1. NAME OF THE MEDICINAL PRODUCT

KIMMTRAK
100 micrograms/0.5 mL concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One 0.5 mL vial contains 100 micrograms (0.1 mg) of tebentafusp, corresponding to a concentration before dilution of 200 mcg/mL (0.2mg/mL).

Tebentafusp is a fusion protein, produced by recombinant DNA technology in *Escherichia coli* cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

Colourless to slightly yellowish solution in a single-dose vial.

Patient safety information card
The marketing of KIMMTRAK is subject to a Risk management plan (RMP) including a 'patient safety information card'. The 'patient safety information card', emphasizes important safety information that the patient should be aware of before and during the treatment. Please explain to the patient the need to review the card before starting treatment.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

KIMMTRAK should be administered under the direction and supervision of a physician experienced in the use of anti-cancer agents and who is prepared to manage cytokine release syndrome in an environment where full resuscitation facilities are immediately available. Hospitalisation is recommended for at least the first three infusions of KIMMTRAK (see section 4.4).

Patients treated with KIMMTRAK must have HLA-A*02:01 genotype determined by any validated HLA genotyping assay.

Posology

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 (see section 6.6). Treatment with KIMMTRAK should be continued while patient is deriving clinical benefit and in the absence of unacceptable toxicities (see section 5.1).

Premedication

To minimize the risk of hypotension associated with cytokine release syndrome (CRS), intravenous fluids should be administered prior to starting KIMMTRAK infusion based on clinical evaluation and the volume status of the patient.

For patients with preexisting adrenal insufficiency on maintenance systemic corticosteroids, adjusting the corticosteroid dose should be considered to manage the risk of hypotension.

Dose adjustments

No dose reductions of KIMMTRAK are recommended. KIMMTRAK should be withheld or discontinued to manage adverse reactions as described in Table 1 and Table 2.

If CRS is suspected, the symptoms should be identified and promptly managed according to recommendations in Table 1. See Table 2 for management guidelines for acute skin reactions.

Table 1: CRS grading and management guidance

CRS grade*	Management
Grade 1 Temperature ≥ 38 °C No hypotension or hypoxia	• Continue treatment and provide symptomatic support. Monitor for escalation in CRS severity.
Grade 2 Temperature ≥ 38 °C Hypotension that responds to fluids and does not require vasopressors Oxygen requirement includes low flow nasal cannula (delivery of oxygen ≤ 6 L/min) or blow-by	• Continue treatment and administer bolus intravenous fluids and oxygen by low flow nasal canula or blow-by oxygen as needed. • If hypotension and hypoxia do not improve within 3 hours or CRS worsens administer high-dose intravenous corticosteroid (e.g. 2 mg/kg/day methylprednisolone or equivalent). • For Grade 2 CRS that is persistent (lasting 2--3 hours) or recurrent (occurrence of ≥ Grade 2 CRS with more than one dose), administer corticosteroid premedication (e.g. dexamethasone 4 mg or equivalent) at least 30 minutes prior to next dose
Grade 3 Temperature ≥ 38 °C Require a vasopressor with or without vasopressin Require high flow nasal cannula (delivery of oxygen > 6 L/min), face mask or non-rebreather mask or Venturi mask	• Withhold KIMMTRAK until CRS and sequelae have resolved • Administer high-dose intravenous corticosteroid (e.g. 2 mg/kg/day methylprednisolone or equivalent). • Administer tocilizumab as needed - Patient weight ≤ 30 kg: 12 mg/kg intravenously over 1 hour - Patient weight ≥ 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg) • Resume KIMMTRAK at same dose level (i.e., do not escalate if Grade 3 CRS occurred during initial dose escalation; resume escalation once dosage is tolerated)

	• For Grade 3 CRS, administer corticosteroid premedication (e.g. dexamethasone 4 mg or equivalent) at least 30 minutes prior to next dose
Grade 4 Temperature ≥ 38 °C Require multiple vasopressors (excluding vasopressin) Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation).	• Permanently discontinue KIMMTRAK • Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent)

* Based on American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading of CRS criteria (Lee et. al 2019).

Table 2: Recommended management and dose modifications for acute skin reactions

Adverse reactions	Severity[a]	Management
Acute skin reactions (see section 4.4)	Grade 2	• Withhold KIMMTRAK until Grade ≤ 1 or baseline. • Administer antipruritic regimen (e.g., non-sedating long-acting antihistamine) • Administer topical corticosteroid treatment for symptomatic rash that does not respond to anti-pruritic regimen. • For persistent symptoms, administer systemic steroids • Resume KIMMTRAK escalation if the current dose is less than 68 mcg, or resume at same dose level if dose escalation has completed

	Grade 3	• Withhold KIMMTRAK until Grade ≤ 1 or baseline. • Administer topical corticosteroid and oral corticosteroids • For persistent reactions not responding to oral steroids, consider intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent) • Resume KIMMTRAK at same dose level (i.e., do not escalate if Grade 3 skin reactions occurred during initial dose escalation; resume escalation once dosage is tolerated)
	Grade 4	• Permanently discontinue KIMMTRAK • Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent)

[a] Based on National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 (NCI CTCAEv4.03).

Special populations

Paediatric population

The safety and efficacy of KIMMTRAK in children under the age of 18 years have not been established. No data are available.

Elderly

No dose adjustment is required for elderly patients (≥ 65 years of age).

Renal impairment

Based on safety and efficacy analyses, dose adjustment is not necessary in patients with mild to moderate renal dysfunction. No dose recommendations can be made for patients with severe renal impairment because of the lack of pharmacokinetic data; therefore, dosing in patients with severe renal impairment should be done with caution and careful monitoring (see section 5.2).

Patients with history of cardiac disease

KIMMTRAK has not been studied in patients with history of significant cardiac disease. Patients with cardiac disease, QT prolongation and risk factors for cardiac failure should be monitored carefully (see section 4.4).

Method of administration

KIMMTRAK is for intravenous use. The recommended infusion period is 15 to 20 minutes.

KIMMTRAK requires dilution with sodium chloride 9 mg/mL (0.9 %) solution for injection

containing human albumin for intravenous infusion. Each vial of KIMMTRAK is intended for use as single-dose only. Do not shake the KIMMTRAK vial.

For instructions on dilution and administration of the medicinal product, see section 6.6.

First three treatment doses

First three doses of KIMMTRAK should be administered in a hospital setting with overnight monitoring for signs and symptoms of CRS for at least 16 hours. Vital signs should be monitored pre dose and at a minimum of every 4 hours until resolution of symptoms. If clinically indicated, more frequent monitoring or prolongation of hospitalization should be performed.

If patients experience Grade 3 or 4 hypotension during any of the first three KIMMTRAK infusions, patients should be monitored every hour for at least 4 hours in an outpatient setting for the next three infusions.

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Subsequent treatment doses

After 68 mcg dose level is tolerated (i.e., absence of Grade ