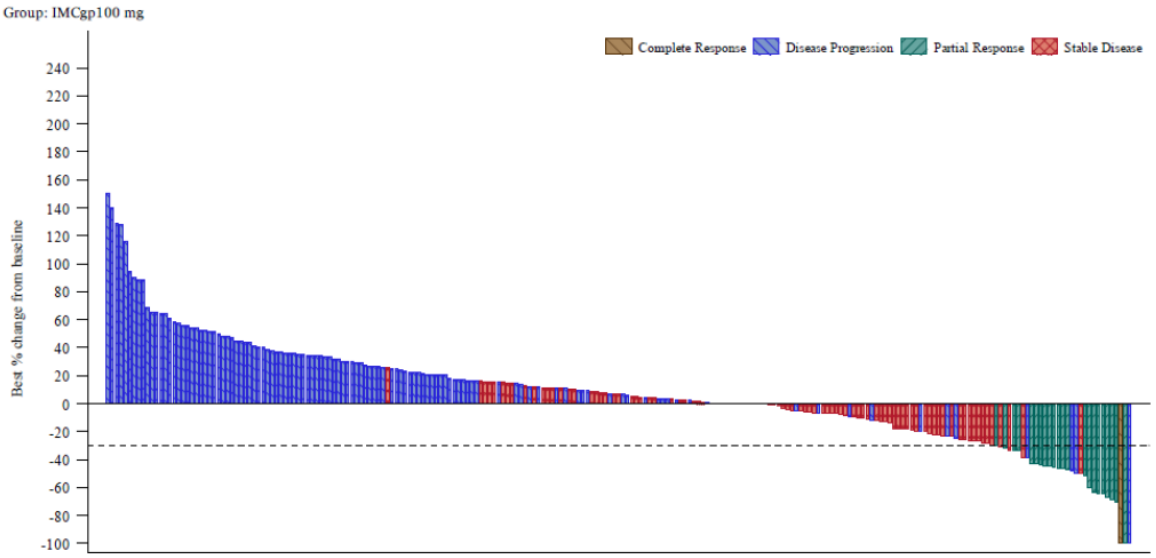
Parameter	Tebentafusp (N=252)	Investigator's Choice (N=126)
Best overall response, n (%)		
Complete response	1 (0.4)	0
Partial response	25 (9.9)	6 (4.8)
Stable disease	52 (20.6)	16 (12.7)
Progressive disease	168 (66.7)	91 (72.2)
Not evaluable	6 (2.4)	9 (7.1)
Objective response rate		
n (%)	26 (10.3)	6 (4.8)
95% CI[a]	6.9, 14.8	1.8, 10.1

[a] 95% CIs are calculated for the rate using the exact Clopper-Pearson method.

CI = confidence interval; ITT = Intent-to-treat.

At the time of the primary analysis of OS (DCO 13 October 2020), not all patients in the pivotal study 202 had the opportunity to undergo 3 planned assessments; therefore, the formal analysis of BOR was not conducted at that time. Since then, all patients have received 3 planned assessments and the results of that analysis, based on a DCO of 12 August 2021, are summarised in Table 6. The updated BOR show similar results as the primary analysis as the ORR with tebentafusp was improved by 1.2%, corresponding to 3 more patients, who had a PR.

Figure 23. Waterfall Plot of Best Percentage Change from Baseline in Tumor Size by Treatment Arm (ITT Analysis Set)



Secondary endpoint – Duration of response (DOR)

Table 30. Summary of Duration of Response (ITT Analysis Set – Subset of Responders)

Parameter	Tebentafusp (N=23)	Investigator's Choice (N=6)
DOR, months [a]		
PFS events, n (%)	9 (39.1)	4 (66.7)
PD	9 (39.1)	4 (66.7)
Death	0	0
Median (95% CI), months	9.9 (5.4, --)	9.7 (2.7, --)
Kaplan-Meier estimates for DOR (95% CI) [No. at risk]		
3 months	84.8 (59.5, 94.9) [n=14]	50.0 (11.1, 80.4) [n=2]
6 months	60.6 (34.2, 7.2) [n=10]	50.0 (11.1, 80.4) [n=2]
9 months	54.5 (28.9, 74.4) [n=7]	50.0 (11.1, 80.4) [n=2]
12 months	46.8 (21.8, 68.4) [n=4]	50.0 (11.1, 80.4) [n=2]
Median follow-up time, months (95% CI) [a]	10.8 (2.8, 13.8)	9.3 (2.8, --)

-- = missing; CI = confidence interval; DOR = duration of response; ITT = Intent-to-treat; PD = progressive disease; PFS = progression-free survival.

[a] Duration of response is defined as the time from the date of first documentation of PR or better to the date of first documentation of PD or death due to any cause, whichever comes first.

[b] Reverse Kaplan-Meier method.

Only patients who have a complete or partial response are included.

Source: Table 14.2.4.

Secondary endpoint – Time to response (TTR)

In the subset of responders (23 in the tebentafusp arm and 6 in the investigator's choice arm), TTR occurred earlier in the tebentafusp arm than the investigator's choice arm, with a median of 2.9 months (range, 1.2 to 22.2) versus 4.1 months (range, 2.0 to 11.8), respectively.

Disease control rate (defined as CR + PR + SD ≥12 weeks) favoured the tebentafusp arm compared with the investigator's choice arm, with rates of 45.6% (95%CI: 39.4, 52.0) and 27.0% (95%CI: 19.5,

35.6), respectively.

Table 31. Summary of Disease Control Rate in Study 202 (ITT Analysis Set)

Parameter	Primary Analysis (DCO: 13 October 2020)		Updated Analysis (DCO: 12 August 2021)	
	Tebentafusp (N=252)	Investigator's Choice (N=126)	Tebentafusp (N=252)	Investigator's Choice (N=126)
Disease control rate (CR/PR/SD ≥24 weeks)				
n (%)	71 (28.2)	20 (15.9)	78 (31.0)	22 (17.5)
95% CI	22.7, 34.2	10.0, 23.4	25.3, 37.1	11.3, 25.2

CI = confidence interval; CR = complete response; DCO = data cutoff; ITT = Intent-to-treat; PR = partial response; SD = stable disease.
Updated DCR SD≥24 weeks has been provided (see table 4) and this has decreased to 31% with tebentafusp.

Table 32. Summary of Duration of Response by Treatment – ITT Analysis Set (Subset of Responders)

Parameter	Tebentafusp (N=26)	Investigator's Choice (N=6)
Duration of response (months)[a], n (%)		
PFS events	16 (61.5)	4 (66.7)
Censored	10 (38.5)	2 (33.3)
Median (95% CI)	9.9 (5.6, 22.1)	9.7 (2.7, --)
Median follow-up time (months)[b]	16.8 (11.1, --)	16.6 (9.3, --)

[a] Duration of response is defined as the time from the date of first documentation of partial response or better to the date of first documentation of progressive disease or death due to any cause, whichever comes first.
[b] Reverse Kaplan-Meier estimate.
Only patients who have a complete or partial response are included.
-- = missing; CI – confidence interval; ITT = Intent-to-treat; PFS = progression-free survival.

If a response to treatment (CR or PR) was observed in both arms, the responses were durable 9.9 vs 9.7 months; however, DOR for the tebentafusp arm was initially immature with only 39.1% events, so the applicant has provided updated DOR data for study 202 at DCO 12 August 2021 (Table 32). With 61.5% of events in the tebentafusp arm and 66.7% of events in the investigator's choice arm, the median DOR remained at 9.9 months in the tebentafusp arm (n=26) and 9.7 months in the investigator's choice arm (n=6).

Health-related Quality of Life

Health-related quality-of-life data were collected using the EORTC QLQ-C30 and EQ-5D,5L PRO instruments.

EORTC-QLQ-C30

In both the tebentafusp and investigator's choice arms, patients were considered to be domain compliant (ie, completed at least 50% of the EORTC QLQ-C30 items) through C17D1, with generally similar rates between the arms. Subsequently, patients in the tebentafusp arm remained domain compliant through C29D1, whereas compliance in the investigator's choice arm decreased to approximately 33% at C29D1.

At baseline, no differences in EORTC-QLQ-C30 scores were observed between the treatment arms for any of the domains. In general, throughout the study, the EORTC-QLC-C30 scores were similar between the treatment arms and remained stable for most domains. However, statistically significant and clinically meaningful LS mean improvements from baseline were observed for fatigue at EOT (10.9 vs 20.1; p=0.0445) and insomnia at C5D1 (-9.3 vs 2.8; p=0.0176), both favouring tebentafusp, and for constipation at EOT (3.2 vs -3.5; p=0.0296), favouring investigator's choice.

Overall, there was no significant difference between the tebentafusp and investigator's choice arms for time to sustained deterioration across the different EORTC-QLQ-C30 domains.

EQ-5D, 5L

In both the tebentafusp and investigator's choice arms, patients were considered to be domain compliant through C17D1, with generally similar rates between the arms. Subsequently, patients in the tebentafusp arm remained domain compliant through C29D1, whereas compliance in the investigator's choice arm decreased to 40.0% at C21D1 and 33.3% at each of C25D1 and EOT.

At baseline, no differences in EQ-5D, 5L scores were observed between the treatment arms for any of the domains. In general, throughout the study, mean change from baseline was similar between the treatment arms for all domains.

Exploratory Efficacy Endpoints

Time to Second Disease Progression

A total of 134 patients (53.2%) in the tebentafusp arm and 70 patients (55.6%) in the investigator's choice arm who were on study treatment had second disease progression events (Table 21).

Table 33. Summary of Time to Second Disease Progression (ITT Analysis Set)

Parameter	Tebentafusp (N=252)	Investigator's Choice (N=126)
Patients with events, n (%)		
PFS2 events	134 (53.2)	70 (55.6)
Death	71 (28.2)	60 (47.6)
Second disease progression	63 (25.0)	10 (7.9)
PFS2, months		
Median (95% CI)	9.2 (8.3, 11.2)	8.3 (6.9, 9.7)
PFS2 probability, % (95% CI)		
6 months	70.7 (63.7, 76.6)	69.6 (59.3, 77.8)
9 months	50.9 (43.1, 58.1)	45.2 (34.1, 55.7)
12 months	37.2 (29.5, 44.9)	37.5 (26.7, 48.3)
18 months	21.2 (14.4, 28.9)	17.9 (9.2, 28.8)
Median follow-up time, months (95% CI) [a]	11.3 (8.3, 14.1)	11.1 (7.2, 16.9)
Combined median follow-up time, months (95% CI) [a]	11.2 (8.4, 13.9)	
Stratified analysis		
Hazard ratio (95% CI) [b]	0.79 (0.59, 1.06)	NA
p value [c]	0.1166	NA
Unstratified analysis		
Hazard ratio (95% CI) [d]	0.80 (0.60, 1.07)	NA
p value [e]	0.1257	NA

ITT = Intent-to-treat; LDH = lactate dehydrogenase; NA = not applicable; PFS2 = second disease progression.

[a] Reverse Kaplan-Meier estimate.

[b] Hazard ratio is from a stratified proportional hazards model stratified by LDH status. A hazard ratio <1 favors tebentafusp.

[c] P value is from a stratified log-rank test stratified by LDH status.

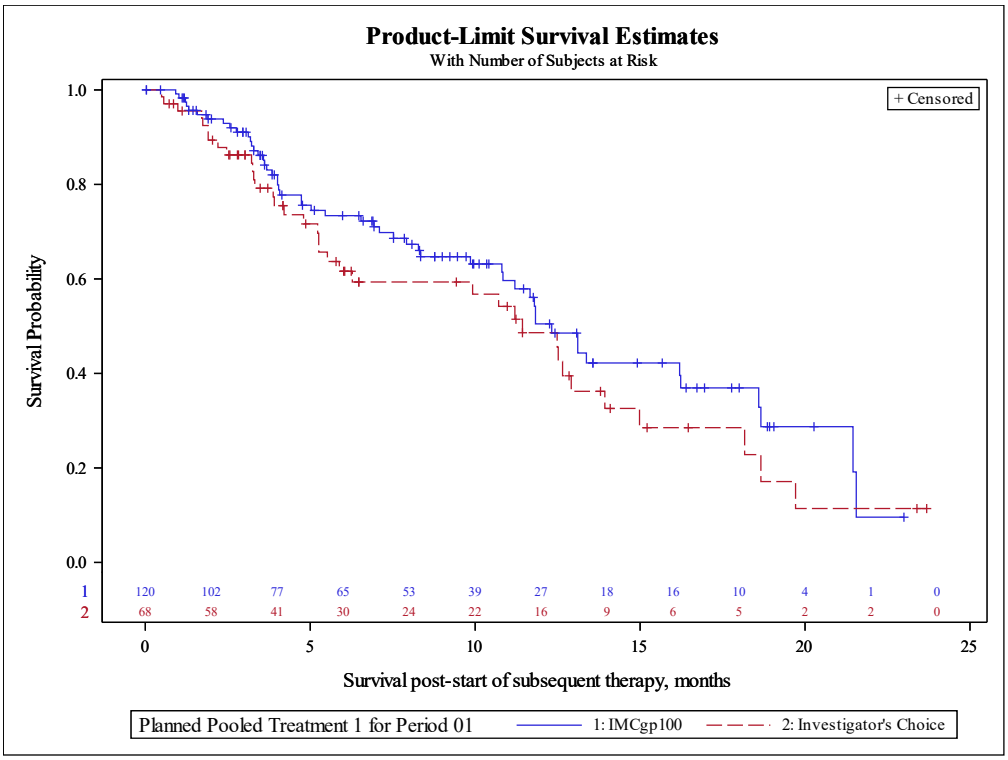
[d] Hazard ratio is from an unstratified proportional hazards model. A hazards ratio <1 favors tebentafusp.

[e] P value is from an unstratified log-rank test.

Time to PFS2 was defined as the time from randomization until second progression or death due to any cause, whichever occurs first.

The median time to second disease progression was similar between the tebentafusp and the control arms (9.2 and 8.3 months, respectively). The applicant has also provided data on PFS2, which was an exploratory endpoint of the pivotal study 202, and included 2 types of events: (1) second PDs monitored from patients who receive treatment beyond progression (TBP) from randomised therapy and (2) deaths. However, patients who went off study treatment and received another anticancer therapy after their initial progression no longer had tumours evaluated on-study. Therefore, for patients who received another anticancer therapy after initial progression, PFS2 events that contributed to the analysis were primarily deaths. Since patients treated with tebentafusp received a higher rate of TBP than control patients (44% vs 16%, respectively), there were slightly more deaths (n=71) vs second PD events (n=63). For control patients, the majority of PFS2 events are deaths (n=60) vs second PD events (n=10).

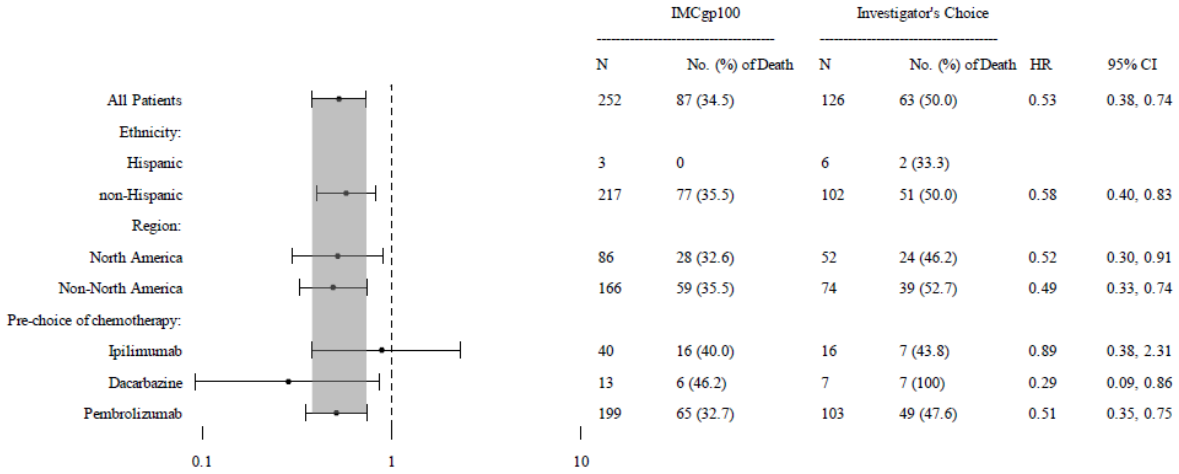
Figure 24. Survival Post Start of Subsequent Therapy by Randomised Treatment (ITT Population with Subsequent Therapy)

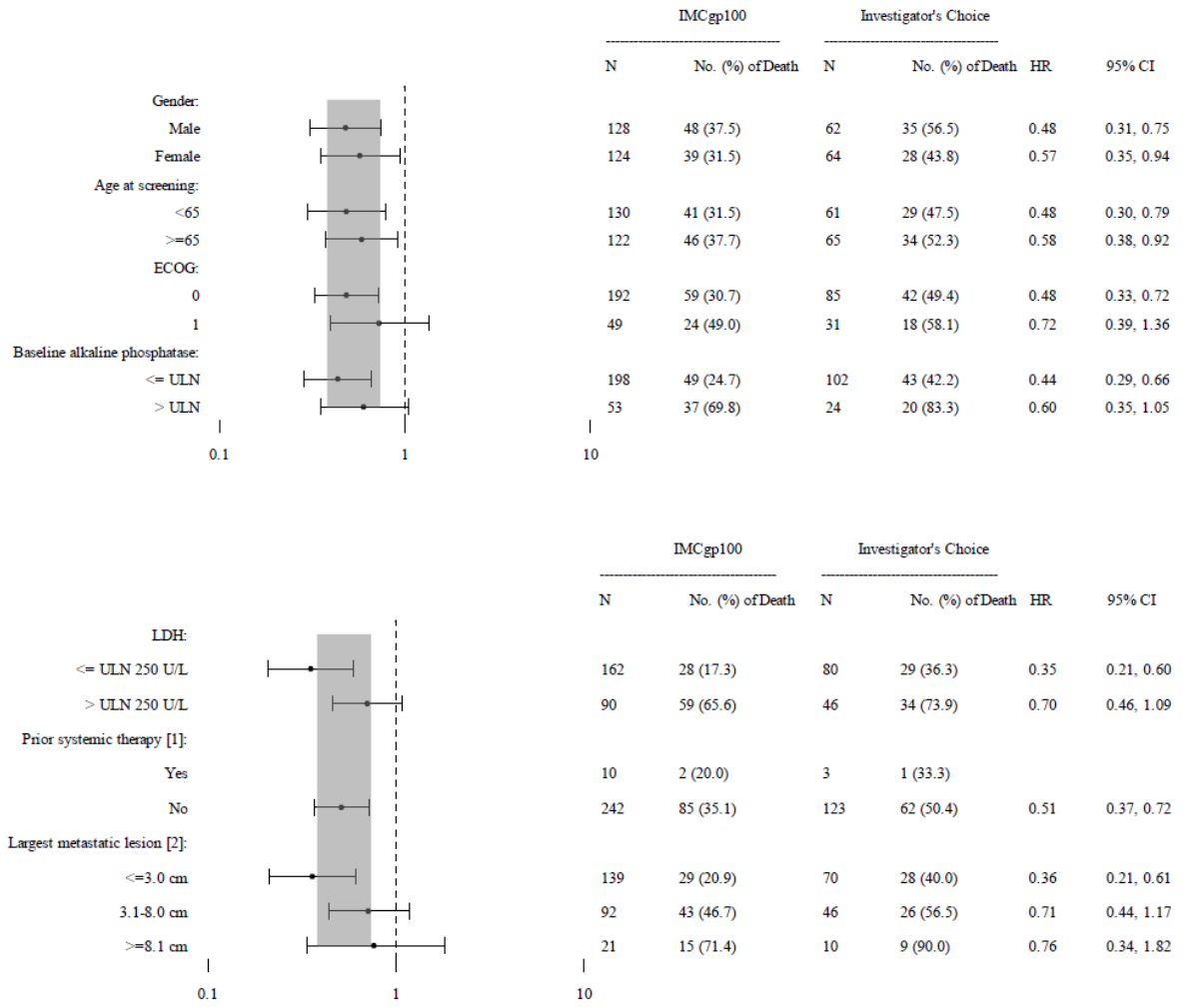


IMCgp100 = tebentafusp; ITT = Intent-to-treat.

Ancillary analyses

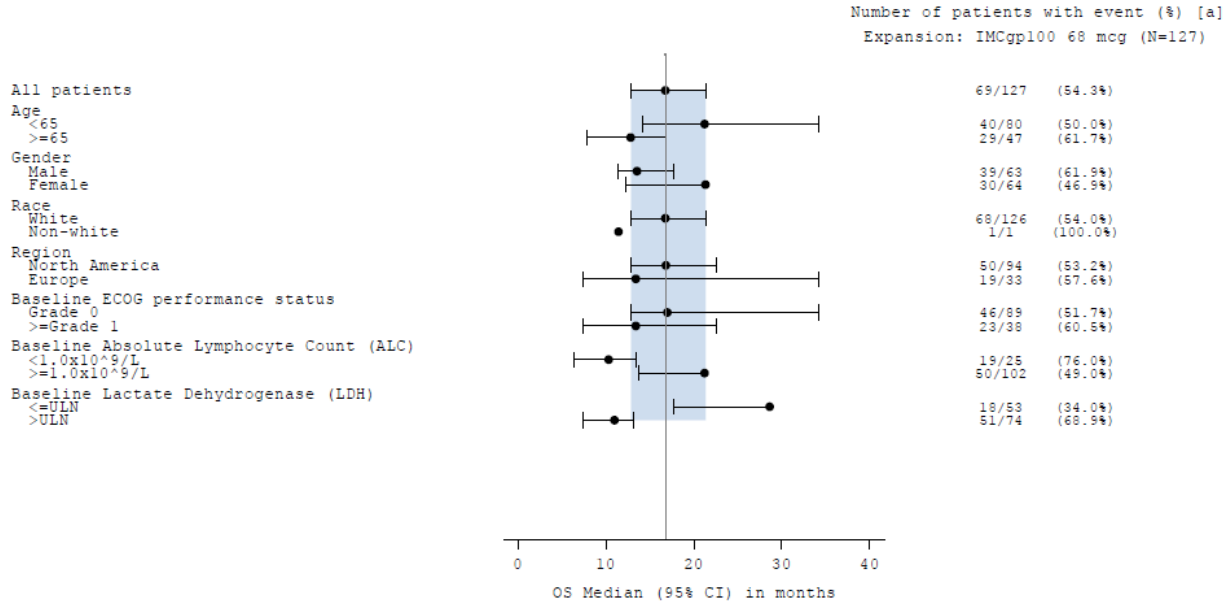
Figure 25. Overall Survival by Subgroups in Study 202 (ITT Analysis Set)

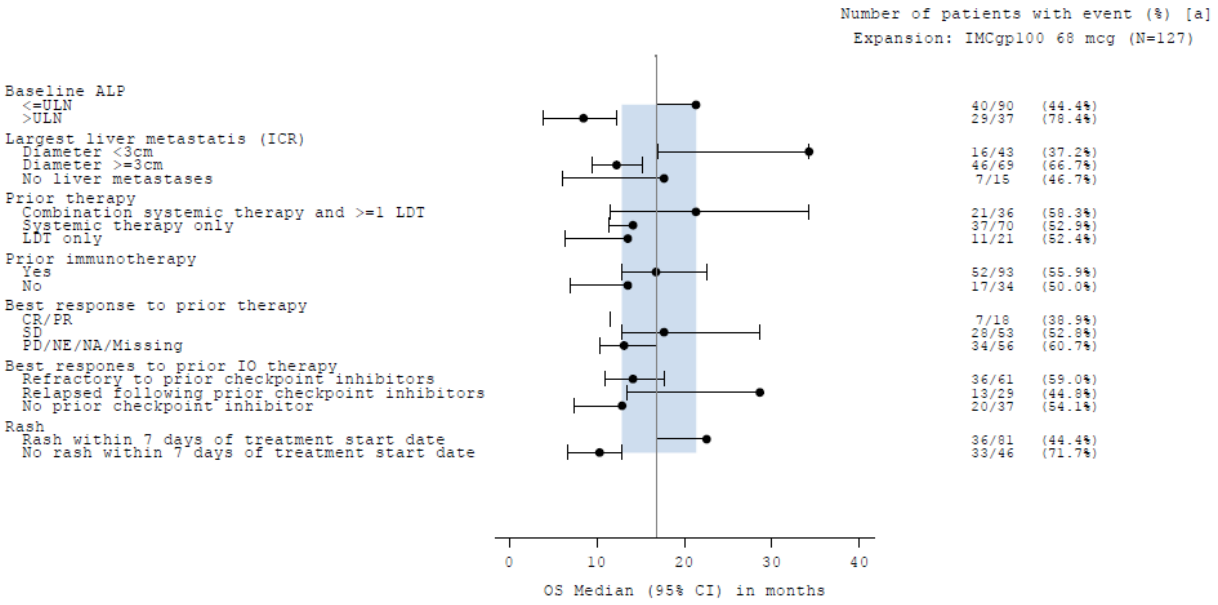




CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IMCgp100 = tebentafusp; ITT = Intent-to-treat; LDH = lactate dehydrogenase; ULN = upper limit of normal.
Source: Module 5.3.5.1, Study 202 CSR, Figure 14.2.6.1.

Figure 26. Overall Survival by Subgroups in Study 102 Phase 2 Expansion (FAS)





CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; FAS = Full Analysis Set; IMCgp100 = tebentafusp; LDH = lactate dehydrogenase; ULN = upper limit of normal.

[a] Event = death due to any cause.

Source: Module 5.3.5.2, Study 102 CSR, Figure 14.2.9.5.4.

Summary of main efficacy results

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

Table 34: Summary of efficacy for trial IMCgp100-202 (Study 202)

Title: A Phase II Randomized, Open-label, Multi-center Study of the Safety and Efficacy of IMCgp100 Compared with Investigator's Choice in HLA-A*0201 Positive Patients with Previously Untreated Advanced Uveal Melanoma			
Study identifier	Protocol Number: IMCgp100-202 EudraCT number: 2015-003153-18		
Design	Multi-centre, open-labelled, randomised (2:1), Phase III study of tebentafusp versus investigator-choice therapy in HLA-A*0201 positive patients with previously untreated advanced uveal melanoma		
	Duration of main phase:		Until disease progression, death or unacceptable toxicity. Treatment beyond progression was allowed. (4 October 2017- 13 October 2020)
	Duration of Run-in phase:		Not applicable
	Duration of follow-up phase:		Not applicable
Hypothesis	Superiority, Phase 3 confirmatory		
Treatments groups	Tebentafusp		Patients (N=252) randomised to tebentafusp followed the proposed dosing regimen: 20 mcg on Day 1, 30 mcg on Day 8, 68 mcg on Day 15, and 68 mcg once every week thereafter
	Investigator's Choice Treatment		Patients treated: 126 Ipilimumab (N=16): 3 mg/kg IV by IV infusion every 3 weeks Dacarbazine (N=7): 1000 mg/m^2 as a 30 to 60 minutes IV infusion every 3 weeks Pembrolizumab (N=103): 2 mg/kg up to a maximum of 200 mg OR 200 mg fixed dose by IV infusion, where approved locally every 3 weeks
Endpoints and definitions	Primary Endpoint	Overall survival (OS)	Time from randomisation to death due to any cause.
	Secondary Endpoint	Progression free survival (PFS)	Time from randomisation to the date of first documented PD (per RECIST v1.1 by investigator assessment) or death due to any cause, whichever occurs first, regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to PD.
	Secondary Endpoints	BOR DCR	Best overall response (BOR) was the best response designation determined by investigator assessment up until progression or last evaluable assessment in the absence of progression; Disease control rate (DCR) was defined as the proportion of patients with a BOR of CR or PR or stable disease (SD) recorded at 12 weeks or later.

Database lock	13 October 2020 (Data cut-off date)		
Results and Analysis			
Analysis description	**Primary Analysis (DCO 13 October 2020)**		
Analysis population and time point description	Intent to treat (ITT) population which includes all participants assigned to treatment whether or not the patient received the assigned treatment. The primary analysis was triggered by the first interim analysis that occurred after 150 death events (60% of the planned total number of deaths).		
Descriptive statistics and estimate variability	**Treatment group**	**Tebentafusp**	**Investigator's choice therapy**
	Number of subjects	252	126
	OS: N (%)	87 (34.5)	63 (50.0)
	Median OS months (95%CI)	21.7 (18.6, 28.6)	16.0 (9.7, 18.4)
Effect estimate per comparison	Hazard Ratio (95%CI)	0.51 (0.37, 0.71)	
	P value (stratified Log-rank test)	<0.0001	
Analysis description	**Updated OS analysis (DCO 12 August 2021)**		
Descriptive statistics and estimate variability	**Treatment group**	**Tebentafusp**	**Investigator's choice therapy**
	Number of subjects	252	126
	OS: N (%)	127 (50.4)	79 (62.7)
	Median OS months (95%CI)	21.7 (19.1, 26.0)	16.7 (11.8, 19.3)
Effect estimate per comparison	Hazard Ratio (95%CI)	0.58 (0.44, 0.77)	
Analysis description	**Secondary Analysis**		
Descriptive statistics and estimate variability	Treatment group	**Tebentafusp**	**Investigator's choice therapy**
	Number of Patients	252	126
	Median PFS months (95%CI)	3.3 (3.0, 5.0)	2.9 (2.8, 3.0)
Effect estimate per comparison	Hazard Ratio (95%CI)	0.73 (0.58, 0.94)	
Descriptive statistics and estimate variability	Treatment group	**Tebentafusp**	**Investigator's choice therapy**
	BOR*, n (%)		
	Complete response	1 (0.4)	0
	Partial response	25 (9.9)	6 (4.8)

	Stable disease	52 (20.6)	16 (12.7)
	ORR* n (%)	26 (10.3)	6 (4.8)
	DCR* (CR/PR/SD ≥ 24 weeks)		
	n (%)	78 (31.0)	22 (17.5)
Notes	* Updated data with DCO 12 AUG 2021, DCR data with CR/PR/SD ≥ 24 weeks as initially planned.		

2.6.5.3. Clinical studies in special populations

Table 35. Frequency of Trial Type by Age Category (Safety Population)

Trial Type	<64 Years (n=347/616)	65-74 Years (n=209/616)	75-84 Years (n=57/616)	>85 Years (n=3/616)
Controlled trials[a] (n=356)	180/356 (50.56)	141/356 (39.61)	33/356 (9.27)	2/356 (0.56)
Non-controlled trials[b] (n=260)	167/260 (64.23)	68/260 (26.15)	24/260 (9.23)	1/260 (0.38)

[a] Includes all patients treated in Study 202.
[b] Includes all patients treated with monotherapy in the following clinical trials: N=84 in Study 01, N=146 in Study 102, and N=30 in Study 201.

The vast majority of patients were in the <75 years category and 356 patients (~58%) were treated in controlled trials.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

HLA-A*02:01 genotype is a mandatory biomarker of efficacy of tebentafusp at his time as the soluble TCR domain of tebentafusp recognises and binds specifically to a peptide derived from gp100 protein that is presented by the HLA-A*02:01 molecule on the tumour cells. Tebentafusp will not bind its target on tumor cells in patients who are negative for the HLA-A*02:01 allele. Therefore, patients without the HLA-A*02:01 type were excluded from trials with tebentafusp as these patients would have no clinical benefit from tebentafusp.

HLA genotyping for the pivotal studies 102 and 202 was completed via the Secore® HLA Sequencing System (One Lambda Inc/Thermo Fisher Scientific Inc) processed by the American Red Cross central laboratory, a CLIA- and ASHI-certified laboratory, using the uTYPE 7.3 RUO software. All samples were processed at 700 Spring Garden Street, Philadelphia, PA 19123. The Secore HLA Sequencing system is CE-IVD approved in Europe.

There are several high-resolution genotyping assay systems in Europe that have the CE-IVD approval in Europe and are routinely used in high-risk patient population to determine HLA-A, -B, -C, -DR, -DQ and -DP locus types for bone marrow typing and transplant. No analytical validation of the Secore® HLA Sequencing assay system was conducted specifically for Studies 102 and 202.

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

Table 36. Overall Survival of Available Study Arms by Line Indication

Treatment Arm	Study	N[a]	1-year OS	Median OS (95% CI, months)
First-Line (1L)				

Treatment Arm	Study	N[a]	1-year OS	Median OS (95% CI, months)
Tebentafusp	IMC Study 202	252	73.2%	21.7 (18.6, 28.6)
IC[b]	IMC Study 202	126	58.5%	16.0 (9.7, 18.4)
Various	Rantala, 2019 meta-analysis	510[c]	51%	12.4 (11.4, 13.7)
Nivo + ipi	Piulats, 2021	52	52%	12.7 (7.1, 18.3)
Mixed 1L and 2L+				
Various	Khoja, 2019 meta-analysis	912	43%	8.9 (IT) 9.2 (CT)
Second-Line and Greater (2L+)				
Tebentafusp	IMC Study 102[d]	127[d]	**61.3%**	**16.8 (12.8, 22.5)**
IC[b]	IMC Study 202	34[e]	35.3%	6.3 (4.2, 12.5)
Various	Rantala, 2019 meta-analysis	287[c]	37%	7.8 (6.5, 9.7)

Abbreviations: 1L = first-line; 2L+ = second-line and greater; CI = confidence interval; CT = chemotherapy; DCO = data cutoff; IC = investigator's choice; ipi = ipilimumab; IT = immunotherapy; mUM = metastatic uveal melanoma; Nivo = nivolumab; OS = overall survival; PD = progressive disease.

[a] Number of mUM patients who were evaluable for efficacy, as reported by the publication cited.

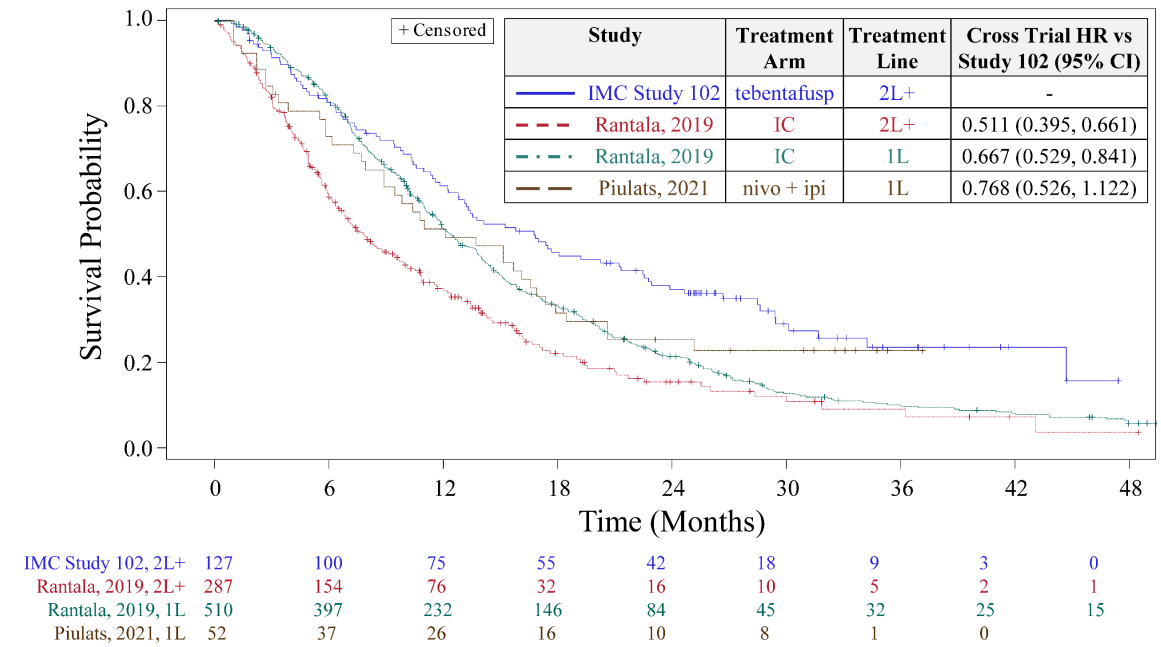
[b] IC included selection of pembrolizumab, ipilimumab, or dacarbazine.

[c] 510 1L patients, 287 2L+ patients, 2949 total patients.

[d] OS at 2-year follow-up; DCO date: 31Mar2021.

[e] Patients randomised to IC who went on to receive systemic subsequent therapy after PD.

Figure 27. Tebentafusp OS in 2L+ Population is Superior to Meta-Analysis and Combination Checkpoint Treatments



Abbreviations: 1L = first-line; 2L+ = second-line and greater; CI = confidence interval; HR = hazard ratio; IC = investigator's choice; ipi = ipilimumab; nivo = nivolumab; OS = overall survival.
Product-limit survival estimates with number of subjects at risk comparing OS from Study 102 2L+ (blue, n = 127); Rantala, 2019: 2L+ (red, n = 287) and 1L (green, n = 510); Piulats, 2021 1L (brown, n = 52).

Table 37. Propensity Score Analysis Results Comparing Tebentafusp 2L+ Patients in Study 102 to Those Treated with Investigator's Choice who Received 2L Therapy in Study 202

Tebentafusp Group (Study 102)	Subsequent Therapy Group (Study 202)	Median OS (95% CI)		HR (95% CI)
		Tebentafusp	Investigator's Choice	
Any line of therapy (N = 123)	Any subsequent therapy (N = 120)	15.2 (12.2, 21.2)	5.3 (3.2, 15.0)	0.40 (0.29, 0.55)
	Checkpoint inhibitors only (N = 119)	15.2 (12.2, 21.2)	5.3 (NE, NE)	0.44 (0.33, 0.60)
Second line only (N = 82)	Any subsequent therapy (N = 76)	17.5 (12.8, 23.9)	5.3 (3.3, 13.9)	0.39 (0.26, 0.58)
	Checkpoint inhibitors only (N=74)	17.5 (12.8, 23.9)	5.3 (3.3, 15.0)	0.42 (0.28, 0.62)

Abbreviations: CI = confidence interval; HR = hazard ratio; NE = not estimable; OS = overall survival. N's for subsequent therapy are after weighting and have been rounded to the nearest whole number.

Table 38. Safety Comparison – Summary of Key Events

Study	Piulats, 2021	Study 102
Treatment N (%)	nivo + ipi (n = 52)	tebentafusp (n = 127)
Treatment line	1L	2L+
Any TEAE	52 (100)	127 (100)

Study	Piulats, 2021	Study 102
Treatment N (%)	nivo + ipi (n = 52)	tebentafusp (n = 127)
Any TEAE leading to discontinuation of study drug	12 (23.1)	7 (5.5)
Treatment-related deaths	2 (3.8)	0

Abbreviations: 1L = first-line; 2L+ = second-line and greater; ipi = ipilumumab; nivo = nivolumab; TEAE = treatment-emergent adverse event

Table 39. Comparison of Baseline Characteristics

Study	Piulats, 2021	Study 102
Treatment Characteristic (N [%], unless stated)	nivo + ipi (n = 52)	tebentafusp (n = 127)
Sex		
Female	23 (44.2)	64 (50.4)
Male	29 (55.8)	63 (49.6)
Age		
Age, years, median (range)	59 (26-84)	61.0 (25-88)
ECOG performance status		
0	44 (84.6)	89 (70.1)
1	8 (15.4)	38 (29.9)
Sites of metastatic disease		
Hepatic only	22 (42.3)	28 (22.0)
Extrahepatic only	11 (21.2)	6 (4.7)
Hepatic ± Extrahepatic	41 (78.8)	121 (95.3)
Size of the biggest liver metastasis[a]		
≤ 3.0 cm	23 (63.9)	43 (33.9)[b]
> 3.0 cm	13 (36.1)	69 (54.3)[b]
Prior lines of therapy		
0	52 (100)	0
1	0	84 (66.1)
2	0	36 (28.3)
3	0	2 (1.6)
4	0	4 (3.1)
5	0	1 (0.8)
Baseline LDH		
LDH ≤ ULN	27 (51.9)	53 (41.7)
LDH > ULN	16 (30.8)	74 (58.3)
Not available	9 (17.3)	0
ALP		
Normal or ≤ ULN	40 (76.9)	90 (70.9)
Increased (> ULN)	7 (13.5)	37 (29.1)
Not available	5 (9.6)	0

Study	Piulats, 2021	Study 102
Treatment Characteristic (N [%], unless stated)	nivo + ipi (n = 52)	tebentafusp (n = 127)

Abbreviations: ALP = alkaline phosphatase; ECOG = Eastern Cooperative Oncology Group; ipi = ipilimumab; LDH = lactate dehydrogenase; nivo = nivolumab; ULN = upper limit of normal.

[a] Note: percentages taken directly from Piulats, 2021 and are based on denominator of N = 36.

[b] Measurement from independent central review.

The applicant has presented comparisons between the Study 202 control patients who started 2L therapy and Study 102 patients were conducted via propensity score methods and according to a prospective statistical analysis plan. The primary comparison involved all patients in Study 102 regardless of the number of prior lines of therapy versus patients in Study 202 from the Investigator's choice arm, who received systemic therapy in the 2L setting (i.e., after progressing on their randomised treatment). Patients who received the same therapy as their Investigator's choice therapy in the 2L setting were excluded.

Factors in the propensity score model included age, gender, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), tumour size, ECOG status, and time since primary diagnosis. For patients from Study 102, baseline values were used. For patients from Study 202, the most recent value prior to the start of 2L therapy was used. A secondary analysis included only patients from Study 202, who received checkpoint inhibitors in the 2L setting. There were too few patients to conduct a comparison involving only those who received the nivo + ipi combination therapy (n = ~14 patients).

The inverse probability of treatment weights (IPTW) using an average treatment effect of the treated weighting scheme was used. With this scheme, each patient in the tebentafusp group received a weight of 1 (ie, they were not weighted) and those from Study 202 who had high PS (ie, they were more similar to the Study 102 patient population) received large weights and those with low PS received low weights. The PS overlap and the balance with respect to baseline covariates was assessed prior to conducting the analysis in order to ensure they were adequate for comparing the treatment groups.

IPTW-weighted Kaplan-Meier curves were prepared for visual comparisons of the survival distributions. Hazard ratios and 95% confidence intervals were calculated from IPTW-weighted Cox proportional hazards models. Multivariate Cox PH models using all of the same covariates used in the PS model were used as a sensitivity analysis to help establish the robustness of the results regardless of the statistical approach.

Baseline characteristics for this study compared with Study 102 can be found in table 38, where key prognostic factors favor the nivolumab and ipilimumab combination study population (i.e., better performance status, smaller liver metastasis, more extrahepatic disease only, and higher percentage of patients with normal LDH and ALP).

2.6.5.6. Supportive studies

Please refer to the assessment of the Dose-response study 102, which is also the supportive study for the applied indication.

Immunogenicity and efficacy

Table 40. Anti-drug Antibody Summary (Safety Analysis Set)

Classification	Patients n/m	Proportion (%)	Titer		
			Median	IQR (Q1, Q3)	Peak/ Fold Increase
ADA prevalence [a]	16/184	8.7	8.0	4.0, 16.0	NA
Evaluable subjects [b]	220	NA	NA	NA	NA
Overall ADA incidence [c]	63/220	28.6	NA	NA	NA
Treatment-induced incidence [d]	61/204	29.9	2050.0	16.0, 24584.0	1048576
Treatment-boosted incidence [e]	2/16	12.5	1026.0	4.0, 2048.0	2048

ADA = anti-drug antibody; IQR = interquartile range; NA = not applicable.

[a] ADA prevalence = (patients with a positive ADA result at baseline / patients tested at baseline for ADA in the Safety Analysis Set).

[b] Evaluable subjects are patients who received at least 1 dose of study drug and have at least 1 ADA assessment post-baseline.

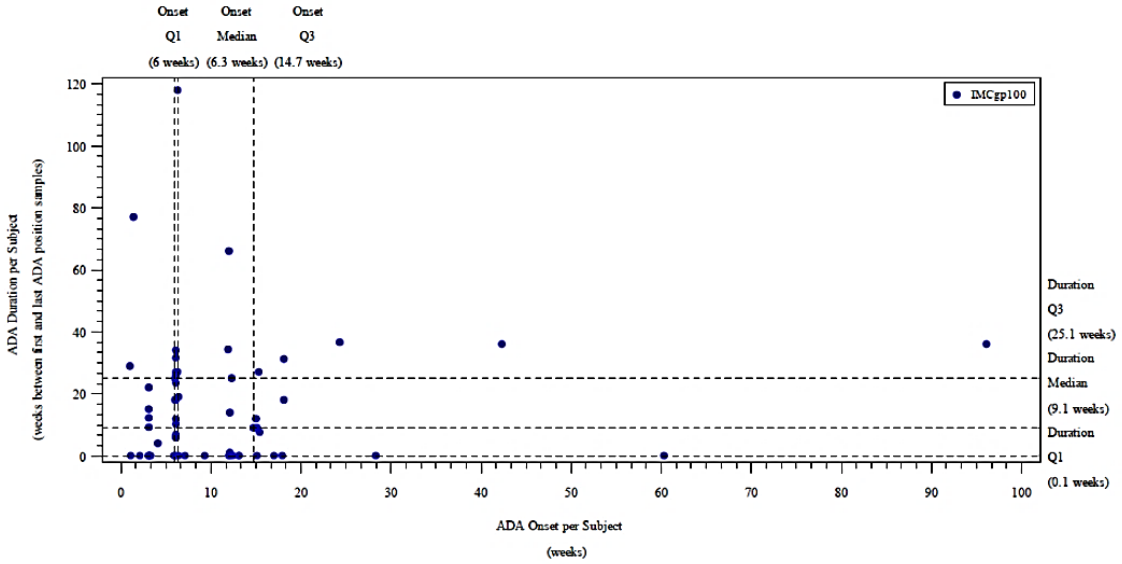
[c] Overall ADA incidence = (patients with a treatment-induced or treatment-boosted ADA response or with positive post-baseline ADA result but no baseline ADA sample / number of evaluable patients).

[d] Treatment-induced incidence = (patients with a positive ADA result post-baseline with negative ADA result at baseline / patients among evaluable subjects with a negative ADA result at baseline).

[e] Treatment-boosted incidence = (patients with a positive ADA result at baseline and positive ADA result post-baseline with a peak fold increase in titer ≥ 4 compared to baseline / patients among evaluable subjects with a positive ADA result at baseline).

Source: Table 14.3.5.2.

Figure 28. Binding Anti-drug Antibody (Safety Analysis Set)



ADA = anti-drug antibody.
Source: Figure 14.3.5.

- The overall incidence of ADA was 28.6% among evaluable patients.
- The incidence of treatment-induced ADA was 29.9%, with a median titre of 1:2,050.
- The incidence of treatment-boosted ADA (ie, increases in pre-existing ADA after tebentafusp administration) was 12.5%, with a median increase of 1,026-fold.
- Median onset of detectable treatment-induced ADA responses was 6.3 weeks.

Treatment-emergent antidrug-antibodies (ADAs) were detected in 33% and 29% of mUM patients in Studies 102 and 202, respectively. In these studies, ADA had a median onset time of 6 to 9 weeks after the first dose of tebentafusp, and median titres of 8192 (Study 102) and 2050 (Study 202).

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The efficacy assessment of the new active substance tebentafusp is based on the pivotal study 202, which is a phase 3, randomised, controlled, open-label, multicentre study comparing tebentafusp monotherapy with Investigator's choice (ipilimumab 12.7%, pembrolizumab 81.8% and dacarbazine 5.6%). Patients were recruited from 58 sites and the majority of the patients were white and recruited from the EU or from a population similar to the EU population. A total of 378 patients with previously untreated metastatic uveal melanoma (mUM) were randomly assigned (2:1) to tebentafusp (n=252) or investigator's choice (n=126). Important supportive evidence was submitted from the phase I-II study 102, which was a single-arm, multicentre study, and the 127 patients, who had previously treated mUM and were treated at the proposed dosing regimen in the dose-expansion phase, formed the basis for the applied line-agnostic indication.

The design of the pivotal study is endorsed and the open-label is acceptable, since the distinct safety profile of tebentafusp necessitated this and would probably have unblinded the study anyway. The choice of comparator as investigator's choice is acceptable since no effective standard of care exists for the targeted patient population with mUM. No scientific advice was given from the CHMP regarding efficacy.

The sample size calculations seem adequate. The increase of the sample size performed while the study was ongoing was based on external information and not on information from the current study.

Patients included in the pivotal study 202 had to have had no prior systemic therapy in the metastatic or advanced setting, including chemotherapy, immunotherapy, or targeted therapy. Prior neoadjuvant or adjuvant systemic therapy was allowed and patients included were only allowed to have (ECOG) performance status score of 0 or 1.

Baseline characteristics showed that the mean age was 61.3 years in the tebentafusp arm, which is younger than for the comparator arm i.e. 63.6 years. Gender was well balanced, and the majority of patients were of ECOG PS 0 (76.2% vs 67.5%) or 1 (19.4% vs 24.6), but this was not entirely balanced and this is in favour of the tebentafusp arm, as patients of ECOG PS 0 have no symptoms of their disease and because ECOG PS is a known and important prognostic factor for cancer patients.

The choroid was most commonly the initial UM site and metastases were seldom observed at initial diagnosis. Mean baseline LDH was higher in the tebentafusp arm, but the patients were stratified according to LDH ≤ or > ULN 250 U/L, and this was well balanced between the two arms. Approximately half of the patients had a largest metastatic lesion of ≤3 cm (55%) and a third (36.5%) of the patients had a largest metastatic lesion of 3.1 -8 cm. Hence, the size of the disease burden of the study patients was considerable, but well balanced across the arms.

The primary objective is to assess overall survival (OS), which is acceptable and endorsed, because this is not subject to bias and deemed highly clinically relevant for the targeted patient population, who have an expected median OS of only ~1 year. The Applicant had dual objectives within the primary objective, to assess OS in the ITT population and to assess OS in the study population who develop a rash, but the latter was not endorsed and results were considered difficult to interpret. Secondary objectives were to assess safety, tolerability and the PK profile of tebentafusp as well as efficacy objectives anti-tumour efficacy measure by progression-free-survival (PFS), best overall response (BOR), the duration of the responses (DOR), time to response (TTR) and disease-control rate (DCR). Overall, the objectives are considered clinically relevant, appropriate and concordant with the endpoints of the pivotal trial.

The applicant presented a table comparing the concordance rate between the LHD results between the

central laboratory and local laboratories. The overall concordance is 90.5 %, which is higher than the threshold pre-specified in the SAP to perform sensitivity analysis for OS. No apparent imbalance between the treatment arms regarding LHD is observed. Hence, the observed minor differences between local and central LHD results are not considered to have an impact on the trial results.

The statistical methods applied for the analysis of OS, PFS and ORR are endorsed.

The strategy implemented to control the type I error is agreed.

However, several changes to the statistical methods were made while the study was ongoing, mostly as part of protocol amendments 3 and 4 (amendments 1 and 2 were done prior to first subject enrolled). These modifications impacted the overall sample size, the interim, the multiplicity adjustment procedure and the PFS definition. Please refer to the protocol amendments in the study conduct section. It is generally difficult to exclude any data-driven decisions.

Nevertheless, despite changes in sample size and interim plans, it is noted that the number of events for this first interim remained approximately the same between the last protocol before first subject enrolled (n=154 in protocol amendment 2), and the latest protocol version (n=150 in protocol amendment 4). Moreover, although the multiplicity adjustment procedure was updated, the significance levels of OS analyses remained based on O'Brien-Fleming boundaries.

Regarding the change in PFS endpoint, it is acknowledged that the latest protocol definition of the censoring rules is more closely aligned with the EMA guideline than the initial version of the protocol, and PFS sensitivity analyses provide additional results with alternative censoring rules. The PFS was initially planned to be assessed by a blinded independent central review (rather than investigator-assessed, from protocol amendment 3). However, given the availability of OS as the primary endpoint, this issue will not be pursued.

Taken together, these protocol changes to the statistical methods are not thought to significantly impact the overall interpretation of the results.

The current version of the SAP is version 3 dated 28 Oct 2020. Several changes were made in the SAP to follow changes made in the protocol. Most changes are not considered to affect the interpretability of the results. It is noted that a change in the time frame for DCR was made and changed from $\geqslant$ 24 weeks to $\geqslant$ 12 weeks. This was not endorsed, and results based on '$\geqslant$ 24' weeks were also included.

Important protocol deviations were summarised by the applicant and it was noted that more deviations were observed in the tebentafusp arm, most often in the category of trial procedures. The applicant provided an overview of the Protocol deviations relating to trial procedures in Study 202. These results showed that in both arms, the most frequent trial procedure-related protocol deviations involved missed safety assessments (15.9% vs 6.3%), with the majority being missed safety labs (8.3% vs 6.3%) or missed vital signs collections (7.5% vs 0%). It is agreed that this is likely related to more the frequent dosing of tebentafusp (weekly vs every 3 weeks) and a more intensive schedule of assessments and visits in the tebentafusp arm. Potential deviations in the timing of imaging assessments were more common in the tebentafusp vs the control arm (4 (1.6%) vs 1 patients (0.8%)). However, the applicant has performed a detailed review, which showed that 4 of the 5 patients (3 on tebentafusp and 1 on the control arm) had deviations in imaging assessments with no impact on PFS. The one remaining patient on the tebentafusp arm had a 2-week delay in their imaging assessment that demonstrated PD. This delay was considered to have no appreciable impact on PFS given additional sensitivity analyses showing the PFS difference between the 2 arms remains statistically significant in favour of tebentafusp even when controlling for attrition bias and evaluation-time bias. Overall, the reported protocol deviations are deemed not to have had any major impact on the overall interpretation of the study results.

A total of 109 patients (43.3%) in the tebentafusp arm and 18 patients (14.3%) in the investigator's choice arm were treated beyond RECIST progression. Thus, we can observe a clear imbalance with a higher proportion of patients from the tebentafusp arm treated beyond progression compared to the Investigator's choice arm. Considering that the study was in an open-label setting, there are concerns that there could be bias in the decision to treat beyond progression, and to which extent the OS results were impacted. It should be noted that the proportion of patients continuing treatment beyond progression within this subset of eligible patients was much higher in tebentafusp arm (59.6%) compared to the investigator's choice arm received TBP (18.6%), while eligibility for TBP was similar in the two groups (respectively 78.6% versus 77.0%) (Table 14.1.9.1). Moreover, it seems that the incidence of subsequent anticancer therapies was higher in the tebentafusp arm compared to the control arm (39.3% vs 32.0%). This suggests that there is a difference in management of TBP across the treatment groups. It cannot be excluded that such a difference could be potentially related to the open-label design. However, considering the size effect observed in primary analysis with consistent sensitivity analysis and the fact that further analysis on TBP would be purely explorative, it is unlikely that further analysis could impact the conclusions on the benefit/risk balance.

The data indicate that for a few patients, radiological progression was not indicative of a poor prognosis; but any firm conclusions are difficult to make, as these patients were carefully selected from clinical and paraclinical parameters. Hence, selection bias is considered to be a part of the results observed for the patients, who were selected for continued treatment despite progressive disease. It was concluded that treatment beyond progression was a part of the overall treatment strategy in the pivotal 202 study. Moreover, since OS was the primary endpoint of this study, it cannot be excluded that this strategy was an essential part of the observed OS benefit. It was not considered meaningful to ask for further analyses to clarify this issue, since the study design and the element of selection bias preclude any absolute conclusions on this issue. Therefore, it was concluded that treatment beyond progression with tebentafusp is acceptable.

Efficacy data and additional analyses

In the pivotal 202 study, the primary endpoint of **OS** was met showing a clinically relevant and statistically significant improvement with tebentafusp, as the median OS was prolonged by 5.7 months from 16 months to 21.7 months, HR 0.51 (95%CI: 0.37, 0.71). The median follow-up time at the time of the primary analysis was ~14 months (DCO 13 October 2020) and approximately 40% of the OS events were observed with 34.5% events in the tebentafusp arm versus 50% events for the control arm. Moreover, the KM curves clearly separate after approximately 3 months of therapy and stay separated. The applicant has provided the requested **updated OS** data, with the DCO of 12 August 2021 and a median duration of follow-up of 22.4 months (~ 8 months longer follow-up), when ~54% OS events were observed. The updated OS continued to favour the tebentafusp arm (HR=0.58; 95%CI 0.44, 0.77). However, this updated analysis occurred after patients on therapy of investigator's choice started to cross over to tebentafusp. It is noted that cross-over was allowed, although data from the primary endpoint of OS was not considered fully mature and this hampers the updated and future results of the primary endpoint of the pivotal trial, which was also the main endpoint that was clinically meaningfully improved. 16 patients from the control arm crossed over and at DCO 12 August 2021, 2 of these patients have died, so no firm conclusions can be drawn at this time. The applicant is recommended to provide Final OS data (which is planned after 250 events in the SAP) as a post-authorisation measure.

Overall, these favourable OS results support a first-line indication for tebentafusp in the treatment of mUM.

In the supportive study 101, the median **OS** was 16.8 months (95%CI: 12.9, 21.3) in the pre-treated study population after a median follow up of ~20 months and 54.3% events (n=127). This result is

significantly better than for historical controls treated with chemotherapy or Anti-PD-1 monotherapy in a 2+ line setting (median OS of 6-9 months, Rantala, 2019; Khoja, 2019), and although this was a single-arm study, these data are considered sufficient to support a line-agnostic indication due to the lack of standard of care options and the rare incidence of the targeted disease (4-6 patients per million in the EU of which 50% develop metastatic disease). Moreover, mUM has been very difficult to treat, with no systemic or local treatment advances in the metastatic setting for decades with any effect on OS. Even though emerging results for the combination therapy with nivolumab and ipilimumab have shown OS in the range of 12-19 months in single-arm studies, the reported efficacy of tebentafusp in the 2+ line setting is considered clinically meaningful and supportive of the applied line-agnostic indication. In order to show, if there was any impact on efficacy with tebentafusp from previous given anti-cancer therapies, it was clarified that the majority of patients in study 102 (88%; 93 of 106) received immunotherapy as their prior systemic therapy; and most of these patients (89%; 83 of 93) received an anti-PD-(L)1. OS by prior PDx use indicates that there was no detrimental effect on OS after prior immunotherapy, which is considered reassuring.

The rash-analyses of OS, which was also a primary objective of the pivotal study, is not considered to have any clinically meaningful purpose, as both patients with and without rash derived benefit of tebentafusp and it is not known in advance who will develop a rash after treatment with tebentafusp.

In the pivotal 202 study, the secondary endpoint of **PFS** did not show any clinically meaningful improvement, although it was statistically significantly improved with tebentafusp, as the median PFS was prolonged by 0.4 months from 2.9 months to 3.3 months, HR 0.73 (95%CI: 0.58, 0.94). The PFS data is considered mature with almost 80% events and a median follow-up of ~11 months. The KM curves never clearly separate and the shape of the curve show that a high number of patients had events at every time point of evaluation, including at the first evaluation after 12 weeks. However, there did not seem to be significant evaluation-time bias according to a sensitivity analysis, so the PFS results are considered robust. Considering the OS gain with tebentafusp, it is considered acceptable that no major improvement of PFS is observed as well. This pattern of efficacy response has often been observed with other immunotherapies.

In the supportive study 101, the median **PFS** was 2.8 months (95%CI: (2.0, 3.7) in the pre-treated population after a median follow up of 25.8 months and 92% events. This is in line with the PFS result for the pivotal study.

The secondary endpoints of the pivotal study 2020 were BOR, ORR, DCR, DOR and TTR. In the tebentafusp arm, the updated **best overall response** (BOR) was 1 patient with a complete response and 25 patients with a partial response (PR 9.9%); while 52 patients (20.6%) had SD as best response. In the investigator's choice arm, there were no CRs; 6 patients (4.8%) with a PR, 16 (12.7%) had SD. The overall response rate ORR was numerically higher in the tebentafusp arm compared with the control arm (10.3% vs 4.8%), but this difference in ORR was not statistically significant nor clinically relevant.

Disease control rate (defined as CR + PR + SD ≥12 weeks) favoured the tebentafusp arm compared with the investigator's choice arm, with rates of 45.6% (95%CI: 39.4, 52.0) and 27.0% (95%CI: 19.5, 35.6), respectively.

SD ≥12 weeks was considered borderline clinically relevant, and this change was introduced during the study, which is not endorsed. Moreover, it is only considered clinically relevant to evaluate the CBR rate using SD $\geqslant$ 24 weeks as initially defined in the protocol for the targeted patient population.

If a response to treatment (CR or PR) was observed in both arms, the responses were durable 9.9 vs 9.7 months; however, **DOR** for the tebentafusp arm was initially immature. The Applicant has provided updated DOR, and at the DCO (12 August 2021), 61.5% of events in the tebentafusp arm and 66.7%

of events in the investigator's choice arm had occurred. The median DOR remained unchanged for both treatment arms and these mature DOR data the few responders (26 vs 6 patients, respectively) are considered highly clinically relevant.

Time to response (TTR) was shorter in the tebentafusp arm compared to the control arm (2.9 months vs 4.1 months); however, the sample size of responders in the pivotal study is limited (n=29), so these data should be interpreted with caution.

In the pivotal study, patients were allowed to receive tebentafusp "while patient is deriving clinical benefit and in the absence of unacceptable toxicities" which is beyond PD by RECIST 1.1, and no crossover to tebentafusp was initially permitted. Although continued treatment beyond progressive disease is decided by the investigator, who are also influenced by important prognostic factors, such as ECOG performance status and LDH levels of the individual patient treated, etc.; it is acknowledged that approximately 40% of patients treated in the tebentafusp arm continued treatment with tebentafusp beyond progression. As mentioned above treatment beyond progression was considered a part of the overall treatment strategy in the pivotal 202 study.

The applicant conducted, as requested, an exploratory analysis of ORR according to irRECIST, and it is agreed that there was no clinically meaningful difference in the tebentafusp arm: 9.9% (25/252) irRECIST vs 9% (22/252) RECIST. However, 11% (28/252) of patients on tebentafusp were 'upgraded' from RECIST PD to a better irRECIST outcome; 25 patients were 'upgraded' from RECIST PD to irSD, 1 patient was 'upgraded' from RECIST SD to irPR, and 2 RECIST PDs were upgraded to irPR. These results with irRECIST are considered promising, as 28 patients had a different outcome that merited continued treatment with tebentafusp from objective criteria. Since irRECIST was not used in the pivotal trial, a recommendation to use irRECIST in the SmPC is not considered warranted.

The applicant has presented **subgroup analyses** of median OS for both the pivotal study 202 and the supportive study 102 expansion. Overall, the OS benefit demonstrated with tebentafusp in Study 202 was observed clearly across important demographic and known prognostic subgroups, such as gender, age <65 versus ≥65 years of age, no prior systemic therapy, and largest metastatic lesion of ≤3 cm. Hence, these are considered supportive of clinically relevant efficacy of tebentafusp for all patients included in the pivotal study.

The applicant has presented comparisons between Piluats 2021 (nivolumab + ipilimumab) and Study 102 patients. Despite the differences in the study populations, with Piluats 2021 being a better prognostic population (1L) than those from Study 102 (2L+), the OS from Study 102 appears better in this cross-trial comparison. This is considered supportive of efficacy of tebentafusp in the 2L+ patient population of mUM. The safety of tebentafusp may also be acceptable compared to checkpoint combination from these data, since a higher rate of treatment-related discontinuations was observed with nivolumab + ipilimumab compared to tebentafusp treatment (23.1% and 5.5%, respectively).

The applicant has provided an analysis of Survival Post Start of Subsequent Therapy by Randomised Treatment in the ITT population and this shows no sign of a detriment on OS for either treatment arm, which is reassuring.

The PRO results for the pivotal study were summarised by the applicant. Any differences observed should be interpreted with caution since the study was open-label. For the same reason, these results are not presented in the SmPC, and this is endorsed.

It is considered that since HLA genotype is not an efficacy or safety biomarker for mUM patients and it is a routine diagnostic test used in other high-risk clinical settings (eg, in organ transplant), there is no relevant information regarding results of HLA-genotyping to be updated in the SmPC. Currently, it is stated in section 4.2 of the SmPC: 'Patients treated with KIMMTRAK must have HLA-A*02:01 genotype determined by any validated HLA genotyping assay.' This is considered acceptable.

A small number of patients developed high-titre ADA (⩾8192) that resulted in increased tebentafusp CL and reduced Cmax exposure. Overall, the development of ADA seems to be in line with other immunotherapeutic drugs; however, numbers are too small for any firm conclusions.

2.6.7. Conclusions on the clinical efficacy

The results from the pivotal study 202 show a clinically relevant improved efficacy with tebentafusp compared to treatments of Investigator's choice regarding OS in the first-line setting. Moreover, efficacy data from the supportive study 102 adds to the totality of the data and supports the applicant's claim for a line-agnostic indication for a targeted disease (mUM), which has not had any available treatments with survival benefit for decades. The Applicant is recommended to provide Final OS data (which is planned after 250 events in the SAP) as a post-authorisation measure.

2.6.8. Clinical safety

Table 41. Pooled Safety Datasets

Study	Number of Patients (Specific Criteria)	
	Pool 1 (Uveal Melanoma Patients)	**Pool 2 (All Melanoma Monotherapy Patients)**
Study 202	245 (20/30/68 mcg [a])	245 (20/30/68 mcg [a])
Study 102	19 (Phase 1, all doses) 127 (Phase 2, 20/30/68 mcg [a])	146 (Phases 1 and 2, all doses)
Study 01	19 (all doses)	81 (all doses)
Study 401	--	3 (all doses)
Study 201	--	30 (all monotherapy)
All Studies	**410**	**505**

[a] 20/30/68 mcg refers to the dosing regimen applied throughout the study. The proposed dosing regimen is 20 mcg at Cycle 1 Day 1, 30 mcg at Cycle 1 Day 8, and 68 mcg at Cycle 1 Day 15 and weekly thereafter.

Altogether, 410 UM patients have received tebentafusp (any dosing) as shown in the table above (study 01+102+202). Their safety data are pooled together and the safety data from study 202 has been compared to the pooled data.

2.6.8.1. Patient exposure

Table 42. Uveal Melanoma Patients: Extent of Exposure (Safety Analysis Set)

Parameter	Study 01 All Doses (N = 19)	Study 102 Phase 1 All Doses (N = 19)	Study 102 Phase 2 20/30/68 mcg (N = 127)	Study 202 20/30/68 mcg (N = 245)	All Studies (N = 410)
Duration of treatment with tebentafusp, weeks					
n	19	19	127	245	410
Mean (SD)	32.11 (45.47)	65.34 (56.29)	35.29 (31.21)	31.11 (27.18)	34.04 (31.98)
Median (min, max)	12.14 (0.1, 165.1)	51.14 (5.1, 200.7)	24.14 (0.1, 152.1)	23.14 (0.1, 145.1)	23.36 (0.1, 200.7)
Duration of treatment with tebentafusp by category, n (%)					
0 - < 12 weeks	9 (47.4%)	3 (15.8%)	30 (23.6%)	53 (21.6%)	95 (23.2%)
12 - < 24 weeks	4 (21.1%)	1 (5.3%)	33 (26.0%)	76 (31.0%)	114 (27.8%)
24 - < 36 weeks	0	3 (15.8%)	17 (13.4%)	45 (18.4%)	65 (15.9%)

Table 42. Uveal Melanoma Patients: Extent of Exposure (Safety Analysis Set)

Parameter	Study 01 All Doses (N = 19)	Study 102 Phase 1 All Doses (N = 19)	Study 102 Phase 2 20/30/68 mcg (N = 127)	Study 202 20/30/68 mcg (N = 245)	All Studies (N = 410)
36 - < 48 weeks	3 (15.8%)	1 (5.3%)	6 (4.7%)	27 (11.0%)	37 (9.0%)
48 - < 72 weeks	1 (5.3%)	5 (26.3%)	26 (20.5%)	25 (10.2%)	57 (13.9%)
72 - < 96 weeks	0	3 (15.8%)	8 (6.3%)	8 (3.3%)	19 (4.6%)
≥ 96 weeks	2 (10.5%)	3 (15.8%)	7 (5.5%)	11 (4.5%)	23 (5.6%)
Total actual dose of tebentafusp received, mcg					
n	19	19	127	245	410
Mean (SD)	1546.5 (2156.74)	3954.8 (3434.23)	2270.1 (2053.07)	1998.8 (1760.44)	2152.5 (2014.34)
Median (min, max)	760.0 (0, 8130)	3120.0 (322, 12607)	1546.0 (20, 9842)	1478.0 (20, 9570)	1546.0 (0, 12607)
Dose intensity of tebentafusp, mcg per week					
n	19	19	127	245	410
Mean (SD)	81.77 (126.08)	61.50 (7.78)	64.78 (12.93)	64.85 (12.92)	65.45 (29.44)
Median (min, max)	49.36 (3.4, 592.2)	63.28 (36.7, 74.5)	64.92 (39.9, 140.0)	65.59 (10.2, 140.0)	65.01 (3.4, 592.2)
Relative dose intensity of tebentafusp, %					
n	NA	19	127	245	391
Mean (SD)	-	94.52 (6.51)	96.73 (6.72)	99.95 (0.43)	98.64 (4.45)
Median (min, max)	-	97.17 (79.2, 100.00)	100.00 (62.6, 100.0)	100.00 (95.4, 100.0)	100.00 (62.6, 100.00)

NA = not applicable; SD = standard deviation.
Note that for patients in Study 401, exposure in their original study (01) will be combined with exposure in Study 401 but summarised as a part of the original study.
Duration of treatment (days) = (date of last study drug administration – date of first study drug administration + 1). Total actual dose received = sum of the total dose levels that a patient received during the study.
Dose intensity (dose per week) = Total actual dose received / (Duration of treatment [weeks]). Relative dose intensity (%) = the percentage of total actual dose delivered relative to the total planned/intended dose through to treatment discontinuation.
Study 01 due to total planned dose not being calculable is NA.
Source: Module 5.3.5.3, Table ISS 01.01.07.01.

Table 43. Uveal Melanoma Patients: Dose Interruptions and Reductions (Safety Analysis Set)

Parameter	Study 01 All Doses (N = 19)	Study 102 Phase 1 All Doses (N = 19)	Study 102 Phase 2 20/30/68 mcg (N = 127)	Study 202 20/30/68 mcg (N = 245)	All Studies (N = 410)
No interruptions and no reduction at any time, n (%)	7 (36.8%)	6 (31.6%)	78 (61.4%)	137 (55.9%)	228 (55.6%)
Interruption or reduction at any time, n (%)	12 (63.2%)	13 (68.4%)	49 (38.6%)	108 (44.1%)	182 (44.4%)
No interruption at any time, n (%)	10 (52.6%)	8 (42.1%)	84 (66.1%)	141 (57.6%)	243 (59.3%)
Number of patients with an interruption, n (%)					
Any	9 (47.4%)	11 (57.9%)	43 (33.9%)	104 (42.4%)	167 (40.7%)

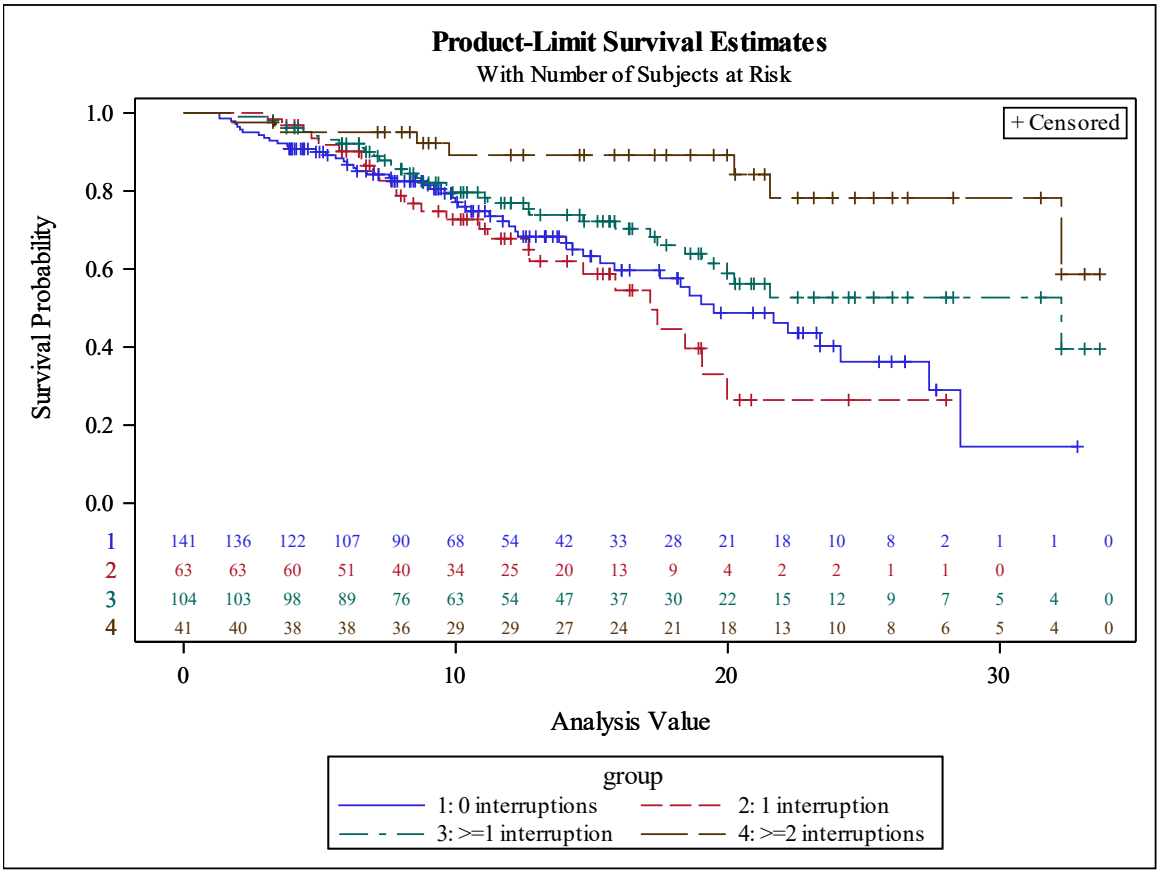
Table 43. Uveal Melanoma Patients: Dose Interruptions and Reductions (Safety Analysis Set)

Parameter	Study 01 All Doses (N = 19)	Study 102 Phase 1 All Doses (N = 19)	Study 102 Phase 2 20/30/68 mcg (N = 127)	Study 202 20/30/68 mcg (N = 245)	All Studies (N = 410)
1 interruption	6 (31.6%)	2 (10.5%)	27 (21.3%)	63 (25.7%)	98 (23.9%)
2 interruptions	1 (5.3%)	1 (5.3%)	7 (5.5%)	17 (6.9%)	26 (6.3%)
3 interruptions	2 (10.5%)	2 (10.5%)	4 (3.1%)	10 (4.1%)	18 (4.4%)
4 interruptions	0	3 (15.8%)	2 (1.6%)	3 (1.2%)	8 (2.0%)
5 interruptions	0	2 (10.5%)	1 (0.8%)	3 (1.2%)	6 (1.5%)
6 interruptions	0	0	0	2 (0.8%)	2 (0.5%)
7 interruptions	0	0	2 (1.6%)	1 (0.4%)	3 (0.7%)
8 interruptions	0	0	0	1 (0.4%)	1 (0.2%)
9 interruptions	0	1 (5.3%)	0	1 (0.4%)	2 (0.5%)
10 interruptions	0	0	0	2 (0.8%)	2 (0.5%)
12 interruptions	0	0	0	1 (0.4%)	1 (0.2%)
Reason for interruption at any time, n (%) [a]					
Adverse event	5 (55.6%)	8 (72.7%)	22 (51.2%)	36 (34.6%)	71 (42.5%)
Delayed administration	6 (66.7%)	2 (18.2%)	4 (9.3%)	21 (20.2%)	33 (19.8%)
Other	3 (33.3%)	9 (81.8%)	29 (67.4%)	71 (68.3%)	112 (67.1%)
No reduction at any time, n (%)	**12 (63.2%)**	**14 (73.7%)**	**113 (89.0%)**	**227 (92.7%)**	**366 (89.3%)**
Number of patients with a reduction, n (%)					
Any	7 (36.8%)	5 (26.3%)	14 (11.0%)	18 (7.3%)	44 (10.7%)
1 reduction	1 (5.3%)	3 (15.8%)	12 (9.4%)	14 (5.7%)	30 (7.3%)
2 reductions	5 (26.3%)	2 (10.5%)	2 (1.6%)	2 (0.8%)	11 (2.7%)
4 reductions	1 (5.3%)	0	0	2 (0.8%)	3 (0.7%)
Reason for reduction, n (%) a					
Adverse event	7 (100.0%)	4 (80.0%)	6 (42.9%)	14 (77.8%)	31 (70.5%)
Other	1 (14.3%)	1 (20.0%)	9 (64.3%)	4 (22.2%)	15 (34.1%)

[a] Patients with multiple interruptions or reductions are counted once per unique reason. Percentages are based on the number of patients with any interruptions or reductions within each treatment group.
Interruptions are only counted if study drug administration restarts following interruption.
Interruptions recorded over consecutive dosing visits are only counted as a single interruption but may have more than one reason recorded in 'Reason for interruption at any time'.
For patients with intra-dose escalation, reductions from protocol dose level are derived at Cycle 1 Day 1 if planned dose is less than 20 mcg, at Cycle 1 Day 8 if planned dose is less than 30 mcg, and at Cycle 1 Day 15 if planned dose is less than the cohort-specified dose level. In cases where a patient remains on 20 mcg or 30 mcg for multiple consecutive doses, each repetition is considered a reduction.
Source: Module 5.3.5.3, Table ISS 01.01.08.01.

Since this was a weekly dosing regimen until progression or unacceptable toxicity, per protocol, patients were not prohibited from taking treatment breaks for up to two consecutive doses for any reason. It is seen that a considerable number of patients (104 (42.2%)) had one or more dose interruptions. The reasons for interruptions were: AEs (34.6%), delayed administration (20.2%) and other (68.3%).

Figure 29. Kaplan-Meier Estimates of Overall Survival by Number of Interruption Categories



In Table 44 it is shown that patients with at least one interruption had a higher median OS (**32.3** months (19.1, NC)) than those without (**19.5** months (15.8, 27.4)) which could reflect that patients, who are on treatment for longer periods are more likely to have an interruption at some point. Patients with interruptions due to AEs had a median OS of **20.2** months (17.4, NC), which is similar to that of patients without interruptions. The median OS for patients with interruptions due to other reasons was not calculable.

Table 44. Overall Survival for Tebentafusp-treated Patients by Interruption Group (Study 202)

Interruption Group	Number of Patients	Median OS in months (95% CI)
No Interruptions	141	19.5 (15.8, 27.4)
≥1 Interruptions (any reason)	104	32.3 (19.1, NC)
Interruptions due to AEs	36	20.2 (17.4, NC)
Interruptions due to other reasons	28	NC (14.7, NC)

CI = confidence interval; NC = not calculable; OS = overall survival.

In the provided **table 43**, it has been specified what the reason for interruptions "other" comprises. A great number of these reasons was not registered; "missing" data in 66 (16.9%) patients overall and 52 (21.2%) patients in study 202. Hereafter, the most frequent reason was "vacation/patient preference"; 33 (8.9%) patients overall and 13 (5.3%) patients in study 202. Other listed reasons were infrequent. The applicant provided the performance status and other central baseline

characteristics of patients with 1 or more and with 2 or more interruptions in Table 45. Baseline characteristics for the 3 groups; patients without interruptions, patients with ≥1 interruption and patients with ≥2 interruptions are very similar and no differences in prognosis would therefore be anticipated.

Table 45. Baseline Characteristics for Tebentafusp-treated Patients by Interruption Group (Study 202)

Baseline Characteristic	Baseline Category	No Interruptions n (%)	≥1 Interruption n (%)	≥2 Interruptions n (%)
N	N	141 (100.0)	104 (100.0)	41 (100.0)
Age	<65	72 (51.1)	54 (51.9)	25 (61.0)
	≥65	69 (48.9)	50 (48.1)	16 (39.0)
Gender	Female	67 (47.5)	53 (51.0)	23 (56.1)
	Male	74 (52.5)	51 (49.0)	18 (43.9)
ECOG	0	107 (75.9)	84 (80.8)	34 (82.9)
	1	31 (22.0)	18 (17.3)	7 (17.1)
Stage at initial diagnosis	Stage I	27 (19.1)	20 (19.2)	10 (24.4)
	Stage II	50 (35.5)	35 (33.7)	11 (26.8)
	Stage III	30 (21.3)	25 (24.0)	10 (24.4)
	Stage IV	14 (9.9)	9 (8.7)	5 (12.2)
LDH	LDH ≤ULN 250 U/L (n, %)	88 (62.4)	70 (67.3)	30 (73.2)
	LDH >ULN 250 U/L (n, %)	53 (37.6)	34 (32.7)	11 (26.8)
ALP	ALP ≤ULN	109 (77.3)	84 (80.8)	35 (85.4)
	ALP >ULN	31 (22.0)	20 (19.2)	6 (14.6)
Liver Mets	<3 cm	84 (59.6)	48 (46.2)	22 (53.7)
	≥3 cm	56 (39.7)	48 (46.2)	15 (36.6)
	No liver lesion	1 (0.7)	8 (7.7)	4 (9.8)

Compared to investigator's choice (pembrolizumab, ipilimumab, dacarbazine), the mean number of completed cycles and mean duration of treatment was higher with tebentafusp. Dose intensity was equal. However, it is important to note that ipilimumab SmPC recommends a treatment duration of 4 cycles of 3 weeks which may have an impact the median treatment duration and number of cycles. This higher number of cycles in the tebentafusp arm may also be explained by the higher percentage of patients who received treatment beyond progression in the experimental arm (27.8% vs 11.9% in tebentafusp and comparator arms respectively).

Table 46. Extent of Exposure to Treatment by Investigator Pre- choice of Therapy Prior to Randomisation (Safety Analysis Set)

Characteristic	Investigator's Choice Prior to Randomisation by Study Arm					
	Dacarbazine		Ipilimumab		Pembrolizumab	
	Tebentafusp (N=12)	Investigator's Choice (N=7)	Tebentafusp (N=40)	Investigator's Choice (N=13)	Tebentafusp (N=193)	Investigator's Choice (N=91)
Number of cycles started						
n	12	7	40	13	193	91
Mean (SD)	7.1 (4.70)	3.6 (2.64)	9.5 (7.95)	3.9 (0.28)	11.3 (8.98)	6.9 (6.48)
Median (Min, Max)	6.0 (2, 19)	3.0 (1.8)	7.0 (1, 39)	4.0 (3, 4)	9.0 (1, 44)	5.0 (1, 32)
Number of cycles completed						
n	12	7	40	13	193	91
Mean (SD)	6.3 (4.14)	3.6 (2.64)	8.1 (7.57)	3.9 (0.28)	9.7 (7.84)	6.9 (6.48)
Median (Min, Max)	5.0 (1, 15)	3.0 (1, 8)	6.0 (0, 38)	4.0 (3, 4)	8.0 (0, 38)	5.0 (1, 32)
Duration of treatment (days)						
n	12	7	40	13	193	91
Mean (SD)	139.6 (98.72)	60.4 (62.17)	187.5 (166.32)	62.5 (5.87)	231.2 (199.33)	131.5 (139.98)
Median (Min, Max)	111.5 (22, 385)	43.0 (1, 169)	131.0 (1, 805)	64.0 (43, 65)	169.0 (1, 1016)	84.0 (1, 658)
Relative dose intensity (%)						
n	12	7	40	13	193	91
Mean (SD)	100.0 (0.00)	100.0 (0.00)	100.0 (0.00)	100.0 (0.00)	99.9 (0.48)	100.0 (0.01)
Median (Min, Max)	100.0 (100, 100)	100.0 (100, 100)	100.0 (100, 100)	100.0 (100, 100)	100.0 (95, 100)	100.0 (100, 100)

Max = maximum; Min = minimum; NA = not applicable; SD = standard deviation.

2.6.8.2. Adverse events

Table 47. Uveal Melanoma Patients: Overall Summary of Adverse Events (Safety Analysis Set)

Patients with	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Any TEAE	19 (100.0%)	19 (100.0%)	127 (100.0%)	245 (100.0%)	410 (100.0%)
TEAE by highest CTCAE Grade					
1	3 (15.8%)	0	2 (1.6%)	14 (5.7%)	19 (4.6%)
2	2 (10.5%)	2 (10.5%)	50 (39.4%)	98 (40.0%)	152 (37.1%)
3	7 (36.8%)	15 (78.9%)	62 (48.8%)	117 (47.8%)	201 (49.0%)
4	7 (36.8%)	2 (10.5%)	13 (10.2%)	15 (6.1%)	37 (9.0%)
5	0	0	0	1 (0.4%)	1 (0.2%)
Any TEAE causally related tebentafusp [a]	19 (100.0%)	19 (100.0%)	127 (100.0%)	243 (99.2%)	408 (99.5%)
Any TEAE with maximum CTCAE of Grade 3 or 4	14 (73.7%)	17 (89.5%)	75 (59.1%)	133 (54.3%)	239 (58.3%)
Any TEAE with maximum CTCAE of Grade 4	7 (36.8%)	2 (10.5%)	13 (10.2%)	15 (6.1%)	37 (9.0%)

Table 47. Uveal Melanoma Patients: Overall Summary of Adverse Events (Safety Analysis Set)

Patients with	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Any TEAE with maximum CTCAE of Grade 3 or 4 and causally related to tebentafusp [a]	12 (63.2%)	15 (78.9%)	59 (46.5%)	109 (44.5%)	195 (47.6%)
Any serious TEAE	6 (31.6%)	10 (52.6%)	43 (33.9%)	69 (28.2%)	128 (31.2%)
Any serious TEAE causally related to tebentafusp [a]	3 (15.8%)	6 (31.6%)	27 (21.3%)	54 (22.0%)	90 (22.0%)
A TEAE leading to permanent discontinuation of tebentafusp	0	0	7 (5.5%)	8 (3.3%)	15 (3.7%)
A TEAE leading to permanent discontinuation of tebentafusp and causally related to tebentafusp [a]	0	0	3 (2.4%)	5 (2.0%)	8 (2.0%)
Any TEAE leading to drug interruptions of tebentafusp	3 (15.8%)	8 (42.1%)	34 (26.8%)	62 (25.3%)	107 (26.1%)
Any TEAE leading to drug interruptions of tebentafusp that were causally related to tebentafusp [a]	1 (5.3%)	5 (26.3%)	22 (17.3%)	44 (18.0%)	72 (17.6%)
Any TEAE leading to dose reductions of tebentafusp	0	4 (21.1%)	3 (2.4%)	13 (5.3%)	20 (4.9%)
Any TEAE leading to dose reductions of tebentafusp that were causally related to tebentafusp [a]	0	4 (21.1%)	3 (2.4%)	12 (4.9%)	19 (4.6%)
A TEAE leading to death	0	0	0	1 (0.4%)	1 (0.2%)
A TEAE leading to death and causally related to tebentafusp [a]	0	0	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events; n = number of patients; TEAE = treatment-emergent adverse event
[a] Determined by the investigator to be possibly related, probably related, definitely related, or related to tebentafusp.
TEAEs are defined as any adverse event (AE) with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first. Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
Serious adverse events (SAEs) include deaths as an outcome of SAEs and non-fatal SAEs.
Patient IMCGP100-202-6302006 had a Grade 3 TEAE of "pulmonary embolism" which increased to Grade 5. This patient is counted under "Grade 5", "maximum CTCAE Grade 3 or 4", and "TEAE leading to death" in this table.
Source: Module 5.3.5.3, Table ISS 02.03.01.01.

Table 48. Uveal Melanoma Patients: Adverse Events Reported in ≥ 10% of Patients in All Studies (Safety Analysis Set)

System Organ Class (SOC)/ Preferred Term (PT)	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Number of patients with any TEAE	**19 (100.0%)**	**19 (100.0%)**	**127 (100.0%)**	**245 (100.0%)**	**410 (100.0%)**
Blood and lymphatic system disorders	**9 (47.4%)**	**9 (47.4%)**	**24 (18.9%)**	**63 (25.7%)**	**105 (25.6%)**
Anaemia	6 (31.6%)	6 (31.6%)	17 (13.4%)	25 (10.2%)	54 (13.2%)
Cardiac disorders	**5 (26.3%)**	**4 (21.1%)**	**37 (29.1%)**	**37 (15.1%)**	**83 (20.2%)**
Tachycardia	2 (10.5%)	2 (10.5%)	15 (11.8%)	24 (9.8%)	43 (10.5%)
Eye disorders	**11 (57.9%)**	**15 (78.9%)**	**68 (53.5%)**	**79 (32.2%)**	**173 (42.2%)**
Periorbital oedema	8 (42.1%)	12 (63.2%)	34 (26.8%)	26 (10.6%)	80 (19.5%)
Gastrointestinal disorders	**17 (89.5%)**	**19 (100.0%)**	**113 (89.0%)**	**194 (79.2%)**	**343 (83.7%)**
Nausea	13 (68.4%)	16 (84.2%)	85 (66.9%)	120 (49.0%)	234 (57.1%)
Vomiting	12 (63.2%)	10 (52.6%)	53 (41.7%)	73 (29.8%)	148 (36.1%)
Abdominal pain	4 (21.1%)	11 (57.9%)	45 (35.4%)	60 (24.5%)	120 (29.3%)
Diarrhoea	5 (26.3%)	9 (47.4%)	34 (26.8%)	61 (24.9%)	109 (26.6%)
Constipation	5 (26.3%)	10 (52.6%)	32 (25.2%)	44 (18.0%)	91 (22.2%)
Abdominal pain upper	3 (15.8%)	5 (26.3%)	25 (19.7%)	50 (20.4%)	83 (20.2%)
Dyspepsia	3 (15.8%)	4 (21.1%)	15 (11.8%)	20 (8.2%)	42 (10.2%)
General disorders and administration site conditions	**18 (94.7%)**	**19 (100.0%)**	**124 (97.6%)**	**231 (94.3%)**	**392 (95.6%)**
Pyrexia	13 (68.4%)	18 (94.7%)	104 (81.9%)	187 (76.3%)	322 (78.5%)
Fatigue	13 (68.4%)	17 (89.5%)	78 (61.4%)	125 (51.0%)	233 (56.8%)
Chills	9 (47.4%)	14 (73.7%)	85 (66.9%)	117 (47.8%)	225 (54.9%)
Oedema peripheral	5 (26.3%)	16 (84.2%)	44 (34.6%)	66 (26.9%)	131 (32.0%)
Face oedema	6 (31.6%)	5 (26.3%)	15 (11.8%)	25 (10.2%)	51 (12.4%)
Influenza like illness	5 (26.3%)	5 (26.3%)	23 (18.1%)	18 (7.3%)	51 (12.4%)
Asthenia	0	0	9 (7.1%)	38 (15.5%)	47 (11.5%)
Hepatobiliary disorders	**2 (10.5%)**	**6 (31.6%)**	**22 (17.3%)**	**51 (20.8%)**	**81 (19.8%)**
Hyperbilirubinaemia	0	3 (15.8%)	10 (7.9%)	28 (11.4%)	41 (10.0%)
Immune system disorders	**3 (15.8%)**	**2 (10.5%)**	**15 (11.8%)**	**55 (22.4%)**	**75 (18.3%)**
Cytokine release syndrome	2 (10.5%)	0	10 (7.9%)	51 (20.8%)	63 (15.4%)
Investigations	**7 (36.8%)**	**13 (68.4%)**	**66 (52.0%)**	**132 (53.9%)**	**218 (53.2%)**
Aspartate aminotransferase increased	1 (5.3%)	5 (26.3%)	23 (18.1%)	56 (22.9%)	85 (20.7%)
Alanine aminotransferase increased	1 (5.3%)	5 (26.3%)	19 (15.0%)	51 (20.8%)	76 (18.5%)
Lipase increased	1 (5.3%)	2 (10.5%)	12 (9.4%)	35 (14.3%)	50 (12.2%)
Blood alkaline phosphatase increased	3 (15.8%)	5 (26.3%)	13 (10.2%)	23 (9.4%)	44 (10.7%)
Weight decreased	1 (5.3%)	4 (21.1%)	20 (15.7%)	16 (6.5%)	41 (10.0%)
Metabolism and nutrition disorders	**7 (36.8%)**	**16 (84.2%)**	**70 (55.1%)**	**110 (44.9%)**	**203 (49.5%)**
Decreased appetite	3 (15.8%)	7 (36.8%)	32 (25.2%)	45 (18.4%)	87 (21.2%)
Hypophosphataemia	3 (15.8%)	4 (21.1%)	15 (11.8%)	27 (11.0%)	49 (12.0%)
Musculoskeletal and connective tissue disorders	**10 (52.6%)**	**18 (94.7%)**	**91 (71.7%)**	**116 (47.3%)**	**235 (57.3%)**
Arthralgia	2 (10.5%)	10 (52.6%)	42 (33.1%)	53 (21.6%)	107 (26.1%)
Back pain	4 (21.1%)	13 (68.4%)	41 (32.3%)	45 (18.4%)	103 (25.1%)
Myalgia	5 (26.3%)	8 (42.1%)	23 (18.1%)	24 (9.8%)	60 (14.6%)

Pain in extremity	3 (15.8%)	10 (52.6%)	18 (14.2%)	24 (9.8%)	55 (13.4%)
Nervous system disorders	**8 (42.1%)**	**17 (89.5%)**	**75 (59.1%)**	**127 (51.8%)**	**227 (55.4%)**
Headache	7 (36.8%)	11 (57.9%)	42 (33.1%)	75 (30.6%)	135 (32.9%)
Dizziness	1 (5.3%)	8 (42.1%)	21 (16.5%)	27 (11.0%)	57 (13.9%)
Paraesthesia	3 (15.8%)	5 (26.3%)	10 (7.9%)	27 (11.0%)	45 (11.0%)
Psychiatric disorders	**1 (5.3%)**	**10 (52.6%)**	**42 (33.1%)**	**45 (18.4%)**	**98 (23.9%)**
Insomnia	0	7 (36.8%)	20 (15.7%)	22 (9.0%)	49 (12.0%)
Respiratory, thoracic and mediastinal disorders	**10 (52.6%)**	**17 (89.5%)**	**69 (54.3%)**	**93 (38.0%)**	**189 (46.1%)**
Cough	4 (21.1%)	8 (42.1%)	29 (22.8%)	44 (18.0%)	85 (20.7%)
Dyspnoea	2 (10.5%)	7 (36.8%)	24 (18.9%)	32 (13.1%)	65 (15.9%)
Skin and subcutaneous tissue disorders	**18 (94.7%)**	**19 (100.0%)**	**122 (96.1%)**	**229 (93.5%)**	**388 (94.6%)**
Pruritus	13 (68.4%)	17 (89.5%)	96 (75.6%)	169 (69.0%)	295 (72.0%)
Rash	12 (63.2%)	6 (31.6%)	56 (44.1%)	135 (55.1%)	209 (51.0%)
Dry skin	5 (26.3%)	12 (63.2%)	50 (39.4%)	77 (31.4%)	144 (35.1%)
Rash maculo-papular	7 (36.8%)	1 (5.3%)	51 (40.2%)	75 (30.6%)	134 (32.7%)
Erythema	4 (21.1%)	10 (52.6%)	36 (28.3%)	60 (24.5%)	110 (26.8%)
Hair colour changes	5 (26.3%)	8 (42.1%)	34 (26.8%)	48 (19.6%)	95 (23.2%)
Skin exfoliation	7 (36.8%)	1 (5.3%)	28 (22.0%)	51 (20.8%)	87 (21.2%)
Skin hypopigmentation	0	5 (26.3%)	24 (18.9%)	22 (9.0%)	51 (12.4%)
Vitiligo	1 (5.3%)	2 (10.5%)	8 (6.3%)	40 (16.3%)	51 (12.4%)
Skin hyperpigmentation	0	6 (31.6%)	21 (16.5%)	19 (7.8%)	46 (11.2%)
Vascular disorders	**10 (52.6%)**	**17 (89.5%)**	**79 (62.2%)**	**131 (53.5%)**	**237 (57.8%)**
Hypotension	8 (42.1%)	14 (73.7%)	53 (41.7%)	95 (38.8%)	170 (41.5%)
Hypertension	3 (15.8%)	2 (10.5%)	19 (15.0%)	38 (15.5%)	62 (15.1%)
Flushing	2 (10.5%)	1 (5.3%)	16 (2.6%)	25 (10.2%)	44 (10.7%)

n = number of patients; PT = preferred term, SOC = system organ class; TEAE = treatment-emergent adverse event
Patients with multiple TEAEs per SOC or PT are counted only once in each row.
Adverse events (AEs) are coded using MedDRA version 23.1.
TEAEs are defined as any AE with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.
Number (%) of patients are sorted alphabetically for SOC and by descending frequency overall for PT. A patient can have one or more PTs reported under a given SOC.
Source: Module 5.3.5.3, Table ISS 02.03.02.01.01.

Table 49. TEAEs by SOC and PT in ≥ 10% of Patients (Safety Analysis Set)

System Organ Class Preferred Term	Tebentafusp (N=245)		Investigator's Choice (N=111)	
	n (%)	EAIR (per 100 PY) [a]	n (%)	EAIR (per 100 PY) [a]
Patients with any TEAE	245 (100.0)	15726.9	105 (94.6)	1436.9
Blood and lymphatic system disorders	**63 (25.7)**	**44.4**	**15 (13.5)**	**29.5**
Anaemia	25 (10.2)	14.6	4 (3.6)	7.5
Immune system disorders	**55 (22.4)**	**35.6**	**0**	**0**
Cytokine release syndrome [b]	51 (20.8)	32.4	0	0
Endocrine disorders	**5 (2.0)**	**2.7**	**23 (20.7)**	**55.0**
Hypothyroidism	3 (1.2)	1.6	12 (10.8)	26.1
Hyperthyroidism	2 (0.8)	1.1	13 (11.7)	27.3
Metabolism and nutrition disorders	**110 (44.9)**	**99.1**	**29 (26.1)**	**66.9**
Decreased appetite	45 (18.4)	26.9	15 (13.5)	29.9
Hypophosphataemia	27 (11.0)	16.5	2 (1.8)	3.8
Nervous system disorders	**127 (51.8)**	**140.0**	**30 (27.0)**	**71.3**
Headache	75 (30.6)	60.1	11 (9.9)	22.3
Dizziness	27 (11.0)	16.6	9 (8.1)	17.5
Paraesthesia	27 (11.0)	16.3	1 (0.9)	1.9
Eye disorders	**79 (32.2)**	**64.5**	**15 (13.5)**	**31.2**
Periorbital oedema	26 (10.6)	16.1	1 (0.9)	1.9
Vascular disorders	**131 (53.5)**	**136.5**	**15 (13.5)**	**30.6**
Hypotension	95 (38.8)	78.1	3 (2.7)	5.7
Hypertension	38 (15.5)	24.2	8 (7.2)	15.3
Flushing	25 (10.2)	14.7	1 (0.9)	1.9

System Organ Class Preferred Term	Tebentafusp (N=245)		Investigator's Choice (N=111)	
	n (%)	EAIR (per 100 PY) [a]	n (%)	EAIR (per 100 PY) [a]
Respiratory, thoracic and mediastinal disorders	**93 (38.0)**	**76.5**	**23 (20.7)**	**49.2**
Cough	44 (18.0)	28.5	11 (9.9)	22.1
Dyspnoea	32 (13.1)	19.4	7 (6.3)	13.2
Gastrointestinal disorders	**194 (79.2)**	**333.3**	**66 (59.5)**	**244.6**
Nausea	120 (49.0)	114.2	29 (26.1)	68.6
Vomiting	73 (29.8)	54.6	10 (9.0)	19.2
Diarrhoea	61 (24.9)	42.7	22 (19.8)	49.7
Abdominal pain	60 (24.5)	40.0	17 (15.3)	34.0
Abdominal pain upper	50 (20.4)	31.5	14 (12.6)	28.1
Constipation	44 (18.0)	26.8	13 (11.7)	26.7
Hepatobiliary disorders	**51 (20.8)**	**32.1**	**17 (15.3)**	**32.9**
Hyperbilirubinaemia	28 (11.4)	16.4	8 (7.2)	15.0
Skin and subcutaneous tissue disorders	**229 (93.5)**	**2141.9**	**51 (45.9)**	**160.4**
Pruritus	169 (69.0)	323.8	26 (23.4)	60.9
Rash	135 (55.1)	176.6	18 (16.2)	37.1
Dry skin	77 (31.4)	59.1	4 (3.6)	7.8
Rash maculo-papular	75 (30.6)	59.9	9 (8.1)	17.6
Erythema	60 (24.5)	42.4	1 (0.9)	1.8
Skin exfoliation	51 (20.8)	34.0	2 (1.8)	3.7
Hair colour changes	48 (19.6)	31.5	0	0
Vitiligo	40 (16.3)	25.8	4 (3.6)	7.7
Musculoskeletal and connective tissue disorders	**116 (47.3)**	**108.2**	**35 (31.5)**	**98.3**
Arthralgia	53 (21.6)	34.8	18 (16.2)	41.1
Back pain	45 (18.4)	28.8	9 (8.1)	18.0
General disorders and administration site conditions	**231 (94.3)**	**1939.6**	**56 (50.5)**	**172.3**
Pyrexia	187 (76.3)	387.7	8 (7.2)	15.2
Fatigue	125 (51.0)	124.4	39 (35.1)	101.4
Chills	117 (47.8)	113.3	4 (3.6)	7.6
Oedema peripheral	66 (26.9)	45.6	3 (2.7)	5.6
Asthenia	38 (15.5)	23.2	9 (8.1)	17.7
Face oedema	25 (10.2)	15.1	2 (1.8)	3.7
Investigations [c]	**132 (53.9)**	**137.9**	**37 (33.3)**	**87.2**
AST increased	56 (22.9)	36.6	11 (9.9)	21.4
ALT increased	51 (20.8)	33.4	12 (10.8)	23.5
Lipase increased	35 (14.3)	21.7	7 (6.3)	13.4

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome; EAIR = exposure-adjusted incidence rate; MedDRA = Medical Dictionary for Regulatory Activities; PY = patient-years; SOC = system organ class; TEAE = treatment-emergent adverse event.

Patients with multiple TEAEs are counted once for each system organ class/preferred term.

Includes TEAEs with an onset date on or after the date of first dose or pre-treatment TEAEs that increase in severity on or after the date of first dose up to an including 90 days following the date of last dose of study drug or up to an including the date of initiation of the first subsequent therapy (whichever occurs first).

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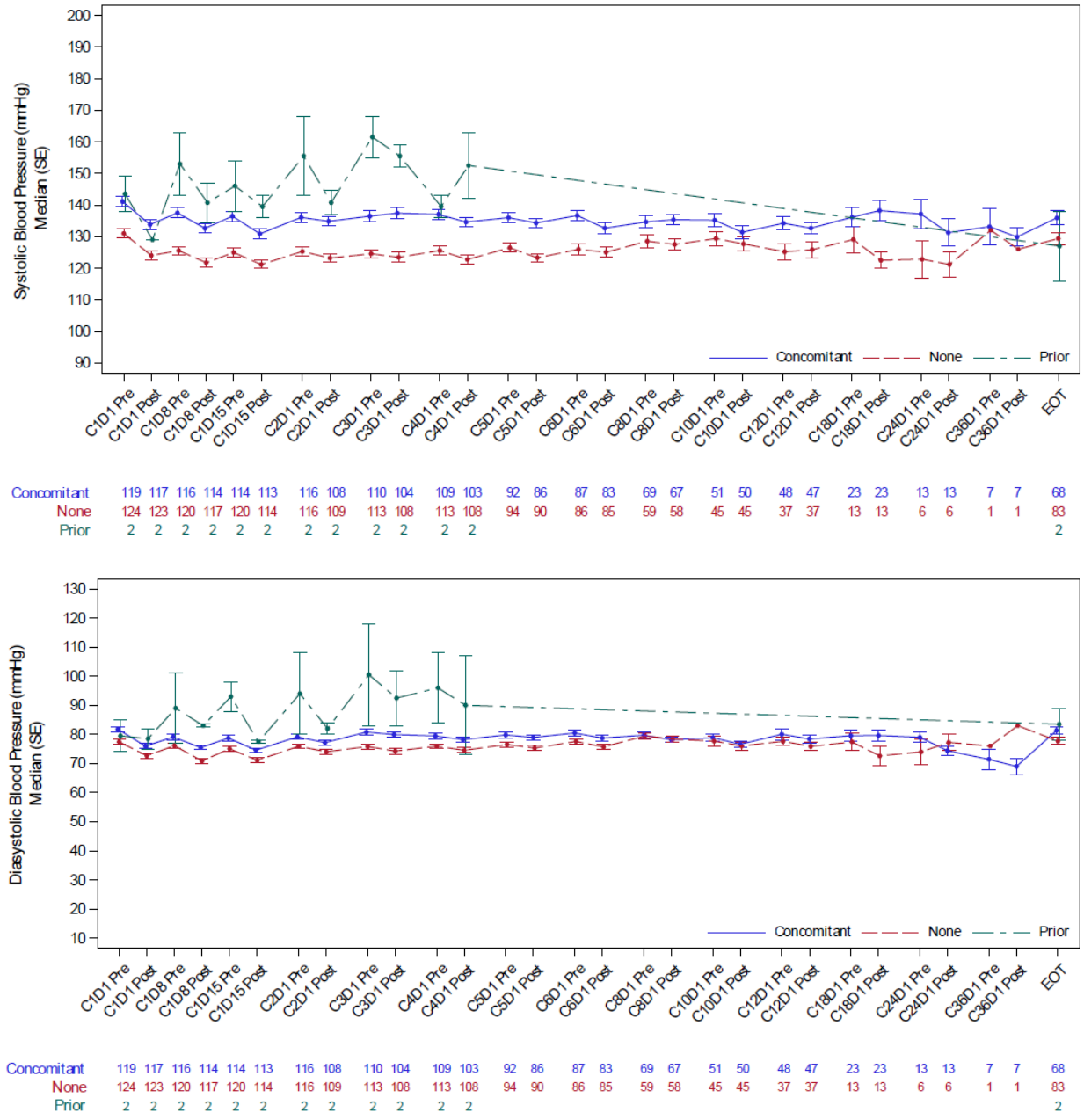
[a] EAIR is defined as the number of patients with the event divided by the total exposure time of all patients who are at risk of the event. For patients with no reported event, the exposure is the time from the date of first dose of study drug until 90 days after the last dose of stud drug or until the start of subsequent anticancer therapy, whichever occurs first. For patients who experience the event, the exposure time is the time from the date of first dose of study drug to the start date of the first event.

[b] As reported by the investigator based on Lee, 2014 criteria. Refer to Section 12.2.3.4.1 for Sponsor-adjudicated CRS based on the more comprehensive 2019 ASTCT consensus grading for CRS (Lee, 2019).

[c] This SOC includes laboratory abnormalities reported as adverse events by the investigator and does not reflect all laboratory abnormalities reported in the study. Refer to Section 12.4.2 for a detailed presented of laboratory abnormalities, including liver enzyme abnormalities (Section 12.4.2.2.1).

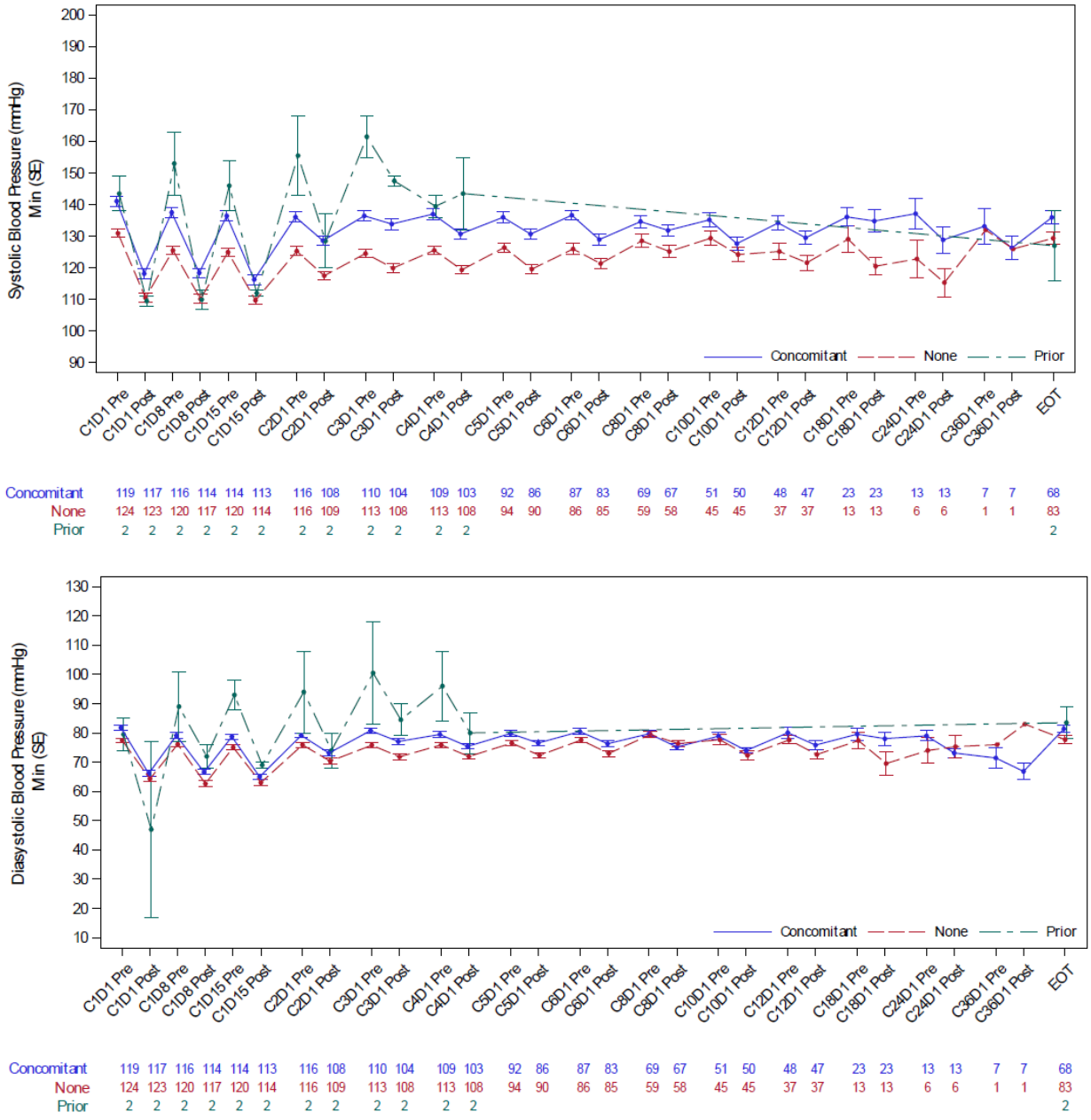
Source: Table 14.3.1.2.

Figure 30. Median Systolic and Diastolic Blood Pressure by Anti – hypertensive Treatment Status (Safety Analysis Set)



Prior medication may include concomitant medication starting after 30 days.
CxDx = Cycle x Day x; IMCgp100 = tebentafusp; SE = standard error.

Figure 31. Minimum Systolic and Diastolic Blood Pressure by Anti-hypertensive Treatment Status (Safety Analysis Set)



Prior medication may include concomitant medication starting after 30 days.
CxDx = Cycle x Day x; IMCgp100 = tebentafusp; SE = standard error.

Grade 3-4 Adverse events

Table 50. Uveal Melanoma Patients: Grade 3 or 4 Adverse Events Reported in ≥ 10% of Patients in Any Study (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Number of patients with any TEAE of maximum CTCAE Grade 3 or 4	14 (73.7%)	17 (89.5%)	75 (59.1%)	133 (54.3%)	239 (58.3%)
Blood and lymphatic system disorders	5 (26.3%)	2 (10.5%)	6 (4.7%)	10 (4.1%)	23 (5.6%)

Table 50. Uveal Melanoma Patients: Grade 3 or 4 Adverse Events Reported in ≥ 10% of Patients in Any Study (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Lymphopenia	5 (26.3%)	2 (10.5%)	4 (3.1%)	7 (2.9%)	18 (4.4%)
Gastrointestinal disorders	**1 (5.3%)**	**5 (26.3%)**	**11 (8.7%)**	**13 (5.3%)**	**30 (7.3%)**
Abdominal pain	0	3 (15.8%)	3 (2.4%)	4 (1.6%)	10 (2.4%)
General disorders and administration site conditions	**4 (21.1%)**	**4 (21.1%)**	**17 (13.4%)**	**21 (8.6%)**	**46 (11.2%)**
Fatigue	0	3 (15.8%)	4 (3.1%)	13 (5.3%)	20 (4.9%)
Pyrexia	3 (15.8%)	1 (5.3%)	6 (4.7%)	9 (3.7%)	19 (4.6%)
Investigations	**3 (15.8%)**	**5 (26.3%)**	**21 (16.5%)**	**37 (15.1%)**	**66 (16.1%)**
Aspartate aminotransferase increased	1 (5.3%)	3 (15.8%)	8 (6.3%)	13 (5.3%)	25 (6.1%)
Alanine aminotransferase increased	1 (5.3%)	2 (10.5%)	5 (3.9%)	8 (3.3%)	16 (3.9%)
Blood alkaline phosphatase increased	0	2 (10.5%)	2 (1.6%)	3 (1.2%)	7 (1.7%)
Metabolism and nutrition disorders	**3 (15.8%)**	**3 (15.8%)**	**19 (15.0%)**	**15 (6.1%)**	**40 (9.8%)**
Hypophosphataemia	3 (15.8%)	2 (10.5%)	10 (7.9%)	10 (4.1%)	25 (6.1%)
Musculoskeletal and connective tissue disorders	**0**	**5 (26.3%)**	**9 (7.1%)**	**4 (1.6%)**	**18 (4.4%)**
Arthralgia	0	3 (15.8%)	2 (1.6%)	2 (0.8%)	7 (1.7%)
Nervous system disorders	**0**	**2 (10.5%)**	**7 (5.5%)**	**7 (2.9%)**	**16 (3.9%)**
Syncope	0	2 (10.5%)	3 (2.4%)	3 (1.2%)	8 (2.0%)
Skin and subcutaneous tissue disorders	**7 (36.8%)**	**6 (31.6%)**	**24 (18.9%)**	**49 (20.0%)**	**86 (21.0%)**
Rash maculo-papular	2 (10.5%)	0	16 (12.6%)	21 (8.6%)	39 (9.5%)
Rash	4 (21.1%)	2 (10.5%)	2 (1.6%)	23 (9.4%)	31 (7.6%)
Erythema	0	3 (15.8%)	1 (0.8%)	0	4 (1.0%)
Rash erythematous	2 (10.5%)	1 (5.3%)	0	1 (0.4%)	4 (1.0%)
Rash macular	0	2 (10.5%)	0	0	2 (0.5%)
Vascular disorders	**2 (10.5%)**	**5 (26.3%)**	**19 (15.0%)**	**28 (11.4%)**	**54 (13.2%)**
Hypertension	1 (5.3%)	1 (5.3%)	8 (6.3%)	21 (8.6%)	31 (7.6%)
Hypotension	2 (10.5%)	3 (15.8%)	10 (7.9%)	8 (3.3%)	23 (5.6%)

CTCAE = Common Terminology Criteria for Adverse Events (version 4.03); n = number of patients; PT = preferred term, SOC = system organ class; TEAE = treatment-emergent adverse event.
Patients with multiple TEAEs per SOC or PT are counted only once in each row.
Adverse events (AEs) are coded using MedDRA version 23.1.
TEAEs are defined as any AE with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.
Number (%) of patients are sorted alphabetically for SOC and by descending frequency overall for PT. A patient can have one or more PTs reported under a given SOC.
Patient IMCGP100-202-6302006 had a Grade 3 TEAE of "pulmonary embolism" which increased to Grade 5. This patient is counted as Grade 3 in this table.
Source: Module 5.3.5.3, Table ISS 02.03.02.03.01.

Table 51. Grade ≥3 TEAEs by SOC and PT in ≥ 1% of Patients (Safety Analysis Set)

System Organ Class Preferred Term	Tebentafusp (N=245)		Investigator's Choice (N=111)	
	n (%)	EAIR (per 100 PY) [a]	n (%)	EAIR (per 100 PY) [a]
Patients with any Grade ≥3 TEAE	133 (54.3)	143.8	40 (36.0)	95.0
Infections and infestations	**9 (3.7)**	**5.0**	**2 (1.8)**	**3.7**
Urinary tract infection	3 (1.2)	1.6	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4 (1.6)**	**2.2**	**2 (1.8)**	**3.7**
Tumour pain	3 (1.2)	1.6	0	0
Blood and lymphatic system disorders	**10 (4.1)**	**5.6**	**2 (1.8)**	**3.7**
Lymphopenia	7 (2.9)	3.9	0	0
Neutropenia	1 (0.4)	0.5	2 (1.8)	3.7
Metabolism and nutrition disorders	**15 (6.1)**	**8.5**	**5 (4.5)**	**9.6**
Hypophosphataemia	10 (4.1)	5.6	1 (0.9)	1.9
Dehydration	0	0	2 (1.8)	3.7
Nervous system disorders	**7 (2.9)**	**3.9**	**6 (5.4)**	**11.6**
Syncope	3 (1.2)	1.7	0	0
Vascular disorders	**28 (11.4)**	**16.9**	**3 (2.7)**	**5.6**
Hypertension	21 (8.6)	12.5	3 (2.7)	5.6
Hypotension	8 (3.3)	4.4	0	0
Respiratory, thoracic and mediastinal disorders	**7 (2.9)**	**3.8**	**7 (6.3)**	**13.1**
Pulmonary embolism	2 (0.8)	1.1	4 (3.6)	7.4
Gastrointestinal disorders	**13 (5.3)**	**7.3**	**8 (7.2)**	**15.3**
Nausea	5 (2.0)	2.7	1 (0.9)	1.9
Abdominal pain	4 (1.6)	2.2	3 (2.7)	5.6
Diarrhoea	3 (1.2)	1.6	3 (2.7)	5.6
Vomiting	3 (1.2)	1.6	0	0
Colitis	0	0	2 (1.8)	3.7
Hepatobiliary disorders	**15 (6.1)**	**8.3**	**5 (4.5)**	**9.3**
Hyperbilirubinaemia	8 (3.3)	4.4	5 (4.5)	9.3
Skin and subcutaneous tissue disorders	**49 (20.0)**	**33.6**	**0**	**0**
Rash	23 (9.4)	13.9	0	0
Rash maculo-papular	21 (8.6)	12.7	0	0
Pruritus	11 (4.5)	6.3	0	0
General disorders and administration site conditions	**21 (8.6)**	**11.9**	**2 (1.8)**	**3.7**
Fatigue	13 (5.3)	7.2	1 (0.9)	1.8
Pyrexia	9 (3.7)	5.0	1 (0.9)	1.8

System Organ Class Preferred Term	Tebentafusp (N=245)		Investigator's Choice (N=111)	
	n (%)	EAIR (per 100 PY) [a]	n (%)	EAIR (per 100 PY) [a]
Investigations [b]	**37 (15.1)**	**22.9**	**9 (8.1)**	**17.3**
AST increased	13 (5.3)	7.3	1 (0.9)	1.8
Lipase increased	10 (4.1)	5.7	6 (5.4)	11.4
ALT increased	8 (3.3)	4.4	2 (1.8)	3.7
GGT increased	4 (1.6)	2.2	0	0
Blood ALP increased	3 (1.2)	1.6	0	0

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; EAIR = exposure-adjusted incidence rate; GGT = gamma-glutamyltransferase; MedDRA = Medical Dictionary for Regulatory Activities; PY = patient-years; SOC = system organ class; TEAE = treatment-emergent adverse event.
Patients with multiple TEAEs are counted once for each system organ class/preferred term.
Includes TEAEs with an onset date on or after the date of first dose or pre-treatment TEAEs that increase in severity on or after the date of first dose up to an including 90 days following the date of last dose of study drug or up to an including the date of initiation of the first subsequent therapy (whichever occurs first).
MedDRA v23.1.

[a] EAIR is defined as the number of patients with the event divided by the total exposure time of all patients who are at risk of the event. For patients with no reported event, the exposure is the time from the date of first dose of study drug until 90 days after the last dose of stud drug or until the start of subsequent anticancer therapy, whichever occurs first. For patients who experience the event, the exposure time is the time from the date of first dose of study drug to the start date of the first event.

[b] This SOC includes laboratory abnormalities reported as adverse events by the investigator and does not reflect all laboratory abnormalities reported in the study. Refer to Section 12.4.2 for a detailed presented of laboratory abnormalities, including liver enzyme abnormalities (Section 12.4.2.2.1).

Source: Table 14.3.1.3.

Adverse drug reactions

Table 52. Related TEAEs by SOC and PT in ≥ 10% of Patients (Safety Analysis Set)

System Organ Class Preferred Term	Tebentafusp (N=245)		Investigator's Choice (N=111)	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Patients with any related TEAE	243 (99.2)	109 (44.5)	91 (82.0)	19 (17.1)
Immune system disorders	**53 (21.6)**	**3 (1.2)**	**0**	**0**
Cytokine release syndrome [a]	51 (20.8)	2 (0.8)	0	0
Endocrine disorders	**3 (1.2)**	**0**	**21 (18.9)**	**0**
Hyperthyroidism	1 (0.4)	0	13 (11.7)	0
Metabolism and nutrition disorders	**79 (32.2)**	**11 (4.5)**	**12 (10.8)**	**1 (0.9)**
Decreased appetite	30 (12.2)	0	6 (5.4)	0
Nervous system disorders	**100 (40.8)**	**4 (1.6)**	**13 (11.7)**	**2 (1.8)**
Headache	53 (21.6)	1 (0.4)	3 (2.7)	1 (0.9)
Eye disorders	**60 (24.5)**	**2 (0.8)**	**6 (5.4)**	**1 (0.9)**
Periorbital oedema	26 (10.6)	0	0	0
Vascular disorders	**117 (47.8)**	**16 (6.5)**	**3 (2.7)**	**1 (0.9)**
Hypotension	93 (38.0)	8 (3.3)	0	0
Flushing	25 (10.2)	0	1 (0.9)	0
Gastrointestinal disorders	**154 (62.9)**	**10 (4.1)**	**39 (35.1)**	**5 (4.5)**
Nausea	105 (42.9)	2 (0.8)	21 (18.9)	0
Vomiting	64 (26.1)	1 (0.4)	7 (6.3)	0
Abdominal pain	33 (13.5)	4 (1.6)	3 (2.7)	1 (0.9)
Diarrhoea	31 (12.7)	2 (0.8)	16 (14.4)	3 (2.7)
Skin and subcutaneous tissue disorders	**228 (93.1)**	**49 (20.0)**	**47 (42.3)**	**0**
Pruritus	169 (69.0)	11 (4.5)	23 (20.7)	0
Rash	135 (55.1)	23 (9.4)	15 (13.5)	0
Rash maculo-papular	74 (30.2)	21 (8.6)	9 (8.1)	0
Dry skin	72 (29.4)	0	4 (3.6)	0
Erythema	56 (22.9)	0	1 (0.9)	0
Skin exfoliation	50 (20.4)	1 (0.4)	2 (1.8)	0
Hair colour changes	48 (19.6)	1 (0.4)	0	0
Vitiligo	40 (16.3)	0	4 (3.6)	0

System Organ Class Preferred Term	Tebentafusp (N=245)		Investigator's Choice (N=111)	
	All Grades n (%)	Grade ≥3 n (%)	All Grades n (%)	Grade ≥3 n (%)
Musculoskeletal and connective tissue disorders	**63 (25.7)**	**1 (0.4)**	**14 (12.6)**	**0**
Arthralgia	27 (11.0)	0	9 (8.1)	0
General disorders and administration site conditions	**226 (92.2)**	**16 (6.5)**	**40 (36.0)**	**1 (0.9)**
Pyrexia	185 (75.5)	9 (3.7)	3 (2.7)	0
Chills	114 (46.5)	1 (0.4)	3 (2.7)	0
Fatigue	101 (41.2)	7 (2.9)	29 (26.1)	1 (0.9)
Asthenia	27 (11.0)	0	8 (7.2)	0
Investigations [b]	**104 (42.2)**	**30 (12.2)**	**26 (23.4)**	**8 (7.2)**
Aspartate aminotransferase increased	47 (19.2)	11 (4.5)	9 (8.1)	0
Alanine aminotransferase increased	43 (17.6)	7 (2.9)	8 (7.2)	2 (1.8)
Lipase increased	32 (13.1)	9 (3.7)	7 (6.3)	6 (5.4)

CRS = cytokine release syndrome; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class; TEAE = treatment-emergent adverse event.
MedDRA v23.1.
[a] As reported by the investigator based on Lee, 2014 criteria. Refer to Section 12.2.3.4.1 for Sponsor-adjudicated CRS based on the more comprehensive 2019 ASTCT consensus grading for CRS (Lee, 2019).
[b] This SOC includes laboratory abnormalities reported as adverse events by the investigator and does not reflect all laboratory abnormalities reported in the study. Refer to Section 12.4.2 for a detailed presented of laboratory abnormalities, including liver enzyme abnormalities (Section 12.4.2.2.1).
Source: Table 14.3.2.6.

Table 53. Uveal Melanoma Patients: Drug-related Adverse Events Reported in ≥ 10% of Patients in All Studies (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Number of patients with any TEAE causally related to tebentafusp [a]	**19 (100.0%)**	**19 (100.0%)**	**127 (100.0%)**	**243 (99.2%)**	**408 (99.5%)**
Eye disorders	**9 (47.4%)**	**13 (68.4%)**	**53 (41.7%)**	**60 (24.5%)**	**135 (32.9%)**
Periorbital oedema	8 (42.1%)	12 (63.2%)	34 (26.8%)	26 (10.6%)	80 (19.5%)
Gastrointestinal disorders	**16 (84.2%)**	**17 (89.5%)**	**90 (70.9%)**	**154 (62.9%)**	**277 (67.6%)**
Nausea	13 (68.4%)	13 (68.4%)	75 (59.1%)	105 (42.9%)	206 (50.2%)
Vomiting	11 (57.9%)	7 (36.8%)	44 (34.6%)	64 (26.1%)	126 (30.7%)
Abdominal pain	2 (10.5%)	8 (42.1%)	19 (15.0%)	33 (13.5%)	62 (15.1%)
Diarrhoea	2 (10.5%)	6 (31.6%)	15 (11.8%)	31 (12.7%)	54 (13.2%)
General disorders and administration site conditions	**18 (94.7%)**	**19 (100.0%)**	**119 (93.7%)**	**226 (92.2%)**	**382 (93.2%)**
Pyrexia	13 (68.4%)	17 (89.5%)	102 (80.3%)	185 (75.5%)	317 (77.3%)
Chills	9 (47.4%)	13 (68.4%)	82 (64.6%)	114 (46.5%)	218 (53.2%)
Fatigue	13 (68.4%)	16 (84.2%)	67 (52.8%)	101 (41.2%)	197 (48.0%)

Table 53. Uveal Melanoma Patients: Drug-related Adverse Events Reported in ≥ 10% of Patients in All Studies (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Oedema peripheral	5 (26.3%)	12 (63.2%)	33 (26.0%)	42 (17.1%)	92 (22.4%)
Face oedema	6 (31.6%)	5 (26.3%)	15 (11.8%)	24 (9.8%)	50 (12.2%)
Immune system disorders	**2 (10.5%)**	**0**	**12 (9.4%)**	**53 (21.6%)**	**67 (16.3%)**
Cytokine release syndrome	2 (10.5%)	0	10 (7.9%)	51 (20.8%)	63 (15.4%)
Investigations	**5 (26.3%)**	**7 (36.8%)**	**38 (29.9%)**	**104 (42.4%)**	**154 (37.6%)**
Aspartate aminotransferase increased	1 (5.3%)	4 (21.1%)	14 (11.0%)	47 (19.2%)	66 (16.1%)
Alanine aminotransferase increased	1 (5.3%)	5 (26.3%)	11 (8.7%)	43 (17.6%)	60 (14.6%)
Lipase increased	1 (5.3%)	1 (5.3%)	9 (7.1%)	32 (13.1%)	43 (10.5%)
Metabolism and nutrition disorders	**6 (31.6%)**	**5 (26.3%)**	**40 (31.5%)**	**79 (32.2%)**	**130 (31.7%)**
Decreased appetite	2 (10.5%)	2 (10.5%)	13 (10.2%)	30 (12.2%)	47 (11.5%)
Musculoskeletal and connective tissue disorders	**7 (36.8%)**	**13 (68.4%)**	**46 (36.2%)**	**63 (25.7%)**	**129 (31.5%)**
Arthralgia	1 (5.3%)	4 (21.1%)	19 (15.0%)	27 (11.0%)	51 (12.4%)
Myalgia	5 (26.3%)	4 (21.1%)	14 (11.0%)	18 (7.3%)	41 (10.0%)
Nervous system disorders	**8 (42.1%)**	**13 (68.4%)**	**58 (45.7%)**	**100 (40.8%)**	**179 (43.7%)**
Headache	7 (36.8%)	6 (31.6%)	30 (23.6%)	53 (21.6%)	96 (23.4%)
Skin and subcutaneous tissue disorders	**18 (94.7%)**	**19 (100.0%)**	**122 (96.1%)**	**228 (93.1%)**	**387 (94.4%)**
Pruritus	12 (63.2%)	17 (89.5%)	94 (74.0%)	169 (69.0%)	292 (71.2%)
Rash	12 (63.2%)	5 (26.3%)	54 (42.5%)	135 (55.1%)	206 (50.2%)
Dry skin	5 (26.3%)	12 (63.2 %)	48 (37.8%)	72 (29.4%)	137 (33.4%)
Rash maculo-papular	6 (31.6%)	1 (5.3%)	50 (39.4%)	74 (30.2%)	131 (32.0%)
Erythema	4 (21.1%)	10 (52.6%)	35 (27.6%)	56 (22.9%)	105 (25.6%)
Hair colour changes	5 (26.3%)	8 (42.1%)	32 (25.2%)	48 (19.6%)	93 (22.7%)
Skin exfoliation	7 (36.8%)	1 (5.3%)	28 (22.0%)	50 (20.4%)	86 (21.0%)
Skin hypopigmentation	0	5 (26.3%)	24 (18.9%)	22 (9.0%)	51 (12.4%)
Vitiligo	1 (5.3%)	2 (10.5%)	8 (6.3%)	40 (16.3%)	51 (12.4%)
Skin hyperpigmentation	0	6 (31.6%)	20 (15.7%)	19 (7.8%)	45 (11.0%)
Vascular disorders	**10 (52.6%)**	**15 (78.9%)**	**68 (53.5%)**	**117 (47.8%)**	**210 (51.2%)**
Hypotension	8 (42.1%)	14 (73.7%)	52 (40.9%)	93 (38.0%)	167 (40.7%)
Flushing	2 (10.5%)	1 (5.3%)	14 (11.0%)	25 (10.2%)	42 (10.2%)

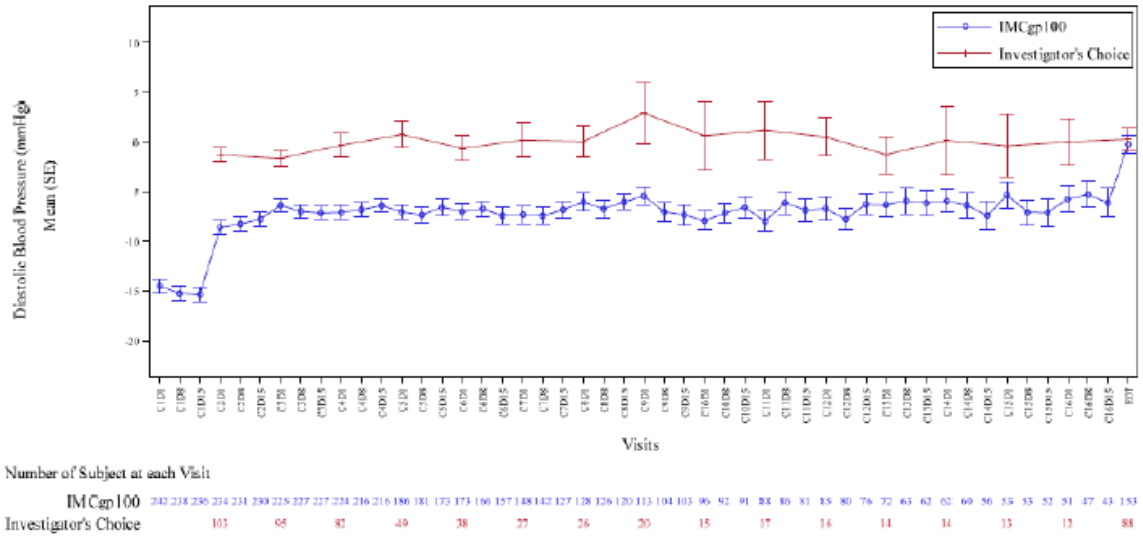
n = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event
[a] Determined by the investigator to be possibly related, probably related, definitely related, or related to tebentafusp.
Patients with multiple TEAEs per SOC or PT are counted only once in each row.
Adverse events (AEs) are coded using MedDRA version 23.1.

Table 53. Uveal Melanoma Patients: Drug-related Adverse Events Reported in ≥ 10% of Patients in All Studies (Safety Analysis Set)

System Organ Class (SOC) Preferred Term (PT)	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)

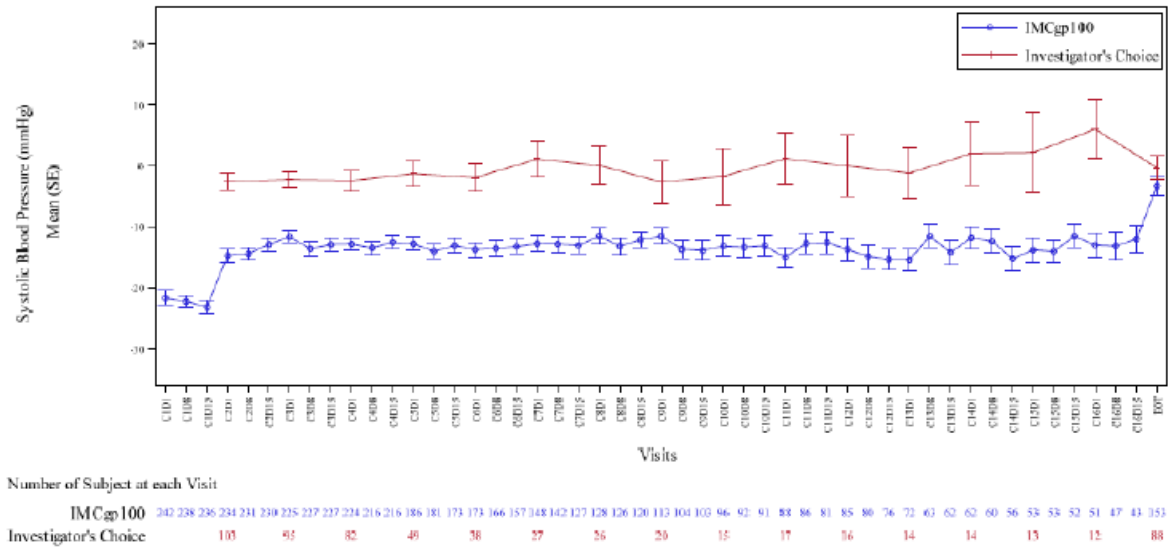
TEAEs are defined as any AE with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.
Number (%) of patients are sorted alphabetically for SOC and by descending frequency overall for PT. A patient can have one or more PTs reported under a given SOC.
Source: Module 5.3.5.3, Table ISS 02.03.02.02.01.

Figure 32. Change from Baseline Over Time in Diastolic Blood Pressure in Study 202 (Safety Analysis Set)



EOT = end of treatment; IMCgp100 = tebentafusp; SE = standard error.
Source: Module 5.3.5.1, Study 202 CSR, Figure 14.3.4.3.1.

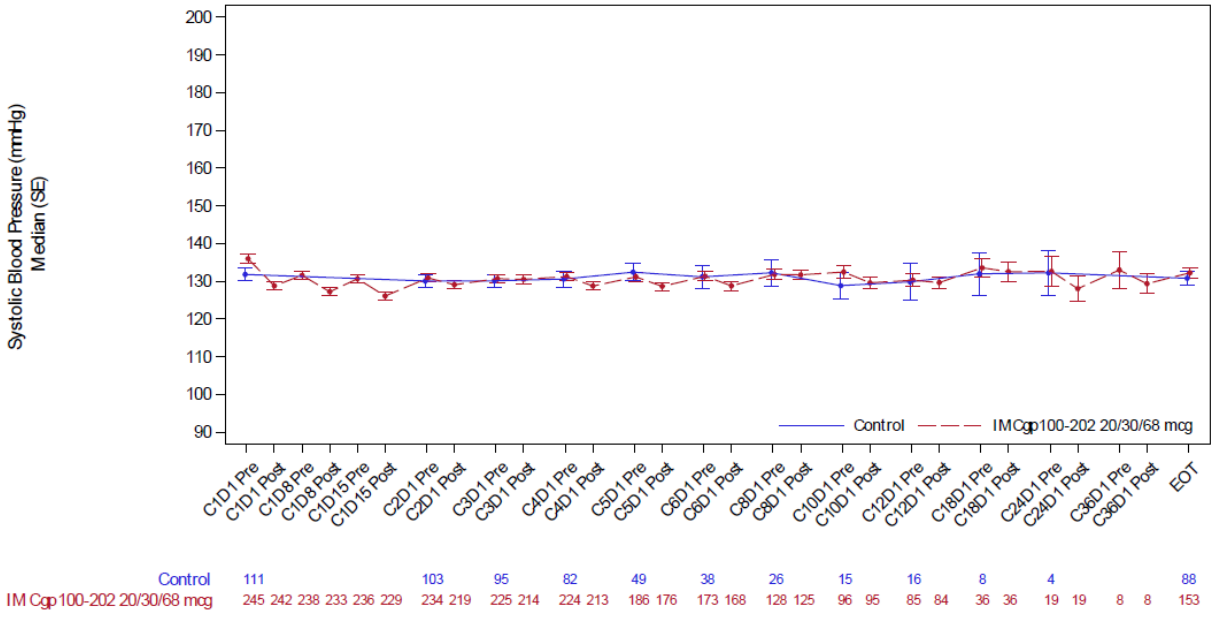
Figure 33. Change from Baseline Over Time in Systolic Blood Pressure in Study 202 (Safety Analysis Set)

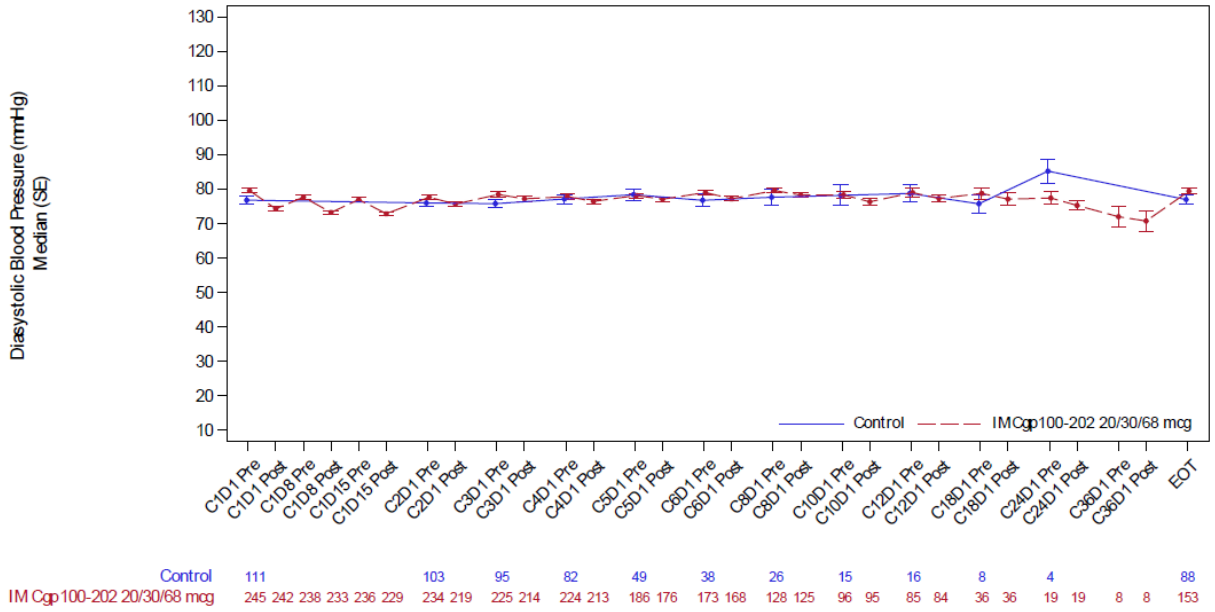


EOT = end of treatment; IMCgp100 = tebentafusp; SE = standard error.
Source: Module 5.3.5.1, Study 202 CSR, Figure 14.3.4.3.1.

During the first month of treatment with tebentafusp, the mean diastolic blood pressure (DBP) decreased 15 mmHg and the mean systolic blood pressure (SBP) decreased 20 mmHg which is consistent with occurrence of CRS at the beginning of the treatment. Furthermore, mean DBP and SBP in the tebentafusp arm remained constantly lower than the mean DBP and SBP in investigator's choice arm by app. 5 and 10 mmHg respectively. This is consistent with the safety profile of tebentafusp.

Figure 34. Absolute Systolic and Diastolic Blood Pressure Pre – Dose Values (Safety Analysis Set)





CxDx = Cycle x Day x; IMCgp100 = tebentafusp; SE = standard error.

Adverse events of special interest

Cytokine Release Syndrome

Table 54. Adjudicated CRS by Study and Maximum Grade (Safety Analysis Set)

Parameter	Study 102 Phase 1 All Doses (N = 19)	Study 102 Phase 2 20/30/68 mcg (N = 127)	Study 202 20/30/68 mcg (N = 245)	All Studies (N = 391)
CRS Grade (ASTCT CRS Consensus Grading), n (%)				
Grade 0	1 (5.26%)	18 (14.17%)	28 (11.43%)	47 (12.02%)
Grade 1	3 (15.79%)	43 (33.86%)	29 (11.84%)	75 (19.18%)
Grade 2	15 (78.95%)	61 (48.03%)	186 (75.92%)	262 (67.01%)
Grade 3	0	4 (3.15%)	2 (0.82%)	6 (0.02%)
Grade 4	0	1 (0.79%)	0	1 (0.002%)

ASTCT = American Society for Transplantation and Cellular Therapy; CRS = cytokine release syndrome
Number missing = 11

Table 55. Treatment Medications in Patients Experiencing CRS and Receiving 20/30/68 mcg in Either Study 102 or Study 202 (Safety Analysis Set)

Treatment Group	Medication Received	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Study 102 20/30/68 mcg (N=133)	Tocilizumab	1 (0.8%)	0	0	1 (0.8%)	2 (1.5%)
	Vasopressors	0	0	1 (0.8%)	1 (0.8%)	2 (1.5%)
	Steroids	7 (5.3%)	19 (14.3%)	3 (2.3%)	1 (0.8%)	27 (20.3%)
	Oxygen	0	5 (3.8%)	4 (3.0%)	1 (0.8%)	10 (7.5%)
	IV Fluids	3 (2.3%)	49 (36.8%)	2 (1.5%)	0	53 (39.8%)
	Antipyretics	68 (51.1%)	57 (42.9%)	3 (2.3%)	1 (0.8%)	104 (78.2%)

Study 202 20/30/68 mcg (N=245)	Tocilizumab	0	2 (0.8%)	0	0	2 (0.8%)
	Vasopressors	0	1 (0.4%) [a]	1 (0.4%)	0	2 (0.8%)
	Steroids	17 (6.9%)	46 (18.8%)	1 (0.4%)	0	57 (23.3%)
	Oxygen	0	19 (7.8%)	1 (0.4%)	0	20 (8.2%)
	IV Fluids	1 (0.4%)	93 (38.0%)	1 (0.4%)	0	93 (38.0%)
	Antipyretics	89 (36.3%)	158 (64.5%)	1 (0.4%)	0	192 (78.4%)

IV = intravenous; CRS = cytokine release syndrome.
[a] Subject 8704002 had intramuscular epinephrine listed as a concomitant medication for contrast allergy and not for CRS, which was never used. Post DCO for the ISS, site has since removed the entry from the database.
Source: Module 5.3.5.3, Table ISS 02.03.08.15.

Figure 35. Treatment algorithm for management of CRS

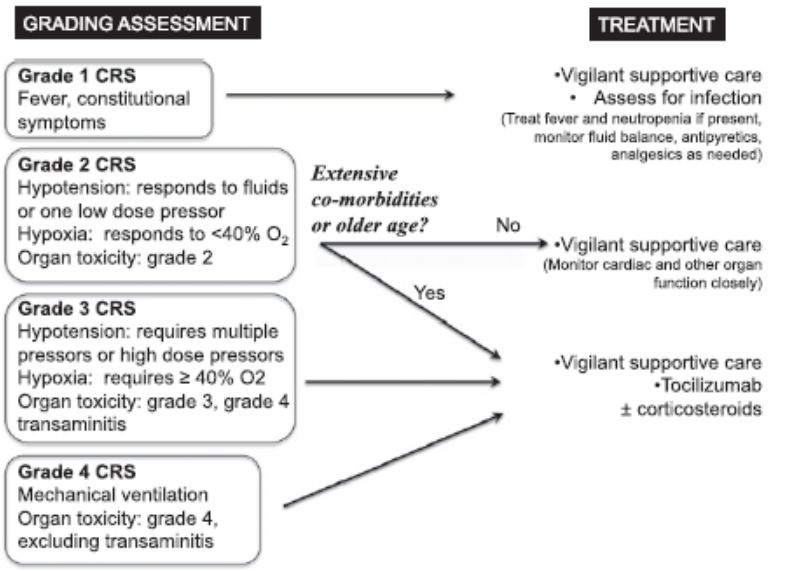
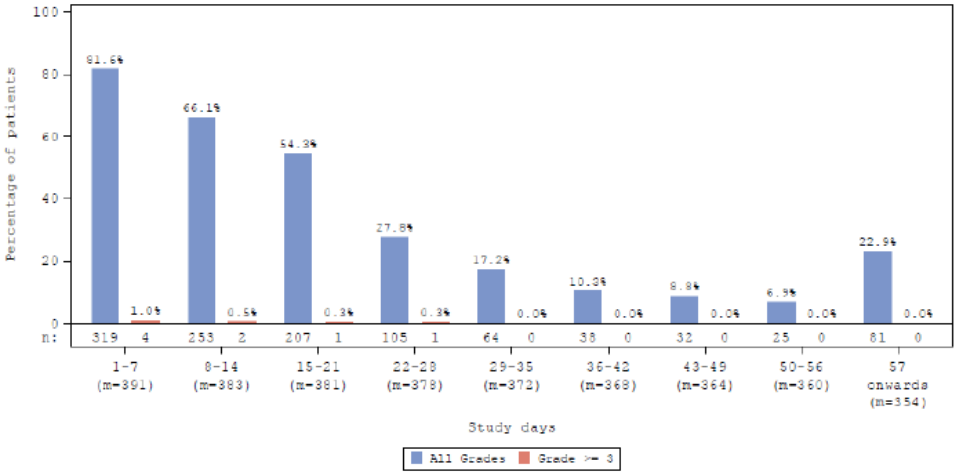


Figure 2. Treatment algorithm for management of CRS based on the revised CRS grading system. The algorithm uses the revised grading system for CRS to direct clinical management for patients with immunotherapy-associated CRS. We recommend vigilant supportive care including empiric treatment of concurrent bacterial infections and maintenance of adequate hydration and blood pressure for every grade. Immunosuppression should be used in all patients with grade 3 or 4 CRS and instituted earlier in patients with extensive comorbidities or older age. Grades 2-4 organ toxicities are dictated by CTCAE v4.0.

(ASTCT guidelines, Lee et al. 2019)

Figure 36. Uveal Melanoma Patients: Incidence of TEAEs of Special Interest for CRS by Time Period (Week) (Safety Analysis Set)



CTCAE = Common Terminology Criteria for Adverse Events (version 4.03).
N* includes only Studies 102 and 202.
Treatment phase adverse events are defined as any adverse event with a start date from day of first dose of study drug up to last dose of study drug. AEs that start prior to treatment but worsen in severity from the date of first dose are also included. The numerator n for each week is the number of patients in the safety analysis set with at least one AE of special interest starting within the given study day window who are still on-treatment when the AE is present. If an AE of special interest spans over multiple weeks, the AE is only counted in the numerator for the week it first occurred. The denominator m for each week is the number of patients in the safety analysis set that have not yet permanently discontinued treatment, as of the first day of the study day window.
Study Day is relative to first day of study drug (Day 1).
Source: Module 5.3.5.3, Figure ISS 02.03.08.13.03

The diagnosis of CRS was based on the most frequently symptoms – pyrexia (64.9%), hypotension (24.9%) and infrequently hypoxia (0.4%). Other common symptoms of CRS were chills (29%), nausea19.6%), vomiting (13.5%), fatigue (12.2%), and headache (10.6%). CRS was graded according to the ASTCT consensus guidelines (Lee et al. 2019) in grade 1-5, with grade 5 being death. This was accepted at the pre-submission meeting with the Rapporteurs. 86% of all tebentafusp treated patients and 89% of patients in study 202 experienced any grade CRS. Most patients had grade 1 (19.2%/11.8%) or grade 2 (67%/75.9%), grade 3 was seen in 0.02%/0.8% and grade 4 in 0.002%/0%. There were no deaths due to CRS and no patients in the investigator's choice arm experienced CRS.

Most patients experienced CRS following each of the first 3 tebentafusp infusions, with decreasing severity and frequency. In the majority of cases, CRS started on the day of infusion (median 1 day) and was resolved the day after the infusion (median duration ~ 2 days). Pyrexia was noted in nearly all cases of CRS and occurred within the first 8 to 10 hours after tebentafusp infusion. CRS only led treatment discontinuation in 1.2% of cases.

Inpatient monitoring for at least 16 hours after dosing for the first 3 infusions was mandated for all patients in the tebentafusp arm due to the rapid (within hours) onset of CRS. Following this induction period, the intensity and severity of these events typically decreased, and inpatient monitoring was reduced. Prophylactic medication (e.g. corticosteroids, antihistamines) was not administered prior to treatment.

In study 202, the medications used to treat CSR were, by frequency, antipyretics 78.4%, iv fluids 38%, corticosteroids 23.3%, oxygen (8.2%), vasopressor (0.8% ~ 2 patients) and tocilizumab (0.8% ~ 2 patients). The majority of patients (61.1%) received only 1 dose of steroids to manage their CRS episode.

CRS is a very common ADR following treatment with tebentafusp. However, it is only in very few cases seen in grade 4 and frequency and intensity diminish with further infusions.

Switch in CRS grading system:

The ASTCT CRS grading system was incorporated in studies 102 and 202 in October 2017. One of the main issues is the retrospective grading.

The FVFP was 04 October 2017 for study 202 and 29 February 2016 for study 102. It is therefore expected that patients in study 202 were almost all included under the version of the protocol with the Lee grading system while not the case for study 102. The Applicant presented adjudicated CRS and maximum grade for studies 102 and 202 with CTCAE grading system (on the model of table 24 of summary of clinical safety) for patients included before the setting of Lee grading system and compare these data to actual Lee grading system for the same patients.

Table 56. Maximum CRS grades as recorded in AE data by investigator versus ASTCT grading criteria (Study 102)

Investigator Assessment (Toxicity Grade) Frequency Overall Percent Row Percent Column Percent	ASTCT 2019 CRS Consensus Grading					
	0 (No CRS)	1	2	3	4	Total
0 (No CRS)	19 13.01 13.97 100.00	42 28.77 30.88 91.30	72 49.32 52.94 94.74	3 2.05 2.21 75.00	0 0.00 0.00 0.00	136 93.15
1	0 0.00 0.00 0.00	2 1.37 66.67 4.35	1 0.68 33.33 1.32	0 0.00 0.00 0.00	0 0.00 0.00 0.00	3 2.05
2	0 0.00 0.00 0.00	2 1.37 40.00 4.35	2 1.37 40.00 2.63	1 0.68 20.00 25.00	0 0.00 0.00 0.00	5 3.42
3	0 0.00 0.00 0.00	0 0.00 0.00 0.00	1 0.68 50.00 1.32	0 0.00 0.00 0.00	1 0.68 50.00 100.00	2 1.37
Total	19 13.01	46 31.51	76 52.05	4 2.74	1 0.68	146 100.00

AE = adverse event; CRS = cytokine release syndrome.

Table 57. Maximum CRS grades as recorded in AE data by investigator versus ASTCT grading criteria (Study 202)

Investigator Assessment (Toxicity Grade) Frequency Overall Percent Row Percent Column Percent	ASTCT 2019 CRS Consensus Grading					
	0 (No CRS)	1	2	3	4	Total
0 (No CRS)	26 10.61 13.40 92.86	24 9.80 12.37 82.76	144 58.78 74.23 77.42	0 0.00 0.00 0.00	0 0.00 0.00	194 79.18
1	2 0.82 10.00 7.14	4 1.63 20.00 13.79	14 5.71 70.00 7.53	0 0.00 0.00 0.00	0 0.00 0.00	20 8.16
2	0 0.00 0.00 0.00	1 0.41 3.45 3.45	26 10.61 89.66 13.98	2 0.82 6.90 100.00	0 0.00 0.00	29 11.84
3	0 0.00 0.00 0.00	0 0.00 0.00 0.00	2 0.82 100.00 1.08	0 0.00 0.00 0.00	0 0.00 0.00	2 0.82
Total	28 11.43	29 11.84	186 75.92	2 0.82	0 0.00	245 100.00

AE = adverse event; CRS = cytokine release syndrome.

All AE PT of CRS within Table 15 were reported using one grading system which was Lee 2014.

Acute skin reactions

Table 58. Uveal Melanoma Patients: Overall Summary of Adverse Events of Special Interest - Acute Skin Reactions (Safety Analysis Set)

Patients with	Study 01 All Doses (N = 19)	Study 102 Phase 1 All Doses (N = 19)	Study 102 Phase 2 20/30/68 mcg (N = 127)	Study 202 20/30/68 mcg (N = 245)	All Studies (N = 410)
Any TEAE	**18 (94.7%)**	**17 (89.5%)**	**120 (94.5%)**	**224 (91.4%)**	**379 (92.4%)**
TEAE by highest CTCAE Grade					
1	4 (21.1%)	1 (5.3%)	43 (33.9%)	68 (27.8%)	116 (28.3%)
2	7 (36.8%)	10 (52.6%)	53 (41.7%)	107 (43.7%)	177 (43.2%)
3	7 (36.8%)	6 (31.6%)	24 (18.9%)	49 (20.0%)	86 (21.0%)
4	0	0	0	0	0
5	0	0	0	0	0
Any TEAE causally related tebentafusp [a]	17 (89.5%)	17 (89.5%)	119 (93.7%)	224 (91.4%)	377 (92.0%)
Any TEAE with maximum CTCAE of Grade 3 or 4	7 (36.8%)	6 (31.6%)	24 (18.9%)	49 (20.0%)	86 (21.0%)
Any TEAE with maximum CTCAE of Grade 4	0	0	0	0	0

Patients with	Study 01 All Doses (N = 19)	Study 102 Phase 1 All Doses (N = 19)	Study 102 Phase 2 20/30/68 mcg (N = 127)	Study 202 20/30/68 mcg (N = 245)	All Studies (N = 410)
Any TEAE with maximum CTCAE of Grade 3 or 4 and causally related to tebentafusp [a]	7 (36.8%)	6 (31.6%)	24 (18.9%)	49 (20.0%)	86 (21.0%)
Any serious TEAE	0	0	4 (3.1%)	14 (5.7%)	18 (4.4%)
Any serious TEAE causally related to tebentafusp [a]	0	0	4 (3.1%)	14 (5.7%)	18 (4.4%)
A TEAE leading to permanent discontinuation of tebentafusp	0	0	0	0	0
A TEAE leading to permanent discontinuation of tebentafusp and causally related to tebentafusp [a]	0	0	0	0	0
Any TEAE leading to drug interruptions of tebentafusp	0	1 (5.3%)	3 (2.4%)	5 (2.0%)	9 (2.2%)
Any TEAE leading to drug interruptions of tebentafusp that were causally related to tebentafusp [a]	0	1 (5.3%)	3 (2.4%)	4 (1.6%)	8 (2.0%)
Any TEAE leading to dose reductions of tebentafusp	0	0	0	5 (2.0%)	5 (1.2%)
Any TEAE leading to dose reductions of tebentafusp that were causally related to tebentafusp [a]	0	0	0	5 (2.0%)	5 (1.2%)
A TEAE leading to death	0	0	0	0	0
A TEAE leading to death and causally related to tebentafusp [a]	0	0	0	0	0

CTCAE = Common Terminology Criteria for Adverse Events (version 4.03); TEAE = treatment-emergent adverse event.
[a] Determined by the investigator to be possibly related, probably related, definitely related, or related to tebentafusp.
TEAEs are defined as any AE with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.
Acute skin reactions are specified by a sponsor-provided list of preferred terms.
Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
Serious adverse events (SAEs) include deaths as an outcome of SAEs and non-fatal SAEs.
All other AESIs are graded according to CTCAE (version 4.03).
Source: Module 5.3.5.3, Table ISS 02.03.08.01.01.

Table 59. Uveal Melanoma Patients: Drug-related Adverse Events of Special Interest Reported in ≥ 10% of Patients in Any Study – Acute Skin Reactions (Safety Analysis Set)

TEAE of Special Interest Category Sub-category Preferred Term	Study 01 All Doses (N = 19)	Study 102 Phase 1 All Doses (N = 19)	Study 102 Phase 2 20/30/68 mcg (N = 127)	Study 202 20/30/68 mcg (N = 245)	All Studies (N = 410)
Acute skin toxicities TEAE of special interest causally related to tebentafusp [a]	**17 (89.5%)**	**17 (89.5%)**	**119 (93.7%)**	**224 (91.4%)**	**377 (92.0%)**
Rash	**16 (84.2%)**	**15 (78.9%)**	**112 (88.2%)**	**203 (82.9%)**	**346 (84.4%)**
Rash	12 (63.2%)	5 (26.3%)	54 (42.5%)	135 (55.1%)	206 (50.2%)
Rash maculo-papular	6 (31.6%)	1 (5.3%)	50 (39.4%)	74 (30.2%)	131 (32.0%)
Skin exfoliation	7 (36.8%)	1 (5.3%)	28 (22.0%)	50 (20.4%)	86 (21.0%)
Rash erythematous	6 (31.6%)	2 (10.5%)	5 (3.9%)	12 (4.9%)	25 (6.1%)
Rash pruritic	1 (5.3%)	4 (21.1%)	5 (3.9%)	15 (6.1%)	25 (6.1%)

TEAE of Special Interest Category Sub-category Preferred Term	Study 01 All Doses (N = 19)	Study 102 Phase 1 All Doses (N = 19)	Study 102 Phase 2 20/30/68 mcg (N = 127)	Study 202 20/30/68 mcg (N = 245)	All Studies (N = 410)
Rash macular	0	8 (42.1%)	0	7 (2.9%)	15 (3.7%)
Dermatitis acneiform	0	2 (10.5%)	8 (6.3%)	1 (0.4%)	11 (2.7%)
Rash papular	0	3 (15.8%)	2 (1.6%)	5 (2.0%)	10 (2.4%)
Blister	0	2 (10.5%)	2 (1.6%)	5 (2.0%)	9 (2.2%)
Dermatitis bullous	0	4 (21.1%)	1 (0.8%)	4 (1.6%)	9 (2.2%)
Pruritis	**12 (63.2%)**	**17 (89.5%)**	**94 (74.0%)**	**169 (69.0%)**	**292 (71.2%)**
Pruritis	12 (63.2%)	17 (89.5%)	94 (74.0%)	169 (69.0%)	292 (71.2%)
Erythema	**4 (21.1%)**	**11 (57.9%)**	**36 (28.3%)**	**66 (26.9%)**	**117 (28.5%)**
Erythema	4 (21.1%)	10 (52.6%)	35 (27.6%)	56 (22.9%)	105 (25.6%)
Photosensitivity reaction	0	3 (15.8%)	2 (1.6%)	7 (2.9%)	12 (2.9%)
Oedema	**8 (42.1%)**	**12 (63.2%)**	**39 (30.7%)**	**45 (18.4%)**	**104 (25.4%)**
Periorbital oedema	8 (42.1%)	12 (63.2%)	34 (26.8%)	26 (10.6%)	80 (19.5%)

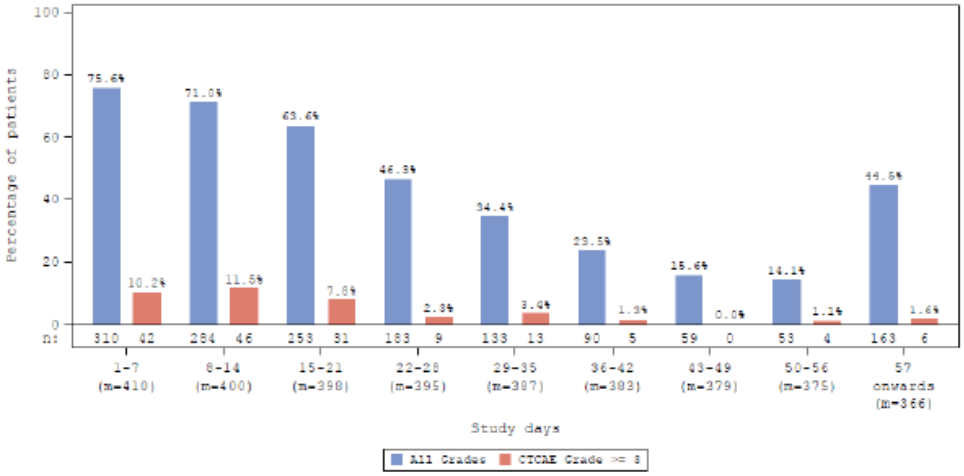
n = number of patients; TEAE = treatment-emergent adverse event.
[a] Determined by the investigator to be possibly related, probably related, definitely related, or related to tebentafusp.
Patients with multiple TEAEs of special interest per category or PT are counted only once in each row.
AEs are coded using MedDRA version 23.1.
TEAEs are defined as any AE with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first. Number (%) of patients are sorted by sponsor-provided order for category and by descending frequency overall for PT. A patient can have one or more PTs reported under a given category.
Acute skin toxicities are specified by a sponsor-provided list of preferred terms.
Source: Module 5.3.5.3, Table ISS 02.03.08.03.01.

Table 60. Summary of Tebentafusp Acute Skin Reaction Management by Medication Type and Grade for Study 202 and 102

Grade (Number of patients with acute skin toxicity)	Type of Corticosteroid Administered				Antihistamines n (%)
	Dermatological or Topical Preparations n (%)	Any Systemic n (%)	Systemic IV n (%)	Systemic Oral n (%)	
Study 202					
Any grade (N=224)	119 (53.1%)	24 (10.7%)	15 (6.7%)	9 (4.0%)	170 (75.95%)
Grade 1 (N=218)	85 (39.0%)	15 (6.9%)	9 (4.1%)	4 (1.8%)	137 (62.85%)
Grade 2 (N=146)	72 (49.3%)	18 (12.3%)	10 (6.8%)	8 (5.5%)	130 (70.5%)
Grade 3 (N=49)	22 (44.9%)	6 (12.2%)	5 (10.2%)	1 (2.0%)	35 (71.4%)
Study 102					
Any grade (N=137)	94 (68.6%)	12 (8.8%)	11 (8.0%)	4 (2.9%)	106 (77.4%)
Grade 1 (N=132)	68 (51.5%)	4 (3.0%)	3 (2.3%)	1 (0.8%)	79 (59.8%)
Grade 2 (N=89)	43 (48.3%)	8 (9.0%)	7 (7.9%)	3 (3.4%)	64 (71.9%)
Grade 3 (N=30)	16 (53.3%)	3 (10.0%)	3 (10.0%)	1 (3.3%)	20 (66.7%)

IV = intravenous
Source: Module 5.3.5.3, Table ISS 05.02.08.102; Module 5.3.5.3, Table ISS 05.02.08.202.

Figure 37. Uveal Melanoma Patients: Incidence of TEAEs of Special Interest by Time Period (Week) (Safety Analysis Set)



CTCAE = Common Terminology Criteria for Adverse Events (version 4.03); TEAE = treatment-emergent adverse event.
Treatment phase adverse events are defined as any adverse event with a start date from day of first dose of study drug up to last dose of study drug. AEs that start prior to treatment but worsen in severity from the date of first dose are also included.
The numerator n for each week is the number of patients in the safety analysis set with at least one adverse event (AE) of special interest starting within the given study day window who are still on-treatment when the AE is present.
If an AE of special interest spans over multiple weeks, the AE is only counted in the numerator for the week it first occurred.
The denominator m for each week is the number of patients in the safety analysis set that have not yet permanently discontinued treatment, as of the first day of the study day window.
Study Day is relative to first day of study drug (Day 1).
Source: Module 5.3.5.3, Figure ISS 02.03.08.13.03

Acute skin reactions were a common ADR seen with tebentafusp treatment. Though, the severity was within grade 1-3 and symptoms mostly revealed themselves within a few days after infusion, no grade 4 or 5 ADR's were seen and the frequency of SAE's was low.

2.6.8.3. Serious adverse event/deaths/other significant events

Table 61. Uveal Melanoma Patients: Serious Adverse Events Regardless of Causality Reported in ≥ 1% of Patients by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Number of patients with any serious TEAE	**6 (31.6%)**	**10 (52.6%)**	**43 (33.9%)**	**69 (28.2%)**	**128 (31.2%)**
Blood and lymphatic disorders	**1 (5.3%)**	**0**	**0**	**1 (0.4%)**	**2 (0.5%)**
Anaemia	1 (5.3%)	0	0	1 (0.4%)	2 (0.5%)
Cardiac disorders	**0**	**0**	**6 (4.7%)**	**0**	**6 (1.5%)**
Atrial flutter	0	0	2 (1.6%)	0	2 (0.5%)
Sinus tachycardia	0	0	2 (1.6%)	0	2 (0.5%)
Gastrointestinal disorders	**1 (5.3%)**	**1 (5.3%)**	**6 (4.7%)**	**7 (2.9%)**	**15 (3.7%)**
Abdominal pain	1 (5.3%)	1 (5.3%)	2 (1.6%)	2 (0.8%)	6 (1.5%)
Nausea	0	0	2 (1.6%)	4 (1.6%)	6 (1.5%)
Diarrhoea	0	0	2 (1.6%)	0	2 (0.5%)

Table 61. Uveal Melanoma Patients: Serious Adverse Events Regardless of Causality Reported in ≥ 1% of Patients by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
General disorders and administration site conditions	**1 (5.3%)**	**1 (5.3%)**	**11 (8.7%)**	**7 (2.9%)**	**20 (4.9%)**
Pyrexia	0	1 (5.3%)	9 (7.1%)	6 (2.4%)	16 (3.9%)
Adverse drug reaction	1 (5.3%)	0	0	0	1 (0.2%)
Hepatobiliary disorders	**0**	**1 (5.3%)**	**4 (3.1%)**	**8 (3.3%)**	**13 (3.2%)**
Hyperbilirubinaemia	0	1 (5.3%)	0	2 (0.8%)	3 (0.7%)
Immune system disorders	**1 (5.3%)**	**0**	**4 (3.1%)**	**25 (10.2%)**	**30 (7.3%)**
Cytokine release syndrome	1 (5.3%)	0	4 (3.1%)	24 (9.8%)	29 (7.1%)
Infections and infestations	**2 (10.5%)**	**0**	**6 (4.7%)**	**4 (1.6%)**	**12 (2.9%)**
Sepsis	0	0	3 (2.4%)	0	3 (0.7%)
Biliary tract infection	1 (5.3%)	0	1 (0.8%)	0	2 (0.5%)
Lower respiratory tract infection	1 (5.3%)	0	0	0	1 (0.2%)
Injury, poisoning and procedural complications	**0**	**1 (5.3%)**	**1 (0.8%)**	**1 (0.4%)**	**3 (0.7%**
Infusion related reaction	0	1 (5.3%)	0	0	1 (0.2%)
Investigations	**2 (10.5%)**	**2 (10.5%)**	**4 (3.1%)**	**3 (1.2%)**	**11 (2.7%)**
Alanine aminotransferase increased	0	1 (5.3%)	3 (2.4%)	1 (0.4%)	5 (1.2%)
Aspartate aminotransferase increased	0	2 (10.5%)	2 (1.6%)	1 (0.4%)	5 (1.2%)
Gamma-glutamyltransferase increased	0	0	2 (1.6%)	0	2 (0.5%)
Laboratory test abnormal	1 (5.3%)	0	0	0	1 (0.2%)
Liver function test increased	1 (5.3%)	0	0	0	1 (0.2%)
Metabolism and nutrition disorders	**1 (5.3%)**	**1 (5.3%)**	**2 (1.6%)**	**1 (0.4%)**	**5 (1.2%)**
Hypophosphataemia	1 (5.3%)	1 (5.3%)	2 (1.6%)	0	4 (1.0%)
Hypocalcaemia	1 (5.3%)	0	0	0	1 (0.2%)
Musculoskeletal and connective tissue	**1 (5.3%)**	**2 (10.5%)**	**3 (2.4%)**	**0**	**6 (1.5%)**
Back pain	1 (5.3%)	0	2 (1.6%)	0	3 (0.7%)
Bone pain	0	1 (5.3%)	0	0	1 (0.2%)
Pain in extremity	0	1 (5.3%)	0	0	1 (0.2%)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**1 (5.3%)**	**0**	**3 (2.4%)**	**3 (1.2%)**	**7 (1.7%)**
Tumour pain	0	0	2 (1.6%)	2 (0.8%)	4 (1.0%)
Tumour haemorrhage	1 (5.3%)	0	0	0	1 (0.2%)
Nervous system disorders	**0**	**1 (5.3%)**	**4 (3.1%)**	**5 (2.0%)**	**10 (2.4%)**
Spinal cord compression	0	0	2 (1.6%)	1 (0.4%)	3 (0.7%)
Aphasia	0	1 (5.3%)	0	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	**0**	**2 (10.5%)**	**4 (3.1%)**	**4 (1.6%)**	**10 (2.4%)**
Pleural effusion	0	0	2 (1.6%)	0	2 (0.5%)
Pulmonary embolism	0	1 (5.3%)	0	1 (0.4%)	2 (0.5%)
Hypoxia	0	1 (5.3%)	0	0	1 (0.2%)
Skin and subcutaneous tissue disorders	**0**	**0**	**4 (3.1%)**	**14 (5.7%)**	**18 (4.4%)**

Table 61. Uveal Melanoma Patients: Serious Adverse Events Regardless of Causality Reported in ≥ 1% of Patients by System Organ Class and Preferred Term (Safety Analysis Set)

System Organ Class Preferred Term	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Rash	0	0	1 (0.8%)	6 (2.4%)	7 (1.7%)
Rash maculo-papular	0	0	3 (2.4%)	4 (1.6%)	7 (1.7%)
Vascular disorders	**2 (10.5%)**	**1 (5.3%)**	**5 (3.9%)**	**5 (2.0%)**	**13 (3.2%)**
Hypotension	2 (10.5%)	1 (5.3%)	3 (2.4%)	5 (2.0%)	11 (2.7%)

n = number of patients; PT = preferred term; SOC = system organ class; TEAE = treatment-emergent adverse event.
Patients with multiple TEAEs per SOC or PT are counted only once in each row.
Adverse events (AEs) are coded using MedDRA version 23.1.
TEAEs are defined as any AE with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.
Number (%) of patients are sorted alphabetically for SOC and by descending frequency overall for PT. A patient can have one or more PTs reported under a given SOC.
Serious adverse events (SAEs) include deaths reportable as SAEs and non-fatal SAEs.
Source: Module 5.3.5.3, Table ISS 02.03.03.01.01.

Deaths

Table 62. Uveal Melanoma Patients: Summary of Deaths by Cause and Timing (Safety Analysis Set)

Parameter	Study 01 All Doses (N = 19) n (%)	Study 102 Phase 1 All Doses (N = 19) n (%)	Study 102 Phase 2 20/30/68 mcg (N = 127) n (%)	Study 202 20/30/68 mcg (N = 245) n (%)	All Studies (N = 410) n (%)
Primary cause of death **Any death [a]**	**5** **(26.3%)**	**14** **(73.7%)**	**70** **(55.1%)**	**84** **(34.3%)**	**173** **(42.2%)**
Disease progression	3 (15.8%)	14 (73.7%)	68 (53.5%)	80 (32.7%)	165 (40.2%)
Unknown	2 (10.5%)	0	0	0	2 (0.5%)
Adverse event	0	0	0	2 (0.8%)	2 (0.5%)
Adverse event leading to death related to tebentafusp [b, d]	0	0	0	0	0
Adverse event leading to death unrelated to tebentafusp [b, e]	0	0	0	2 (0.8%)	2 (0.5%)
Other	0	0	2 (1.6%)	2 (0.8%)	4 (1.0%)
Timing of death					
On-treatment up until ≤ 30 days after the last dose of tebentafusp	0	1 (5.3%)	7 (5.5%)	5 (2.0%)	13 (3.2%)
> 30 days after the last dose of tebentafusp [c]	5 (26.3%)	13 (68.4%)	63 (49.6%)	79 (32.2%)	160 (39.0%)

[a] As recorded on death electronic case report form (eCRF) page or adverse event (AE)/serious adverse event (SAE) eCRF page.
[b] As recorded on AE/SAE eCRF page.
[c] This row may include deaths that are not treatment-emergent, i.e., with a death date greater than 90 days after last dose of study drug or start of alternative cancer therapy post treatment discontinuation (whichever occurs first).
[d] Determined by the investigator to be possibly related, probably related, definitely related, or related to Tebentafusp
[e] Includes fatal AEs that are not treatment emergent and therefore do not appear in Table 10. No relationship to deaths that led to treatment discontinuation that appear in Table 14.
Percentages are based on the number of patients in the safety analysis set within each treatment group.

Source: Module 5.3.5.3, Table ISS 02.03.07.01.01.

2.6.8.4. Laboratory findings

Findings

Table 63. Significant shifts in hematology parameters by CTCAE grade (Safety Analysis Set)

Parameter	Tebentafusp (N=245)					Investigator's Choice (N=111)				
	n	Any Grade Worsening	Any ≥2 Grade Worsening	Any Grade Worsening to Grade 3 or 4	Any ≥2 Grade Worsening to Grade 3 or 4	n	Any Grade Worsening	Any ≥2 Grade Worsening	Any Grade Worsening to Grade 3 or 4	Any ≥2 Grade Worsening to Grade 3 or 4
Hemoglobin, g/L (low)	245	124 (50.6)	10 (4.1)	3 (1.2)	1 (0.4)	110	24 (21.8)	0	1 (0.9)	0
Hemoglobin, g/L (high)	245	23 (9.4)	0	0	0	110	5 (4.5)	0	0	0
Leukocytes, 10^9/L (low)	245	43 (17.6)	9 (3.7)	3 (1.2)	3 (1.2)	110	8 (7.3)	2 (1.8)	2 (1.8)	2 (1.8)
Leukocytes, 10^9/L (high)	245	0	0	0	0	110	0	0	0	0
Platelets, 10^9/L (low)	245	38 (15.5)	1 (0.4)	0	0	110	16 (14.5)	1 (0.9)	1 (0.9)	1 (0.9)
Lymphocytes, 10^9/L (low)	245	222 (90.6)	200 (81.6)	136 (55.5)	134 (54.7)	109	29 (26.6)	8 (7.3)	2 (1.8)	2 (1.8)
Lymphocytes, 10^9/L (high)	245	9 (3.7)	9 (3.7)	0	0	109	0	0	0	0
Neutrophils, 10^9/L (low)	245	35 (14.3)	9 (3.7)	5 (2.0)	5 (2.0)	110	9 (8.2)	3 (2.7)	2 (1.8)	2 (1.8)

CTCAE = Common Terminology Criteria for Adverse Events.
Source: Table 14.3.4.1.3.

Table 64. Significant shifts in hepatic chemistry parameters by CTCAE grade (Safety Analysis Set)

Parameter	Tebentafusp (N=245)					Investigator's Choice (N=111)				
	n	Any Grade Worsening	Any ≥2 Grade Worsening	Any Grade Worsening to Grade 3 or 4	Any ≥2 Grade Worsening to Grade 3 or 4	n	Any Grade Worsening	Any ≥2 Grade Worsening	Any Grade Worsening to Grade 3 or 4	Any ≥2 Grade Worsening to Grade 3 or 4
ALT, IU/L (high)	241	126 (52.3)	34 (14.1)	22 (9.1)	22 (9.1)	109	32 (29.4)	5 (4.6)	2 (1.8)	2 (1.8)
Albumin, g/L (low)	242	114 (47.1)	29 (12.0)	5 (2.1)	3 (1.2)	108	17 (15.7)	4 (3.7)	1 (0.9)	1 (0.9)
ALP, IU/L (high)	244	82 (33.6)	15 (6.1)	8 (3.3)	5 (2.0)	110	42 (38.2)	2 (1.8)	2 (1.8)	1 (0.9)
AST, IU/L (high)	241	132 (54.8)	33 (13.7)	30 (12.4)	27 (11.2)	108	43 (39.8)	8 (7.4)	3 (2.8)	3 (2.8)
Bilirubin, µmol/L (high)	245	65 (26.5)	25 (10.2)	11 (4.5)	10 (4.1)	110	16 (14.5)	10 (9.1)	8 (7.3)	7 (6.4)

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events.
Source: Table 14.3.4.1.6.

Table 65. Potential Hy's law cases (Safety Analysis Set)

Potential Hy's Law Criteria Timing Restriction	Tebentafusp (N=245) n (%)	Investigator's Choice (N=111) n (%)
(ALT or AST ≥3×ULN) and total bilirubin ≥2×ULN		
At any time during on-treatment/follow-up [a]	17 (6.9)	5 (4.5)
Within 1 week [b]	16 (6.5)	5 (4.5)
Within 1 day [c]	16 (6.5)	5 (4.5)
Within 1 day with a duration ≥7 days [d]	11 (4.5)	5 (4.5)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULN = upper limit of normal.
[a] ALT/AST and total bilirubin results at any time after first dose of study drug up to 90 days after last dose of study drug.
[b] ALT/AST result within 1 week (±7 days) of total bilirubin result, during on-treatment/follow-up.
[c] ALT/AST result within 1 day (±1 day) of total bilirubin result, during on-treatment/follow-up.
[d] ALT/AST result within 1 day (±1 day) of total bilirubin result with a duration of ≥7 days, during on-treatment/follow-up.
Duration calculated as consecutive days where high levels of both ALT/AST and total bilirubin are maintained, without going below the potential Hy's Law criteria.
Source: Table 14.3.4.2.

Table 66. Significant shifts in other chemistry parameters by CTCAE grade (Safety Analysis Set)

Parameter	Tebentafusp (N=245)					Investigator's Choice (N=111)				
	n	Any Grade Worsening	Any ≥2 Grade Worsening	Any Grade Worsening to Grade 3 or 4	Any ≥2 Grade Worsening to Grade 3 or 4	n	Any Grade Worsening	Any ≥2 Grade Worsening	Any Grade Worsening to Grade 3 or 4	Any ≥2 Grade Worsening to Grade 3 or 4
Amylase, IU/L (high)	243	56 (23.0)	19 (7.8)	10 (4.1)	10 (4.1)	105	19 (18.1)	3 (2.9)	1 (1.0)	1 (1.0)
Calcium, mmol/L (low)	244	109 (44.7)	25 (10.2)	4 (1.6)	4 (1.6)	108	18 (16.7)	3 (2.8)	2 (1.9)	2 (1.9)
Calcium, mmol/L (high)	244	32 (13.1)	0	0	0	108	4 (3.7)	0	0	0
Creatinine, µmol/L (high)	245	213 (86.9)	16 (6.5)	1 (0.4)	1 (0.4)	110	82 (74.5)	4 (3.6)	0	0
Glucose, mmol/L (low)	243	43 (17.7)	11 (4.5)	1 (0.4)	1 (0.4)	108	5 (4.6)	1 (0.9)	0	0
Glucose, mmol/L (high)	243	161 (66.3)	51 (21.0)	8 (3.3)	5 (2.1)	108	43 (39.8)	5 (4.6)	5 (4.6)	2 (1.9)
Lipase, IU/L (high)	241	91 (37.8)	49 (20.3)	36 (14.9)	36 (14.9)	103	29 (28.2)	13 (12.6)	6 (5.8)	5 (4.9)
Magnesium, mmol/L (low)	244	84 (34.4)	0	0	0	108	9 (8.3)	0	0	0
Magnesium, mmol/L (high)	244	21 (8.6)	1 (0.4)	1 (0.4)	1 (0.4)	108	2 (1.9)	0	0	0
Phosphate, mmol/L (low)	241	124 (51.5)	101 (41.9)	29 (12.0)	19 (7.9)	102	20 (19.6)	15 (14.7)	2 (2.0)	0
Potassium, mmol/L (low)	245	43 (17.6)	12 (4.9)	2 (0.8)	2 (0.8)	110	9 (8.2)	1 (0.9)	1 (0.9)	1 (0.9)
Potassium, mmol/L (high)	245	72 (29.4)	23 (9.4)	4 (1.6)	4 (1.6)	110	17 (15.5)	2 (1.8)	1 (0.9)	1 (0.9)
Sodium, mmol/L (low)	245	73 (29.8)	7 (2.9)	7 (2.9)	7 (2.9)	110	18 (16.4)	1 (0.9)	1 (0.9)	1 (0.9)
Sodium, mmol/L (high)	245	12 (4.9)	2 (0.8)	0	0	110	2 (1.8)	0	0	0

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events.
Source: Table 14.3.4.1.6.

Electrocardiogram Findings

The Applicant has stated that there were no clinically meaningful trends in ECG findings and associated cardiac AEs in either treatment arm. Please refer to the assessment below.

Phase 2 dose expansion cohort, cardiac disorders (regardless of causality) were reported in 38 (29.9%) patients. The most commonly reported (>1% of patients) cardiac AEs related to ECG abnormalities were tachycardia (11.8%), sinus tachycardia in (9.4%), sinus bradycardia (3.9%), atrial fibrillation (3.1%), atrial flutter (2.4%), and supraventricular tachycardia (1.6%). No AEs of torsades de pointes were reported. Grade 3 and Grade 4 atrial fibrillation, atrial flutter, and tachycardia was reported in 7 patients (5.5%), and all of these events were considered treatment-related.

Cardiac AEs led to **treatment discontinuation** in 2 patients; 1 due to grade 4 atrial fibrillation after day 1 treatment, 1 due to grade 3 left ventricular dysfunction after day 8 treatment. Both of these cardiac AEs occurred in the setting of sponsor assessed Grade 3 CRS and were considered related to tebentafusp treatment by the investigator. No events of Grade 5 severity were reported.

A tabulated presentation of the cardiac disorders and ECG findings of patients treated with tebentafusp in the 102 and 202 studies has been provided.

Table 67. Summary of Cardiac Adverse Events in Uveal Melanoma Population (N=410)

System Organ Class Preferred Term (MedDRA v23.1)	Number (%) of Patients			
	Any TEAE	Grade 3 or 4 TEAE	SAE	Discontinuation Due to TEAE
Cardiac disorders				
Tachycardia	43 (10.5)	1 (0.2)	0	0
Sinus tachycardia	23 (5.6)	0	2 (0.5)	0
Sinus bradycardia	8 (2.0)	0	0	0
Bradycardia	5 (1.2)	0	0	0
Angina pectoris	4 (1.0)	3 (0.7)	0	0
Atrial fibrillation	4 (1.0)	2 (0.5)	1 (0.2)	1 (0.2)

System Organ Class Preferred Term (MedDRA v23.1)	Number (%) of Patients			
	Any TEAE	Grade 3 or 4 TEAE	SAE	Discontinuation Due to TEAE
Palpitations	4 (1.0)	0	0	0
Atrial flutter	3 (0.7)	1 (0.2)	2 (0.5)	0
Atrioventricular block first degree	2 (0.5)	0	0	0
Supraventricular tachycardia	2 (0.5)	0	0	0
Atrioventricular block	1 (0.2)	0	0	0
Cardiac failure	1 (0.2)	0	1 (0.2)	0
Cardiomegaly	1 (0.2)	0	0	0
Conduction disorder	1 (0.2)	0	0	0
Hypertensive heart disease	1 (0.2)	0	0	0
Left ventricular dysfunction	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Pericardial effusion	1 (0.2)	0	0	0
Ventricular arrhythmia	1 (0.2)	0	0	0
Ventricular tachycardia	1 (0.2)	0	0	0
Investigations				
Electrocardiogram QT prolonged	2 (0.5)	0	0	0
Electrocardiogram T wave inversion	2 (0.5)	0	0	0
ECG signs of myocardial infarction	1 (0.2)	0	0	0
Electrocardiogram ST-T change	1 (0.2)	0	0	0
Heart rate irregular	1 (0.2)	0	0	0

MedDRA = Medical Dictionary for Regulatory Activities; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Source: Module 2.7.4, Table ISS-02.03.02.01.01, Table ISS-02.03.02.03.01, Table ISS-02.03.03.01.01, and Table ISS-02.03.04.01.01.

Table 68. ECGs-Shift table for QTcF absolute values in Uveal Melanoma Population (N=410)

Visit	Baseline (msec)	Worst On-treatment/Follow-up Value (msec)					
		≤450 n (%)	>450-480 n (%)	>480-500 n (%)	>500 n (%)	Missing n (%)	Total n (%)
First 4 weekly doses	≤450	351 (90.7)	35 (9.0)	1 (0.3)	0	0	387 (100.0)
	>450-480	2 (13.3)	11 (73.3)	2 (13.3)	0	0	15 (100.0)
	>480-500	0	2 (100.0)	0	0	0	2 (100.0)
	>500	0	0	0	0	0	0
	Total	353 (87.4)	48 (11.9)	3 (0.7)	0	0	404 (100.0)
After 4 weekly doses	≤450	323 (90.2)	26 (7.3)	3 (0.8)	6 (1.7)	0	358 (100.0)
	>450-480	5 (33.3)	5 (33.3)	4 (26.7)	1 (6.7)	0	15 (100.0)
	>480-500	2 (100.0)	0	0	0	0	2 (100.0)
	>500	0	0	0	0	0	0
	Total	330 (88.0%)	31 (8.3)	7 (1.9)	7 (1.9)	0	375 (100.0)
Overall	≤450	335 (85.7)	46 (11.8)	4 (1.0)	6 (1.5)	0	391 (100.0)
	>450-480	2 (13.3)	8 (53.3)	4 (26.7)	1 (6.7)	0	15 (100.0)
	>480-500	0	2 (100.0)	0	0	0	2 (100.0)
	>500	0	0	0	0	0	0
	Missing	1 (50.0)	0	0	0	1 (50.0)	2 (100.0)
	Total	338 (82.4)	56 (13.7)	8 (2.0)	7 (1.7)	1 (0.2)	410 (100.0)

ECG = electrocardiogram; QTcF = QT interval corrected using Fridericia's formula.
Source: Module 2.7.4, Table ISS-03.04.03.02.01.

In Table 68 prolongation of QTcF to >500 msec occurred in 7 patients whereas, in Table 20 only 2 patients are registered with QT prolonged. None of the 7 patients with QTcF prolongation >500 msec reported in Table 21 experienced associated AEs as reported by the investigator (Table 20). The AEs of

QT prolongations reported in 2 patients from Table 67 were grade 1 in severity and did not lead to treatment modification or discontinuations.

A total of 7 patients (2.9%) who received tebentafusp and 0 patients who received investigator's choice had an increase from baseline in QTcF > 60 msec (CSR, table 14.3.4.5.2). And, a total of 7 patients treated with tebentafusp in the uveal melanoma population (n=410) experienced prolongation of QTcF compared to baseline to values of >500 msec. Increase in QTcF of > 60 msec from baseline and a prolongation of QTcF to >500 msec are known risk factors of developing life-threatening arrhythmias such as Torsade de Pointes. No patients in the IC arm experienced prolongations of QTcF and the seen prolongations are considered drug-induced by treatment with tebentafusp.

2.6.8.5. In vitro biomarker test for patient selection for safety

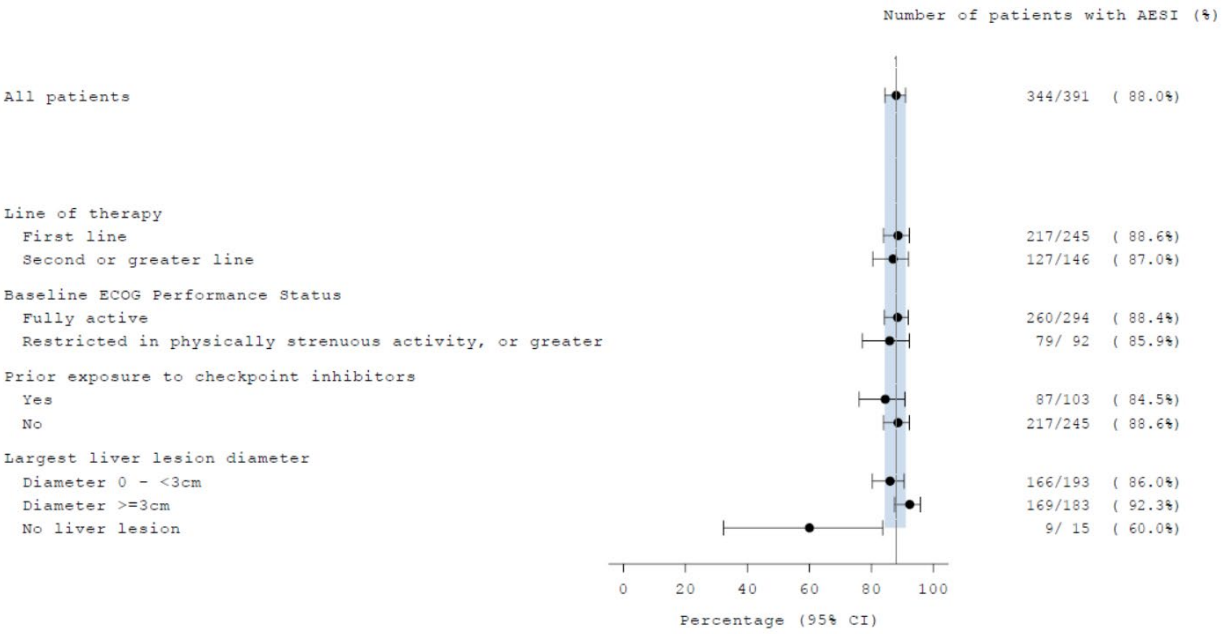
Not applicable

2.6.8.6. Safety in special populations

Intrinsic Factors

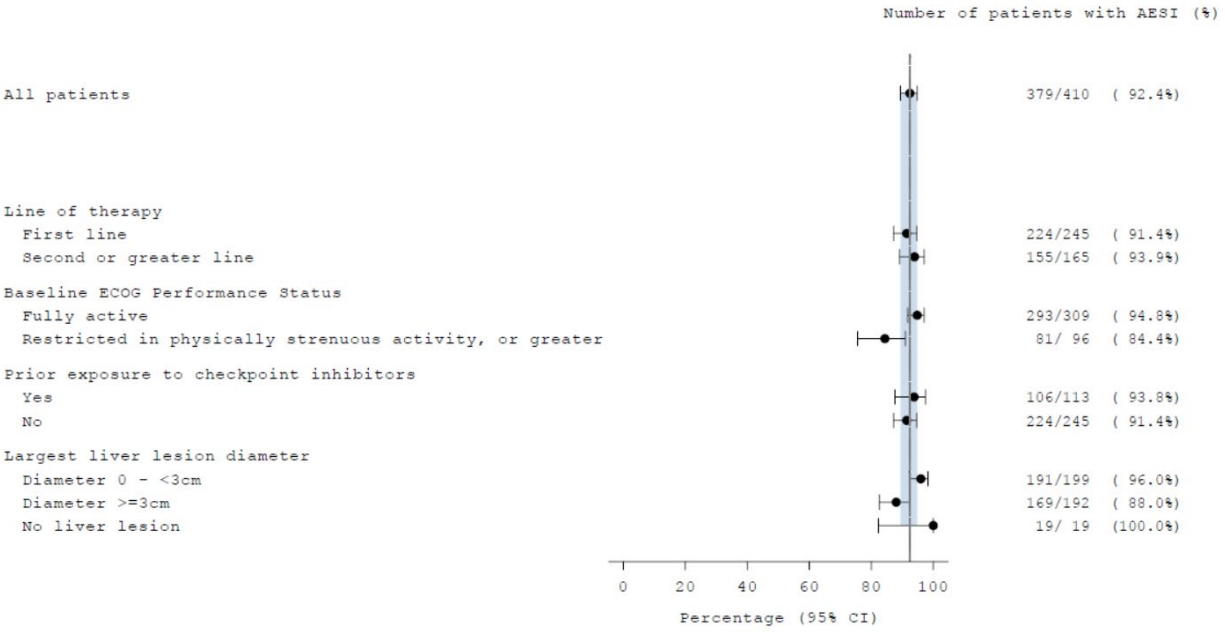
Uveal Melanoma Patients: Age, Gender, and Race

Figure 38. Uveal Melanoma Patients: Overall Incidence of CRS (All Grades) by Disease Characteristic Subgroup (N=391) [a, b]



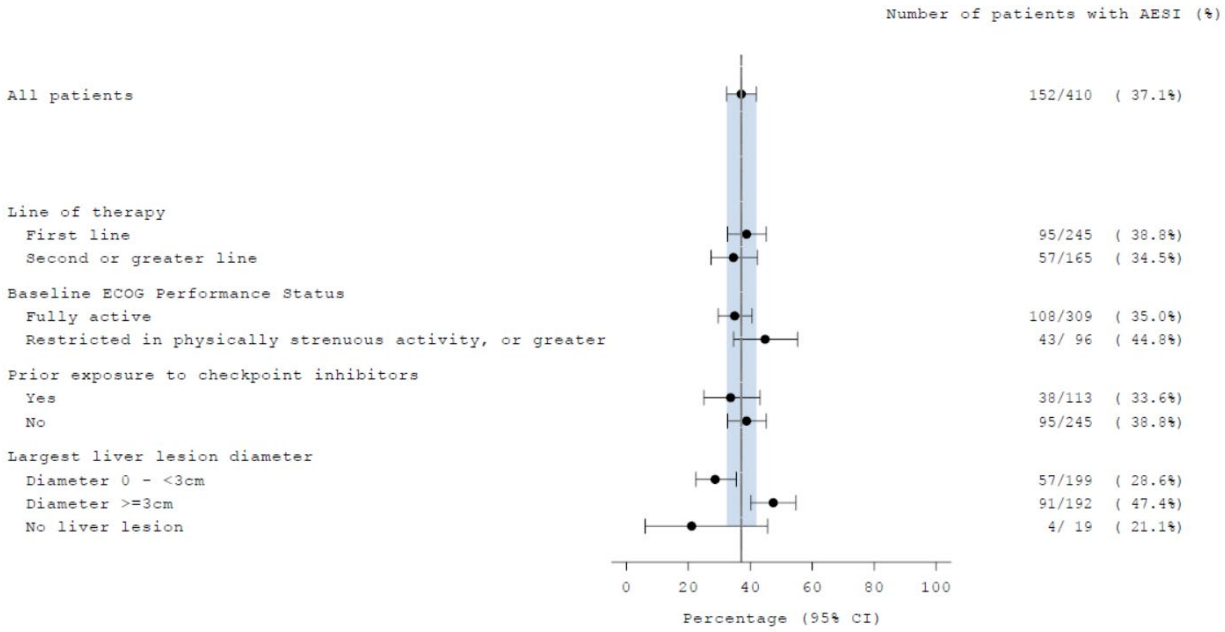
AESI = adverse event of special interest; CI = confidence interval; CRS = cytokine release syndrome; ECOG = Eastern Cooperative Oncology Group.
[a] AESI from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.
[b] Includes only Studies 102 and 202.
Source: Module 5.3.5.3, Figure ISS 02.03.09.02.01.

Figure 39. Uveal Melanoma Patients: Overall Incidence of Acute Skin Reactions (All Grades) by Disease Characteristic Subgroup (N=410)[a]



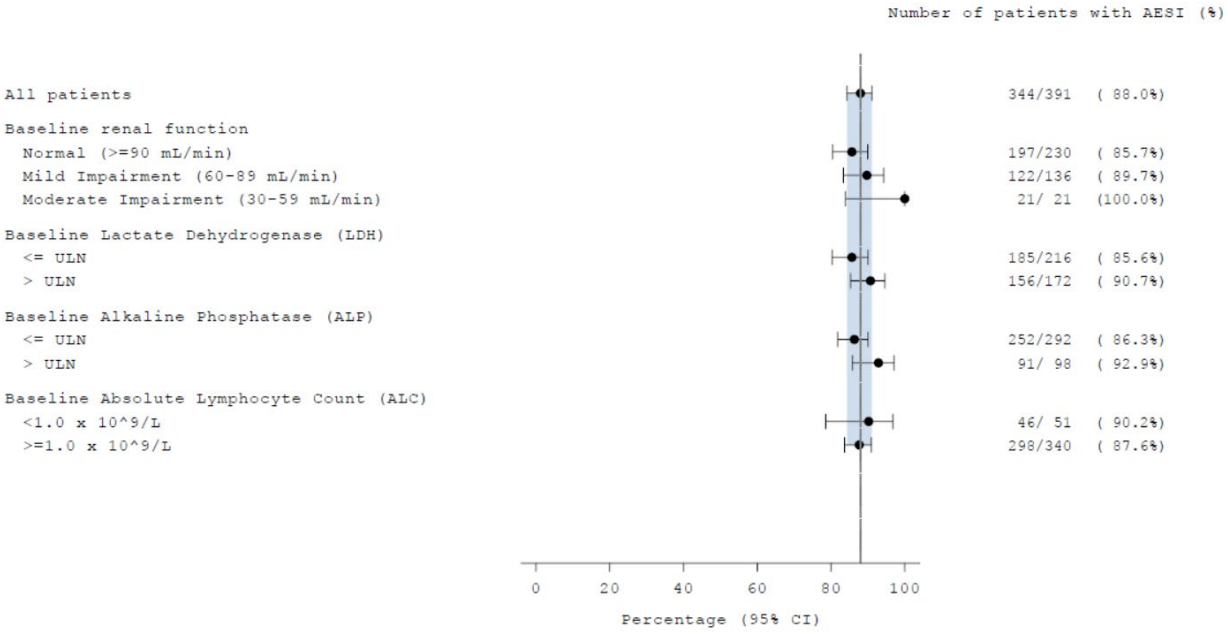
AESI = adverse event of special interest; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group
[a] AESI from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.
Source: Module 5.3.5.3, Figure ISS 02.03.09.02.01.

Figure 40. Uveal Melanoma Patients: Overall Incidence of LFT Elevations (All Grades) by Disease Characteristic Subgroup (N=410)[a]



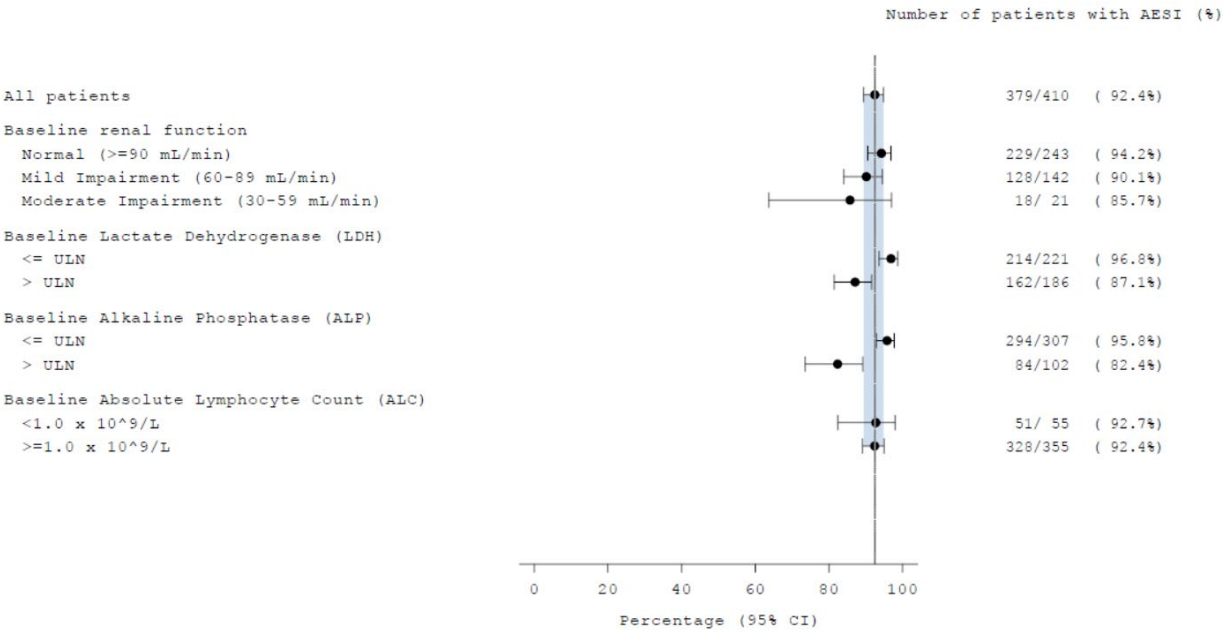
AESI = adverse event of special interest; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group; LFT = liver function tests.
[a] AESI from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.
Source: Module 5.3.5.3, Figure ISS 02.03.09.02.01.

Figure 41. Uveal Melanoma Patients: Overall Incidence of CRS (All Grades) by Disease Characteristic Subgroup (N=391)[a, b]



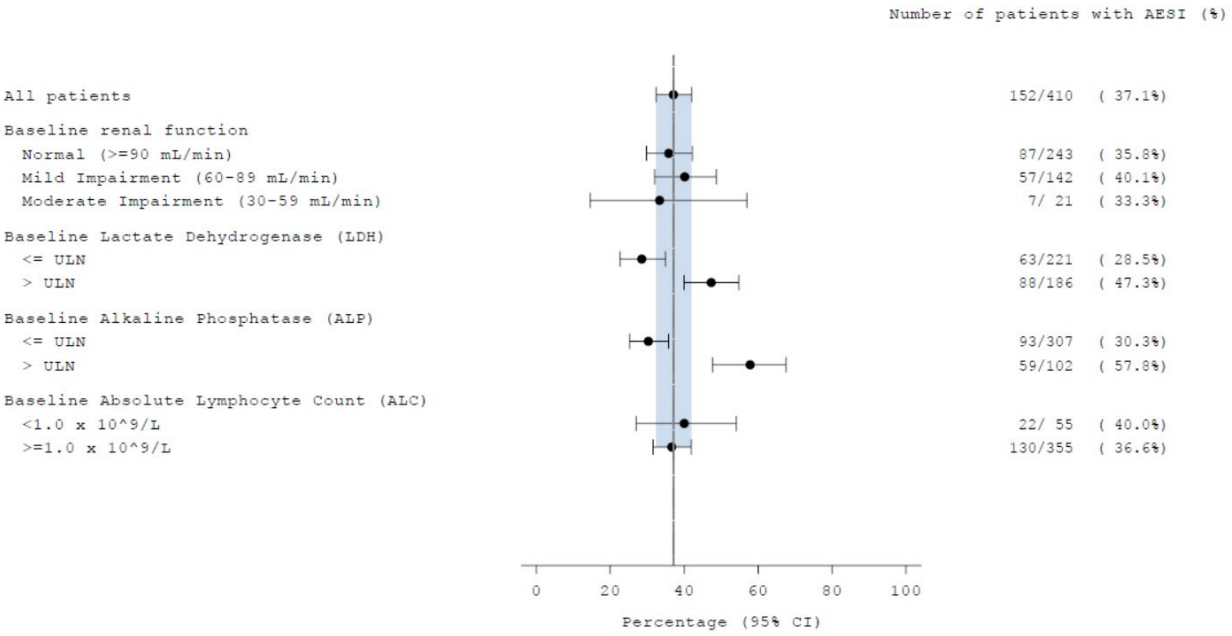
AESI = adverse event of special interest; CI = confidence interval; CRS = cytokine release syndrome; ULN = upper limit of normal.
[a] AESI from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.
[b] Includes only Studies 102 and 202.
Source: Module 5.3.5.3, Figure ISS 02.03.09.03.01.

Figure 42. Uveal Melanoma Patients: Overall Incidence of Acute Skin Reactions (All Grades) by Disease Characteristic Subgroup (N=410)[a]



AESI = adverse event of special interest; CI = confidence interval; ULN = upper limit of normal.
[a] AESI from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.
Source: Module 5.3.5.3, Figure ISS 02.03.09.03.01.

Figure 43. Uveal Melanoma Patients: Overall Incidence of LFT Elevations (All Grades) by Disease Characteristic Subgroup (N=410)[a]



AESI = adverse event of special interest; CI = confidence interval; ULN = upper limit of normal.
[a] AESI from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.
Source: Module 5.3.5.3, Figure ISS 02.03.09.03.01.

The Applicant provided the assessment in special populations of all TEAE, grade ≥3 TEAE, grade ≥4, SAE, leading to treatment discontinuation, leading to treatment interruption.

Table 27 Incidence of Treatment-emergent Adverse Events Across Subgroups – Uveal Melanoma Population (Safety Analysis Set)

Subgroup	Number (%) of Patients					
	All TEAEs	Grade ≥3 TEAEs	Grade ≥4 TEAEs	SAEs	AEs Leading to Discontinuation	AEs Leading to Interruption
Line of therapy						
First line (N=245)	245 (100.0)	133 (54.3)	16 (6.5)	69 (28.2)	8 (3.3)	62 (25.3)
Second line or greater (N=165)	165 (100.0)	106 (64.2)	22 (13.3)	59 (35.8)	7 (4.2)	45 (27.3)
Baseline ECOG						
0: Fully active (N=309)	309 (100.0)	180 (58.3)	24 (7.8)	88 (28.5)	6 (1.9)	77 (24.9)
1: Restricted in physical strenuous activity, or greater (N=96)	96 (100.0)	56 (58.3)	14 (14.6)	40 (41.7)	9 (9.4)	30 (31.3)
Prior exposure to checkpoint inhibitors						
Yes (N=113)	113 (100.0)	73 (64.)	14 (12.4)	42 (37.2)	6 (5.3)	29 (25.7)
No (N=297)	297 (100.0)	166 (55.9)	24 (8.1)	86 (29.0)	9 (3.0)	78 (26.3)
Largest liver lesion diameter						
Diameter 0 to <3 cm (N=199)	199 (100.0)	114 (57.3)	12 (6.0)	52 (26.1)	2 (1.0)	37 (18.6)
Diameter ≥3 cm (N=192)	192 (100.0)	113 (58.9)	25 (13.0)	71 (37.0)	12 (6.3)	60 (31.3)
No liver lesion (N=19)	19 (100.0)	12 (63.2)	1 (5.3)	5 (26.3)	1 (5.3)	10 (52.6)
Baseline renal function						
Normal (≥90 mL/min) (N=243)	243 (100.0)	143 (58.8)	22 (9.1)	77 (31.7)	5 (2.1)	63 (25.9)
Mild impairment (60-89 mL/min) (N=142)	142 (100.0)	83 (58.5)	13 (9.2)	43 (30.3)	7 (4.9)	36 (25.4)
Moderate impairment (30-59 mL/min) (N=21)	21 (100.0)	11 (52.4)	2 (9.5)	7 (33.3)	2 (9.5)	6 (28.6)
Baseline lactate dehydrogenase						
≤ULN (N=221)	221 (100.0)	121 (54.8)	11 (5.0)	51 (23.1)	2 (0.9)	48 (21.7)
>ULN (N=186)	186 (100.0)	115 (61.8)	26 (14.0)	75 (40.3)	13 (7.0)	58 (31.2)
Baseline alkaline phosphatase						
≤ULN (N=307)	307 (100.0)	173 (56.4)	22 (7.2)	78 (25.4)	4 (1.3)	74 (24.1)
>ULN (N=102)	102 (100.0)	66 (64.7)	16 (15.7)	50 (49.0)	11 (10.8)	33 (32.4)
Baseline absolute lymphocyte count						
$<1.0 \times 10^9$/L (N=55)	55 (100.0)	28 (50.9)	8 (14.5)	22 (40.0)	2 (3.6)	12 (21.8)
$\geq 1.0 \times 10^9$/L (N=355)	355 (100.0)	211 (59.4)	30 (8.5)	106 (29.9)	13 (3.7)	95 (26.8)
Sex						
Male (N=209)	209 (100.0)	121 (57.9)	24 (11.5)	63 (30.1)	7 (3.3)	58 (27.8)
Female (N=201)	201 (100.0)	118 (58.7)	14 (7.0)	65 (32.3)	8 (4.0)	49 (24.4)

Note: Percentages are based on the number of patients per subgroup level in the safety analysis set.
AE = adverse event; ECOG = Eastern Cooperative Oncology Group; SAE = serious adverse event; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.

Extrinsic factors

Region - Uveal Melanoma Patients

The extrinsic factor: region (North America vs. non-North America) was tested to see if it had any influence on the development of CRS, acute skin reactions or LFT elevations/hepatotoxicity, which it did not have.

Table 69. Summary of Treatment-emergent Adverse Events by Age Group

MedDRA Terms	Age Group (Years)			
	<65 (N=235) n (%)	65-74 (N=137) n (%)	75-84 (N=36) n (%)	≥85 (N=2) n (%)
Total AEs	235 (100.00)	137 (100.00)	36 (100.00)	2 (100.00)
Serious AEs total	75 (31.91)	45 (32.85)	8 (22.22)	0
Fatal	1 (0.43)	0	0	0

MedDRA Terms	Age Group (Years)			
	<65 (N=235) n (%)	**65-74 (N=137) n (%)**	**75-84 (N=36) n (%)**	**≥85 (N=2) n (%)**
Hospitalisation/prolong existing hospitalisation	67 (28.51)	42 (30.66)	8 (22.22)	0
Life-threatening	8 (3.40)	4 (2.92)	0	0
Disability/incapacity	2 (0.85)	0	1 (2.78)	0
Other (medically significant)	15 (6.38)	9 (6.57)	0	0
AE leading to drop-out	7 (2.98)	5 (3.65)	2 (5.56)	1 (50.00)
Psychiatric disorders	53 (22.55)	39 (28.47)	5 (13.89)	1 (50.00)
Nervous system disorders	130 (55.32)	80 (58.39)	16 (44.44)	1 (50.00)
Accidents and injuries	0	0	0	0
Cardiac disorders	47 (20.00)	31 (22.63)	5 (13.89)	0
Vascular disorders	137 (58.30)	83 (60.58)	16 (44.44)	1 (50.00)
Cerebrovascular disorders	0	0	0	0
Infections and infestations	88 (37.45)	50 (36.50)	10 (27.78)	1 (50.00)
Anticholinergic syndrome	0	0	0	0
Quality of life decreased	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	42 (17.87)	24 (17.52)	5 (13.89)	1 (50.00)
Other AE appearing more frequently in older patients[a]	**156 (66.38)**	**103 (75.18)**	**25 (69.44)**	**2 (100.00)**
Cough	41 (17.45)	39 (28.47)	5 (13.89)	0
Fatigue	126 (53.62)	86 (62.77)	19 (52.78)	2 (100.00)
Hypertension	30 (12.77)	28 (20.44)	4 (11.11)	0
Hypomagnesaemia	13 (5.53)	14 (10.22)	5 (13.89)	1 (50.00)
Lymphopenia	14 (5.96)	18 (13.14)	3 (8.33)	1 (50.00)

[a] Includes all preferred terms occurred at an incidence rate that was ≥5 percentage points higher for patients aged ≥65 years of age compared to patients aged <65 years of age.

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.

No clinically significant differences or clear populations at risk by various age cut-offs are identified.

2.6.8.7. Immunological events

The potential influence of anti-drug antibodies (ADA), that occurred in approximately a third of patients in study 202, has been presented in previous sections.

2.6.8.8. Safety related to drug-drug interactions and other interactions

No drug-drug and drug-disease interactions studies were conducted with tebentafusp.

Patients who are receiving concomitant CYP450 substrates (particularly those with a narrow therapeutic index) should be monitored for toxicity (e.g., warfarin) and/or drug concentrations (e.g., cyclosporine).

2.6.8.9. Discontinuation due to adverse events

Dose interruptions and reductions

Table 70. Uveal Melanoma Patients: Dose Interruptions and Reductions (Safety Analysis Set)

Parameter	Study 01 All Doses (N = 19)	Study 102 Phase 1 All Doses (N = 19)	Study 102 Phase 2 20/30/68 mcg (N = 127)	Study 202 20/30/68 mcg (N = 245)	All Studies (N = 410)
No interruptions and no reduction at any time, n (%)	7 (36.8%)	6 (31.6%)	78 (61.4%)	137 (55.9%)	228 (55.6%)
Interruption or reduction at any time, n (%)	12 (63.2%)	13 (68.4%)	49 (38.6%)	108 (44.1%)	182 (44.4%)
No interruption at any time, n (%)	10 (52.6%)	8 (42.1%)	84 (66.1%)	141 (57.6%)	243 (59.3%)
Number of patients with an interruption, n (%)					
Any	9 (47.4%)	11 (57.9%)	43 (33.9%)	104 (42.4%)	167 (40.7%)
1 interruption	6 (31.6%)	2 (10.5%)	27 (21.3%)	63 (25.7%)	98 (23.9%)
2 interruptions	1 (5.3%)	1 (5.3%)	7 (5.5%)	17 (6.9%)	26 (6.3%)
3 interruptions	2 (10.5%)	2 (10.5%)	4 (3.1%)	10 (4.1%)	18 (4.4%)
4 interruptions	0	3 (15.8%)	2 (1.6%)	3 (1.2%)	8 (2.0%)
5 interruptions	0	2 (10.5%)	1 (0.8%)	3 (1.2%)	6 (1.5%)
6 interruptions	0	0	0	2 (0.8%)	2 (0.5%)
7 interruptions	0	0	2 (1.6%)	1 (0.4%)	3 (0.7%)
8 interruptions	0	0	0	1 (0.4%)	1 (0.2%)
9 interruptions	0	1 (5.3%)	0	1 (0.4%)	2 (0.5%)
10 interruptions	0	0	0	2 (0.8%)	2 (0.5%)
12 interruptions	0	0	0	1 (0.4%)	1 (0.2%)
Reason for interruption at any time, n (%) [a]					
Adverse event	5 (55.6%)	8 (72.7%)	22 (51.2%)	36 (34.6%)	71 (42.5%)
Delayed administration	6 (66.7%)	2 (18.2%)	4 (9.3%)	21 (20.2%)	33 (19.8%)
Other	3 (33.3%)	9 (81.8%)	29 (67.4%)	71 (68.3%)	112 (67.1%)
No reduction at any time, n (%)	**12 (63.2%)**	**14 (73.7%)**	**113 (89.0%)**	**227 (92.7%)**	**366 (89.3%)**
Number of patients with a reduction, n (%)					
Any	7 (36.8%)	5 (26.3%)	14 (11.0%)	18 (7.3%)	44 (10.7%)
1 reduction	1 (5.3%)	3 (15.8%)	12 (9.4%)	14 (5.7%)	30 (7.3%)
2 reductions	5 (26.3%)	2 (10.5%)	2 (1.6%)	2 (0.8%)	11 (2.7%)
4 reductions	1 (5.3%)	0	0	2 (0.8%)	3 (0.7%)
Reason for reduction, n (%) a					
Adverse event	7 (100.0%)	4 (80.0%)	6 (42.9%)	14 (77.8%)	31 (70.5%)
Other	1 (14.3%)	1 (20.0%)	9 (64.3%)	4 (22.2%)	15 (34.1%)

[a] Patients with multiple interruptions or reductions are counted once per unique reason. Percentages are based on the number of patients with any interruptions or reductions within each treatment group.
Interruptions are only counted if study drug administration restarts following interruption.
Interruptions recorded over consecutive dosing visits are only counted as a single interruption but may have more than one reason recorded in 'Reason for interruption at any time'.
For patients with intra-dose escalation, reductions from protocol dose level are derived at Cycle 1 Day 1 if planned dose is less than 20 mcg, at Cycle 1 Day 8 if planned dose is less than 30 mcg, and at Cycle 1 Day 15 if planned dose is less than the cohort-specified dose level. In cases where a patient remains on 20 mcg or 30 mcg for multiple consecutive doses, each repetition is considered a reduction.
Source: Module 5.3.5.3, Table ISS 01.01.08.01.

Dose discontinuations

Table 71. Uveal Melanoma Patients: Drug Related Adverse Events Resulting in Study Drug Discontinuation Reported in Patients by System Organ Class and Preferred Term (Safety Analysis Set)

MedDRA System Organ Class Preferred Term	Study 01 All Doses (N = 19)	Study 102 Phase 1 All Doses (N = 19)	Study 102 Phase 2 20/30/68 mcg (N = 127)	Study 202 20/30/68 mcg (N = 245)	All Studies (N = 410)
Number of patients with any TEAE leading to permanent discontinuation of tebentafusp and causally related to tebentafusp [a]	**0**	**0**	**3 (2.4%)**	**5 (2.0%)**	**8 (2.0%)**
Cardiac disorders	**0**	**0**	**2 (1.6%)**	**0**	**2 (0.5%)**
Atrial fibrillation	0	0	1 (0.8%)	0	1 (0.2%)
Left ventricular dysfunction	0	0	1 (0.8%)	0	1 (0.2%)
General disorders and administration site conditions	**0**	**0**	**1 (0.8%)**	**1 (0.4%)**	**2 (0.5%)**
Fatigue	0	0	0	1 (0.4%)	1 (0.2%)
Multiple organ dysfunction syndrome	0	0	1 (0.8%)	0	1 (0.2%)
Hepatobiliary disorders	**0**	**0**	**0**	**1 (0.4%)**	**1 (0.2%)**
Hepatotoxicity	0	0	0	1 (0.4%)	1 (0.2%)
Immune system disorders	**0**	**0**	**1 (0.8%)**	**2 (0.8%)**	**3 (0.7%)**
Cytokine release syndrome	0	0	1 (0.8%)	1 (0.4%)	2 (0.5%)
Anaphylactic reaction	0	0	0	1 (0.4%)	1 (0.2%)
Vascular disorders	**0**	**0**	**0**	**1 (0.4%)**	**1 (0.2%)**
Hypotension	0	0	0	1 (0.4%)	1 (0.2%)

n = number of patients; TEAE = treatment-emergent adverse event.
[a] Determined by the investigator to be possibly related, probably related, definitely related, or related to tebentafusp.
Patients with multiple TEAEs per SOC or PT are counted only once in each row.
Adverse events (AEs) are coded using MedDRA version 23.1.
TEAEs are defined as any AE with a start date from day of first dose of study drug up to 90 days after last dose of study drug or until start of alternative cancer therapy post treatment discontinuation, whichever occurs first.
Number (%) of patients are sorted alphabetically for SOC and by descending frequency overall for PT. A patient can have one or more PTs reported under a given SOC.
Source: Module 5.3.5.3, Table ISS 02.03.04.02.01.

Table 27 Overall Summary of Treatment-emergent Adverse Events (Safety Analysis Set)

Patients with:	Tebentafusp (N=245) n (%)	Investigator's Choice (N=111) n (%)
Any TEAE	245 (100.0)	105 (94.6)
Any related TEAE [a]	243 (99.2)	91 (82.0)
TEAE by highest CTCAE grade		
1	14 (5.7)	24 (21.6)
2	98 (40.0)	41 (36.9)
3	117 (47.8)	36 (32.4)
4	15 (6.1)	2 (1.8)
5	1 (0.4)	2 (1.8)
Any TEAE with CTCAE Grade ≥3	133 (54.3)	40 (36.0)
Any related TEAE with CTCAE Grade ≥3	109 (44.5)	19 (17.1)
Any TESAE	69 (28.2)	26 (23.4)
Any related TESAE	54 (22.0)	8 (7.2)
Any TEAE leading to death	1 (0.4)	2 (1.8)
Any related TEAE leading to death	0	0
Any TEAE leading to study drug discontinuation	8 (3.3)	7 (6.3)
Any related TEAE leading to study drug discontinuation	5 (2.0)	5 (4.5)
Any TEAE leading to dose or infusion interruption	62 (25.3)	27 (24.3)
Any related TEAE leading to dose or infusion interruption	44 (18.0)	23 (20.7)

AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event.
Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.
Includes AEs with an onset date on or after the date of first dose or pre-treatment AEs that increase in severity on or after the date of first dose up to an including 90 days following the date of last dose of study drug or up to an including the date of initiation of the first subsequent therapy (whichever occurs first).
[a] As assessed by the investigator. Missing responses are counted as related.
Source: Table 14.3.1.1.

The main reason for interruption was "other" (67.4% and 68.3% in studies 201 and 202, respectively) followed by "adverse event" (51.2% and 34.6% in studies 201 and 202 respectively) and "delayed administration" (9.3 % and 20.2% in studies 201 and 202 respectively). Regarding dose reduction, 10.7% of all patients and 7.3% of patients in study 202 experienced a dose reduction, with 7.5% and 5.7%, respectively, being due to treatment-related AE's. Moreover, the main reason for dose reduction was different in studies 102 and 202. Indeed "adverse event" was the main reason for dose reduction in the pivotal study 202 (77.8% of patients) followed by "other" (22.2% of patients) while "other" was the main reason for dose reduction in study 102 (64.3% of patients) followed by adverse events (42.9%).

Table 72 . Summary of Other Reasons for Dose Interruptions (Safety Population and Tebentafusp Treated Patients)

Reason	Number (%) of Patients		
	Study 102 Tebe 20/30/68 mcg (N=127)	Study 202 Tebe 20/30/68 mcg (N=245)	Overall Tebe 20/30/68 mcg (N=372)
Missing	11 (8.66)	52 (21.22)	63 (16.94)
Vacation/patient preference	20 (15.75)	13 (5.31)	33 (8.87)
Adverse event	1 (0.79)	4 (1.63)	5 (1.34)
COVID-19 lockdown	0	4 (1.63)	4 (1.08)
Drug supply or preparation issue	0	4 (1.63)	4 (1.08)
Recovering from surgery	1 (0.79)	1 (0.41)	2 (0.54)
Suspected progressive disease	0	2 (0.82)	2 (0.54)
Drug supply issue	0	1 (0.41)	1 (0.27)

COVID-19 = coronavirus disease 2019; Tebe = tebentafusp.

The applicant provided the reasons reported as "other" for dose interruptions. In table 13, it is seen that 18 patients experienced any dose reduction; 14 patients 1 reduction, 2 patients 2 reductions and 2 patients 4 reductions. In the supportive studies, additional patients experienced dose reductions. Table 4 (below) is listing patients with dose reductions and the reasons for these. Of the 18 patients, Table 13, 4 patients experienced dose reductions due to other reasons and 14 patients experienced dose reductions due to AEs as summarised below:

• 2 patients experienced an actual dose reduction to 54 mcg from the prior maintenance dose of 68 as per the trial protocol for Grade 3/4 AEs.

• 12 patients experienced dose reductions (i.e., a delay in intra-patient dose escalation to target dose) due to AEs and received a repeat of the previous dose (20 or 30 mcg) consistent with guidance for CRS and acute skin toxicity management in the trial protocol and consistent with proposed guidance in the SmPC. The reasons for reduction of the planned dose in these patients were most commonly related to CRS, acute skin toxicities and LFT abnormalities (below table).

Dose reductions were primarily due to AEs and occurred mainly in the intra-patient dose escalation. The dose reduction was then in the form of a delay in escalation of dose where the patient continues with the same dose (20 or 30 mcg) as previously given until toxicity allows for increase to next dose-step. This delay was registered as dose reduction.

Table 73. Listing of Dose Reductions (Delay in Intra – patient Dose Escalation to Target Dose)

Patient Number	Reduced Dose(mcg)	Reduced Dose day	Previous Dose (mcg)	Previous Dose day	Reason for Reduced Dose	AE Resulting in Reduced Dose	Next Dose (in mcg) after the AE onset (study day)
IMCgp100-202-3501009	20	22	20	1	Adverse events	Hypotension	20 (41)
	20	41	20	22	Adverse events	Blood creatinine increased, Hyperbilirubinaemia, Hypotension, Hepatic failure	
IMCgp100-202-3504007	30	15	30	7	Adverse events	Rash	68 (21)
IMCgp100-202-6101013	20	8	20	1	Adverse events	Hypotension, Cytokine release syndrome	20 (16)
	20	16	20	8	Adverse events	Cytokine release syndrome, Hypotension, Rash maculo-papular	20 (22)
IMCgp100-202-6101014	30	17	30	9	Adverse events	Rash maculo-papular	30 (24)
	30	31	30	24	Adverse events	Cytokine release syndrome, Rash maculo-papular	30 (38)
	30	38	30	31	Adverse events	Rash maculo-papular	30 (45)
	30	45	30	38	Adverse events	Rash maculo-papular	68 (52)
IMCgp100-202-6101015	20	8	20	1	Adverse events	Rash maculo-papular	30 (15)
IMCgp100-202-6101016	20	8	20	1	Adverse events	Hypotension, Dyspnoea, Oxygen saturation decreased, Cytokine release syndrome	30 (15)
	30	15	20	8	Adverse events	Cytokine release syndrome	68 (22)
IMCgp100-202-6101018	30	29	30	8	Adverse events	Hepatic necrosis	
IMCgp100-202-6101034	30	15	30	8	Adverse events	Cytokine release syndrome	68 (22)

Patient Number	Reduced Dose(mcg)	Reduced Dose day	Previous Dose (mcg)	Previous Dose day	Reason for Reduced Dose	AE Resulting in Reduced Dose	Next Dose (in mcg) after the AE onset (study day)
IMCgp100-202-6207006	30	29	30	9	Adverse events	Uveitis	68 (36)
IMCgp100-202-6207011	30	15	30	9	Adverse events	Cytokine release syndrome	68 (22)
IMCgp100-202-8714004	20	41	20	29	Adverse events	Hepatotoxicity, Hypotension	20 (50)
	20	50	20	41	Adverse events	Hepatotoxicity, hypotension	20 (57)
	20	57	20	50	Adverse events	Hepatotoxicity, Hypotension	20 (64)
	20	64	20	57	Adverse events	Hepatotoxicity, hypotension	30 (71)
IMCgp100-202-8722001	20	12	20	1	Adverse events	Herpes zoster	30 (20)

2.6.8.10. Post marketing experience

Tebentafusp currently is not marketed in any country; therefore, no post marketing data is available.

2.6.9. Discussion on clinical safety

Overall, a total of 372 (245+127) patients in the pivotal study 202 and the supportive study 102 received at least 1 dose of tebentafusp with the dosing regimen suggested for the current application. The cohort is representative of the European population and bearing in mind the low incidence of uveal malignant melanoma, the number of treated patients is considered representative and sufficient for a robust safety assessment. The patients on average received treatment for a relatively long period of time and received full dose when treated.

With a mean duration of treatment of 34 weeks and mean relative dose intensity of 98.6%, the exposure to tebentafusp is considered clinically relevant and robust. However, patient-initiated treatment breaks for up to 2 consecutive doses were accepted. The Applicant provided further data showing, that there is no indication that treatment interruptions are associated with worse survival compared to patients without interruptions. On the contrary, there seems to be a positive association

between longer time on treatment, allowing for more interruptions, and longer median survival. Treatment interruptions do therefore not interfere negatively with response to treatment and can be undertaken as it was done in the clinical trial (for up to 2 weeks at a time). This has also been sufficiently described in the SmPC.

Patients were per protocol allowed treatment breaks for up to 2 consecutive treatments and the most frequent reason for interruption was "events other than an AE". The allowance of treatment breaks is clinically important information for the treating physician, especially with a treatment that is administered weekly (~very often). Patients with incurable cancer in life-prolonging treatment can feel very obliged to uphold continuous treatment. It is therefore of great importance if minor treatment breaks can be taken without affecting the efficacy of the treatment.

In order to clarify if and what influence interruptions in treatment had on survival, the applicant provided data comparing OS in patients with treatment interruptions to that of patients without. The Applicant has presented OS curves for patients without interruptions compared to patients with 1 interruption vs 1 or more interruptions vs 2 or more interruptions. The OS curves without corrections for the immortal time bias suggest that more interruptions are associated with longer survival. This could be due to the immortal time bias since interruptions are infrequent and tend to be spaced out over time, resulting in patients needing to live longer in order to have more interruptions.

Treating the occurrence of a second interruption as a time-dependent covariate in a Cox regression model resulted in a HR (95% CI) for death of 0.32 (0.14, 0.73), also suggesting an association between more interruptions and improved OS.

There is no indication that treatment interruptions are associated with worse survival compared to patients without interruptions. On the contrary, there seems to be a positive association between longer time on treatment, allowing for more interruptions, and longer median survival. Treatment interruptions do therefore not interfere negatively with response to treatment and can be undertaken as it was done in the clinical trial.

In the SmPC, section 5.1, it is described that treatment breaks of up to 2 consecutive weeks were allowed due to the high frequency of treatment and the long treatment period, for some patients.

The applicant provided extend of exposure by investigator's choice before randomisation. Data show that the numerically lower number of cycles observed in investigator's choice arm is not driven only by ipilimumab arm. As number of cycles is limited to 4 for ipilimumab according to ipilimumab SmPC, it could have biased the comparison in the number cycles received. However, even in pembrolizumab and dacarbazine arm, median number of cycles started and received as well as duration of treatment are in favour of tebentafusp. This is noteworthy, as tebentafusp has a more extensive ADR profile than the treatments of the investigator's choice, and further supports that the toxicities of tebentafusp are widely manageable.

The safety profile of tebentafusp is, due to its mode of action, fundamentally different from that of immune checkpoint inhibitors (ICIs) or chemotherapy, which were the therapies used in the investigator's choice arm. This is reflected in the differences between the most frequent AE's seen in study 202. ≥99% of patients in both arms experienced treatment related TEAE's, any grade. However, a large fraction of tebentafusp treated patients (47.6% (all) and 44.5% (202)) experienced grade 3 and 4 treatment-related AEs compared to only 17.1% in the investigator's choice arm. Also, the incidence of SAE's for patients treated with tebentafusp was considerably higher than in the control arm. Differences in frequencies of the same AE between studies can be observed such as PT of periorbital oedema which varied from 63.2% in study 102 phase 1 (all dose) to 26.8% in study 102 phase 2 and 10.6% in study 202. While this discrepancy may be explained in part by the fact, that higher doses were administered in phase 1 of study 102, tebentafusp was administered at the intended

dose in phase 2 of study 102 and study 202. The applicant justifies that this discrepancy is likely due to difference in coding of AEs by investigators rather than a real difference in incidence of AE. It is noted that none of these events led to treatment discontinuation. Oedema is listed as ADR in Table 3 of the SmPC.

The PT of pain in extremities, observed in ≥ 10% of tebentafusp-treated patients, is also included in Table 3 of SmPC.

Due to the anticipated risk of hypotension in case of CRS, patients with anti-hypertensive treatment were required to temporarily suspend their anti-hypertensive treatment causing hypertension during the first few weeks of treatment. The applicant provided blood pressure according to 3 groups of patients: those who had their anti-hypertensive treatment withdrawn (n=2), those who remained under anti-hypertensive treatment (n=119) and those who were not on anti-hypertensive treatment (n=124). Overall, patients with and without anti-hypertensive treatment were balanced within tebentafusp group, and mean BP (systolic and diastolic) were higher in patients with anti-hypertensive treatment compared to patients without anti-hypertensive treatment. Both curves globally follow that same pattern with a BP decrease post-administration of Kimmtrak and an increase up to the next treatment.

Mean BP of the 2 patients who had their anti-hypertensive treatment withdrawn prior the start of tebentafusp showed BP elevations. Considering that only 2 patients had their anti-hypertensive treatment withdrawn vs 119 not withdrawn, the safety profile from patients receiving anti-hypertensive treatment is in majority provided by patients still on anti-hypertensive treatment. Based on review of the final safety data from Study 202, the risk for exacerbation of underlying cardiac conditions outweighed the potential benefit of holding anti-hypertensives to reduce the risk of CRS. Therefore, the applicant proposed not holding anti-hypertensives for patients receiving tebentafusp. This approach is consistent with recommendations in the USPI for tebentafusp as well as CRS management guidelines. TEAE of hypertension occurred 21/245 patients (8.6%, 12.5 per 100 PY) vs 3/111 (2.7%, 5.6 per 100 PY) in tebentafusp and investigator's choice respectively. According to the above analysis, iatrogenic hypertension cannot be put forward as only 2 patients had their anti-hypertensive treatment withdrawn. PT hypertension was added in SmPC Section 4.8, ADR Table 3.

The applicant provided an analysis of absolute DBP and SBP measurements limited to pre-dose and median of post-dose. It is acknowledged that both curves are superposed. This also means that tebentafusp causes a slight hypotension following each administration even in absence of CRS. Nevertheless, hypotension is transitory since pre-dose in both arms data clearly overlap. Overall, it is endorsed that events of hypotension appears concurrently with CRS and are transitory, without major impact on treatment compliance.

In spite of the more extensive toxicity of tebentafusp, this did not lead to a high rate of dose reductions or permanent drug discontinuations (3.7% (all) and 3.3% (202)) and overall, the toxicity of tebentafusp can be accepted, as it is manageable.

Cytokine release syndrome (CRS) and acute skin toxicity are very common ADRs following treatment with tebentafusp. However, only few cases of grade 4 were seen, symptoms mostly revealed within few days after infusion and frequency and intensity diminished with further infusions beyond the first few. No grade 5 events were observed. The conditions are therefore overall regarded manageable with the appropriate treatment facilities and precautions taken. In the SmPC, CRS, as well as the management of CRS, is described. It is also described under which conditions and facilities patients should be treated due to the high risk of CRS.

CRS in both studies were prospectively graded with CTCAE then Lee, 2014 grading criteria and retrospectively assessed with ASCTC CRS consensus criteria. So, 2 different grading criteria were

nevertheless used prospectively. However, all events of CRS in study 102 and 202 were reported according to Lee 2014. It appears overall that the ASTCT 2019 being more specific, it identifies more CRS events as grade 1 and 2 than CTCAE/Lee, 2014 in both studies. Grade 3 and 4 events are low in both studies using each grading system. 0 and 7.9% of patients experienced CRS in study 102 phase 1 and 2 respectively, while 20.8% of patients experienced CRS in study 202. The lower PT of CRS in study 102 is probably due to the evolution of grading system CTCAE>Lee 2014. Indeed, in the beginning of study 102, different symptoms and signs of CRS were reported according to CTCAE rather than the PT CRS. This is supported by the fact that no CRS were reported according to CTCAE.

Acute skin reactions were a common ADR seen with tebentafusp treatment. Though, the severity was within grade 1-3 and symptoms mostly revealed themselves within a few days after infusion, no grade 4 or 5 ADRs were seen and the frequency of SAE's was low. Acute skin syndrome is therefore considered manageable and the safety acceptable.

Table 2 of the SmPC for the management and dose modification for acute skin reactions describes the severity of acute skin reaction with a grading system in line with study 202 protocol recommendations.

The incidence of SAEs for patients treated with tebentafusp is high and substantial compared to the incidence in the control arm. However, in spite of the high level of AEs and SAEs related to tebentafusp treatment, the permanent discontinuation rate was 3.7% and 3.3% in all patients and in study 202 respectively, with 2% treatment-related permanent discontinuation in both groups. The rate of SAE's is therefore considered acceptable.

The degree of hospitalisation is markedly higher within the tebentafusp arm compared to the investigator's choice arm; 40.5% vs 21.4%. This is due to extensions of protocol-mandated hospitalisations, the need for prolonged patient monitoring and to SAEs. The requirement for overnight hospitalisation and frequent vital signs monitoring for the first 3 treatment doses (dose-escalation) is stated in the SmPC 4.2 in the paragraph "*First three treatment doses*". Furthermore, it is clearly stated in the SmPC, that hospitalisation in connection with the first 3 treatment doses can be prolonged and that hospitalisation in order to monitor patients can be needed.

In study 01, the deaths of 2 patients (03-A725 and 03-B505) were reported with primary cause of death due to "unknown" reasons. The deaths occurred 143 and 173 days respectively after discontinuation of tebentafusp. Narratives for the patients with death due to "unknown" have been provided. It is agreed that deaths were in both cases most likely due to disease progression and not related to tebentafusp.

Serious adverse events (SAEs) that were considered treatment-related were substantially higher in the tebentafusp arm (22%) compared to the investigator's choice arm (7%) in study 202. The most common were CRS and skin toxicity. The high rate of SAEs are described as manageable and, from the presented data, it is agreed that causes of death reported as "due to AE", "other" or "unknown" were not related to treatment with tebentafusp.

The most frequent severe laboratory abnormality was lymphocytes decreased, which is due to the MoA of tebentafusp. The decreases were transient, observed shortly after infusion and clinically asymptomatic although a large part was grade 3 or 4. Other haematology parameter variations (haemoglobin, leukocytes, neutrophils and platelets) were primarily of grade 1 and a low incidence of grade 2 or worse.

SAEs due to changes in hepatic chemistry was seen in 1 patient and not considered drug-related. None were grade 5 events, and none resulted in treatment discontinuation. The changes in other chemical parameters such as amylase, calcium, creatinine, glucose, lipase, magnesium, phosphate, potassium and sodium were considerable in comparison with the extent seen in the investigator's choice arm.

These changes are considered treatment related and have, in recognition of this, been listed in the table 3 of ADRs in the SmPC.

Regarding the patient with left ventricular dysfunction (Patient 1028121), the patient, besides CRS, had clinical symptoms of myocardial infarction failure after the day 8 infusion of tebentafusp with angina pectoris and troponin increase. The patient was relevantly treated and examined; coronary angiography findings were normal. Symptoms resolved and the patient's LVEF was persistently 56% at and after being discharged from the hospital after 1 week. Treatment was permanently discontinued. The patient was CT scanned 1 month after being discharged, showing progression, especially in the liver metastases. The patient died a month after the CT scan. It is agreed that the patient had most likely not developed heart failure due to tebentafusp treatment and most likely died from disease progression.

SAEs related to ECG abnormalities were reported in 5 patients. A description in section 4.2 of the SmPC, of cardiac events and conditions and precautions that should be taken in relation to these was reflected. Cardiac failure was added to the mentioned cardiac conditions in the SmPC section 4.8, the ADR table. Furthermore, SmPC section 4.2 states that tebentafusp has not been studied in patients with history of significant cardiac disease. Recommendations for treatment of patients with history of cardiac disease has been described in SmPC, section 4.4.

In study 102 and 202 clinically significant cardiac disease was an exclusion criterion. In section 4.4 of the SmPC, a paragraph on "Cardiac disease" has been added with a description of when to perform ECGs and how to handle ECG changes. Moreover, a description of the changes observed in the QTc interval has been added, since prolongations of ≥500 msec and/or an increase in QTc of ≥60 msec from baseline value are also a known risk factors of developing life-threatening arrhythmias, such as Torsade de Pointes.

Furthermore, ECG was not described as a part of the required surveillance regarding tebentafusp treatment. It seems highly clinically relevant to recommend ECG surveillance during and after treatment with tebentafusp, as up to 30% of patients experienced cardiac disorders, even though this might be in conjunction with CRS. This is sufficiently addressed in section 4.4. of the SmPC.

It is seen that atrial fibrillation has occurred as both grade 3/4 TEAE and as SAE and "atrial fibrillation" was therefore added to the mentioned cardiac conditions in 4.8, ADRs, table 3 of the SmPC.

Although no cardiac events were registered in the patients with QTcF prolongations at this time, QTcF prolongations are sufficiently addressed as ADRs in the SmPC. The applicant has also addressed ECG measuring before and during treatment as well as suggested interventions in case of QTcF prolongations in section 4.4. The augmented risk of additional administration of other medications known to induce QTcF prolongation is also described.

It is endorsed that higher numerical point estimates appears in subgroups with poor prognosis factors (larger liver lesion, higher LDH) and in patients in second line or later, patient who previously received a checkpoint inhibitor, ECOG 1 vs ECOG 0, baseline ALP and baseline lymphocyte count. These differences are not unexpected. Moreover, the subgroup non-white/missing appears to have more all-grade hepatic toxicities (pool 1 and pool 2) and more acute skin toxicities of grade ≥ 2 and of grade ≥ 3 (pool 1 and pool 2). The Applicant clarified that subgroup "non-white/missing" consists mainly of patient with missing data. In these conditions, it is acknowledged that any interpretation of data would be inadequate.

In the presented analyses, no specific subgroups or intrinsic/extrinsic factors were appointed to be of special interest with regards to developing CRS, acute skin toxicity or hepatotoxicity. Although, ADAs occurred in approximately a third of patients in study 202, the potential influence on safety has not been discussed in the context of safety and therefore, the applicant should provide the sample analysis

report for study 202 and commit to submit the final NAb report once finalised (please refer to clinical pharmacology). Moreover, available data do not allow firm conclusions to be drawn on the effect of ADAs on efficacy or the safety profile of tebentafusp. The Applicant has clearly stated in the SmPC that there was no evidence of ADA impact on safety or efficacy of tebentafusp, although the small number of patients who developed high titre ADA precludes firm conclusions regarding their clinical impact.

Data on dose reductions of 2 patients is insufficient for safety evaluation. SmPC 4.2 reflects that no dose reductions are recommended, instead adverse reactions should be managed by withholding or discontinuing tebentafusp treatment. The management and dose modification tables in the SmPC Section 4.2, table 1 provides guidance on when to withhold dose or delay dose escalation based on severity of acute skin reactions and CRS. The extent of treatment interruptions, reductions and discontinuation is within the range of what would be expected in the metastatic setting of uveal melanoma and is acceptable. Clear guidance in the SmPC regarding, when dose interruption and/or a stop in dose-escalation is provided.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.10. Conclusions on the clinical safety

Tebentafusp has a quite extensive degree of toxicity. There were more treatment-related AEs and SAEs than what was seen with investigator's choice (immune checkpoint inhibitors and chemotherapy). However, the ADRs diminished over time with continued treatment beyond the first few (often 3) treatment cycles, the incidence of grade 4 AEs was low and no grade 5 were registered. The discontinuation rate and dose reduction rate were low and no treatment related deaths were reported. The overall conclusion from the presented data is, that the toxicity from tebentafusp, although wide-ranging, is manageable.

The adverse drug reactions from tebentafusp can, to a great extent, be explained by its mode of action. The most frequent ones being CRS and (acute) skin toxicity. The nature and high frequency of the ADRs, especially CRS, is quite different from most of the currently available anti-cancer treatments and implies that the conditions, under which the patients receive their treatment, need to be suitable. Hence, the right clinical set-up is very important when treating patients with tebentafusp. This information is sufficiently reflected in the SmPC.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 74. Summary of safety concerns

Summary of safety concerns	
Important identified risks	Cytokine release syndrome Acute skin reactions
Important potential risks	None
Missing information	Use in pregnancy and lactation Use in patients with clinically significant cardiac disease

2.7.2. Pharmacovigilance plan

Table 75. On-going 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				
Category 3 - Required additional pharmacovigilance activities				
Survey to assess the effectiveness of the risk minimisation measures Planned	The study will assess the following: a) Physicians' understanding of the important safety information detailed in the Treatment Guide for Healthcare Professionals to minimise the severity of CRS with tebentafusp. b) Healthcare professionals' distribution of the Patient Guide to patients treated with tebentafusp	Cytokine release syndrome	Study protocol submitted to the PRAC	Within 3 months post authorisation
			Data collection	18 months after market launch in the relevant countries
			Final study report	6 months after the end of data collection

2.7.3. Risk minimisation measures

Table 76. Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Cytokine release syndrome (Important identified risk)	Routine risk minimisation measures: • *Guidance on premedication, monitoring and management for CRS based on severity in SmPC section 4.2* • *Warning that tebentafusp can cause CRS, what to expect and how to manage CRS in SmPC section 4.4* • *Warning to monitor patients with cardiac disease, QT prolongation and risk factors for cardiac failure in SmPC sections 4.2 and 4.4* • *Recommendation to perform an ECG in all patients before and*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	after treatment with Kimmtrak in SmPC section 4.4 • *Warning for the patient to inform their doctor or nurse immediately or seek urgent medical attention if they develop symptoms of CRS in PL section 2* • *Guidance that the patient may be given fluids by infusion and the dose of corticosteroids adjusted to help prevent low blood pressure from CRS in SmPC section 4.2 and PL sections 2 and 3* • *Warning for the patient to talk to their doctor or nurse before they are given tebentafusp about heart problems including QT interval prolongation in PL section 2* • *Adverse reaction in SmPC section 4.8* • *Side effect in PL section 4* • *Restricted prescription* Additional risk minimisation measures: • *Treatment Guide for Healthcare professionals* • *Patient Guide*	
Acute skin reactions (Important identified risk)	Routine risk minimisation measures: • *Guidance on management of acute skin reactions based on severity in SmPC section 4.2* • *Warning that tebentafusp can cause acute skin reactions, what to expect and how to manage acute skin reactions in SmPC section 4.4* • *Warning for the patient to inform their doctor or nurse immediately or seek urgent medical attention if they develop symptoms of skin reactions in PL section 2* • *Adverse reaction in SmPC section 4.8* • *Side effect in PL section 4* • *Restricted prescription* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *None*

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Use in pregnancy and lactation (Missing information)	Routine risk minimisation measures: • *Warning not to use tebentafusp during pregnancy in SmPC section 4.6 and PL section 2* • *Recommendation to use effective contraception in SmPC sections 4.4 and 4.6 and PL section 2* • *Guidance that animal reproduction studies have not been conducted in SmPC sections 4.6 and 5.3* • *Warning that breast-feeding should be discontinued during treatment with tebentafusp in SmPC section 4.6 and PL section 2* • *Restricted prescription* Additional risk minimisation measures: • *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *None*
Use in patients with clinically significant cardiac disease (Missing information)	Routine risk minimisation measures: • *Warning to monitor patients with cardiac disease, QT prolongation and risk factors for cardiac failure in SmPC sections 4.2 and 4.4* • *Recommendation to perform an ECG in all patients before and after treatment with Kimmtrak in SmPC section 4.4* • *Information that patients with clinically significant cardiac disease were excluded from study participation in SmPC sections 4.2 and 5.1* • *Warning for the patient to talk to their doctor or nurse before they are given tebentafusp about heart problems including QT interval prolongation in PL section 2* • *Restricted prescription* Additional risk minimisation measures: *None*	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • *None* Additional pharmacovigilance activities: • *None*

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is {DD.MM.YYYY.}. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Labelling exemptions

A request of translation exemption of the labelling as per Art 63(1) of Directive 2001/83/EC has been submitted by the applicant and has been found acceptable by the QRD Group for the following reasons:

the very low prevalence of the disease and low production volumes, and that the product will be handled and administered only by healthcare professionals.

The labelling subject to translation exemption as per the QRD Group decision above will however be translated in all languages in the Annexes published with the EPAR on EMA website, but the printed materials will only be translated in the language(s) as agreed by the QRD Group.

2.9.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Kimmtrak (tebentafusp) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Kimmtrak is indicated as monotherapy for the treatment of human leukocyte antigen (HLA) A*02:01 positive adult patients with unresectable or metastatic uveal melanoma.

3.1.2. Available therapies and unmet medical need

Metastatic uveal melanoma is an uncurable disease, which has not had any systemic treatment advances with a survival benefit for decades. Approximately 50% of the patients diagnosed with primary and localised uveal melanoma develop metastatic disease, usually in the form of multiple liver metastases. Since there are no standard of care for these patients with mUM, who are recommended to participate in a clinical trial, there exists a high unmet medical need for new and effective treatments. Once patients develop metastatic UM (mUM), the prognosis and outcomes are dismal, with a median survival of approximately 12 months (Rantala, 2019; Khoja, 2019).

3.1.3. Main clinical studies

The pivotal study is an ongoing Phase 3, open-label, multicentre randomised study evaluating the efficacy and safety of tebentafusp versus investigator's choice (dacarbazine, ipilimumab, and pembrolizumab) in adult HLA-A*02:01-positive patients with metastatic uveal melanoma (mUM), who have not received prior systemic therapy in the metastatic setting. The patients included were randomised 2:1 to receive either tebentafusp or therapy of the investigator's choice and the treatment options in the comparator arm are endorsed (n=378). The pivotal phase 3 study 202 is supported by results from the phase 1-2 study 102 (n=127).

The pivotal study was fully recruited from 54 sites (14 countries) in less than 3 years and at the time of the data cut-off 13 October 2020, the median follow-up for all patients was initially 14.1 months. Further updated efficacy data has been provided with the DCO 12 August 2021 and approximately 8 months longer follow up for OS (total median FU: 22.4 months).

3.2. Favourable effects

The primary endpoint of the pivotal study, overall survival (**OS**), was prolonged in the primary analysis at a 40% event rate by 5.7 months with tebentafusp from 16 months to 21.7 months, HR 0.51 (95%CI: 0.37, 0.71). The KM curves clearly separate after approximately 3 months of therapy and stay separated. The **updated OS** data at a 54% event rate continued to favour the tebentafusp arm (median OS 21.7 months vs 16.7 months, HR=0.58; 95%CI 0.44, 0.77).

The primary endpoint of the supportive study showed a median OS of 16.8 months in a pre-treated study population after a median follow up of ~20 months and 54.3% OS events.

In the pivotal study, the secondary endpoint of progression-free survival (**PFS**) was statistically significantly improved with tebentafusp, as the median PFS was prolonged by 0.4 months from 2.9 months to 3.3 months, HR 0.73 (95%CI: 0.58, 0.94). In the supportive study, median PFS was 2.8 months (95%CI: (2.0, 3.7) in the pre-treated population.

3.3. Uncertainties and limitations about favourable effects

The primary analysis of OS in the pivotal study was considered rather mature with 40% observed OS events, and of these 34.5% events were observed in the tebentafusp arm versus 50% events in the control arm after a median follow-up of ~14 months (DCO 13 October 2020). Mature updated OS data with 50.4% and 62.7% events, in each arm respectively, have been provided. However, it is noted that this updated analysis occurred after patients on therapy of investigator's choice started to cross-over to tebentafusp and this hampers the updated and future results of the primary endpoint of the pivotal trial, which was also the main endpoint that was clinically meaningfully improved. Final OS data will be provided as a post-authorisation measure (REC).

The PFS data from both studies are considered mature. In the pivotal study, the KM curves never clearly separate and the shape of the PFS KM curve show that a high number of patients had events at every time point of evaluation, including at the first evaluation after 12 weeks. However, there did not seem to be significant evaluation-time bias and the PFS results are considered robust.

3.4. Unfavourable effects

The most frequent AE's reported for the tebentafusp-treated patients of the pivotal study 202 were in all patients/study 202 were: cytokine release syndrome (89%), pyrexia (78.5%/76.3%), pruritus (72%/69%), nausea (57.1%/49%), fatigue (56.5%/51%), chills (54.9%/47.8%), rash (51%/55.1%), hypotension (41.5%/38.8%), vomiting (36.1%/29.8%), dry skin (35.1/31.4%) and headache (32.9%/30.6%).

For the investigator's choice arm these were: fatigue (35.1%), nausea (26.1%), pruritus (23.4%), diarrhoea (19.8%), rash (16.2%), arthralgia (16.2%), abdominal pain (15.3%), decreased appetite (13.5%), hyperthyroidism (11.7%) and hypothyroidism (10.8%).

Any AEs of grade 3 or 4 were reported in 58.3% of all patients and in 54.3% of patients in study 202, respectively and the majority were treatment-related. The most frequent grade 3-4 AE were in all patients/ patients in study 202: rash maculo-papular (9.5%/8.6%), rash (7.6%/9.4%), hypertension (7.6%/8.6%), hypophosphataemia (6.1%/4.1%), ASAT increase (6.1%/5.3%), hypotension (5.6%/3.3%), fatigue (4.9%/5.3%) and pyrexia (4.6%/3.7%).

3.5. Uncertainties and limitations about unfavourable effects

None.

3.6. Effects Table

Table 77. Effects Table for tebentafusp for HLA-A*02:01-positive adult patients with mUM (data cut-off: 13 OKT 2020).

Effect	Short Description	Unit	Treatment Tebentafusp N=252	Control INV choice N=126	Uncertainties/ Strength of evidence
Favourable Effects for the Pivotal study 202					

Effect	Short Description	Unit	Treatment Tebentafusp N=252	Control INV choice N=126	Uncertainties/ Strength of evidence
OS	Overall survival	Months	21.7	16	HR 0.51 (95%CI: 0.37, 0.71) 40% events
Updated OS	Overall survival	Months	21.7	16.7	HR 0.58 (95%CI:0.44, 0.77) 54% events, cross-over allowed, DCO 12 AUG 2021
PFS	Progression-free survival	Months	3.3	2.9	HR 0.73 (95%CI: 0.58, 0.94) 78% events observed
Favourable effects for the supportive study 101 (n=127)					
OS	Overall survival	Months	16.8	NA	54% of total events
PFS	Progression-free survival	Months	2.8	NA	92.1% events observed
Unfavourable Effects (All studies safety pool (n=410) versus Investigators choice (n=126)					
Grade ≥3 AEs	%		47.6	44.5	
SAEs	%		31.2	23.4	
AEs leading to disc.	%		3.3	6.3	
AEs leading to death	%		0.4	1.8	No treatment-related deaths with tebentafusp

Abbreviations: INV: Investigators choice (dacarbazine, ipilimumab, or pembrolizumab); disc: discontinuation

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The benefit of tebentafusp compared to treatments by Investigator's choice in the first-line setting of metastatic uveal melanoma is considered highly clinically meaningful, since updated mature OS data show a survival benefit of 5.0 months (HR 0.58). The efficacy data from study 102 are considered supportive of the applied line-agnostic indication because data show that treatment with tebentafusp results in clinically meaningful efficacy in a pre-treated population as well. This should be interpreted in the context that there is no standard of care for patients with mUM, neither in the first-line setting nor beyond. This data showed an encouraging OS of 16.8 months, which is markedly better than historic controls treated with chemotherapy or Anti-PD-1 monotherapy in a 2+ line setting and has a median OS of 6-9 months, while acknowledging the uncertainties inherent in cross-study comparisons, not

least with regard to time-to-event endpoints that are strongly affected by heterogeneity with regard to the underlying prognosis of the study populations.

These clinically relevant data from both the first and later-line settings should be considered in the context that there has been no standard of care with any survival benefit for the targeted disease of metastatic uveal melanoma available for decades.

Even though there were no clinically relevant differences in PFS and ORR with tebentafusp, the clinically significant survival benefit is considered a robust result and is considered in line with similar results observed with other immunotherapies, where a clinically meaningful improvement of OS is not necessarily supported by PFS benefit. Moreover, updated OS results with more events (54%) did not change the results significantly.

The main reported adverse events related to treatment with tebentafusp are cytokine release syndrome, rash, pyrexia, pruritis, fatigue, nausea, chills, hypo/hyperpigmentation, abdominal pain, oedema, hypotension, dry skin, headache and vomiting. However, the ADRs diminished over time with continued treatment beyond the first few (often 3) treatment cycles and the incidence of high-grade events was low. The discontinuation rate due to any AE was also low (3.3%) and no treatment related deaths were reported. The overall conclusion from the presented data is, that the toxicity from tebentafusp, although wide-ranging, is manageable and can be explained by its mode of action. The nature and high frequency of the ADRs, especially cytokine-release syndrome (CRS), is quite different from most of the currently available anti-cancer treatments and implies that the conditions, under which the patients receive their treatment, need to be suitable. Hence, the right clinical set-up is very important when treating patients with tebentafusp.

3.7.2. Balance of benefits and risks

The efficacy of tebentafusp is considered clinically relevant in the first-line and beyond treatment setting (line agnostic) of patients with HLA-A*02:01-positive unresectable or metastatic uveal melanoma and the toxicity appears manageable. It can therefore be concluded that the benefits outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

Not applicable

3.8. Conclusions

The overall benefit/risk balance of Kimmtrak is positive, subject to the conditions stated in section ‘Recommendations’.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Kimmtrak is favourable in the following indication:

Kimmtrak is indicated as monotherapy for the treatment of human leukocyte antigen (HLA) A*02:01

positive adult patients with unresectable or metastatic uveal melanoma.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Kimmtrak in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at highlighting the monitoring process and facilitating the prompt diagnosis and treatment of cytokine release syndrome (CRS) to reduce its severity.

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

- Physician educational material
- Patient information pack

Physician educational material:

- The Summary of Product Characteristics
- Treatment Guide for Healthcare Professionals

Treatment Guide for Healthcare Professionals:

- Details on how to monitor patients for the first three infusions and for subsequent infusions.
- Details of how to minimise the risk of hypotension associated with CRS.
- Description of the symptoms of CRS, including severity, frequency, time to onset, treatment, and resolution, in patients treated with Kimmtrak.
- Details on how to manage CRS based on severity grade, including the recommendation to administer corticosteroid premedication for Grade 2 CRS that is persistent or recurrent or any Grade 3 CRS.
- Description of the ECG schedule and management requirements based on the ECG results.
- Recommendation to carefully monitor patients with cardiac disease, QT prolongation and risk factors for cardiac failure.
- Information on the importance of informing patients of the risk of CRS and the need to immediately contact their doctor or nurse if they develop symptoms of CRS.
- Information on the importance of reporting adverse reactions with details of how to report.

The patient information pack:

- Package leaflet
- Patient Guide

Patient Guide:

- Information on the risk of CRS associated with Kimmtrak with a description of the symptoms.
- Information on the importance of immediately contacting a doctor or nurse if the patient develops symptoms of CRS.
- Details of what the patient should expect regarding the monitoring schedule.
- Information on the importance of reporting side effects with details of how to report.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that tebentafusp is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.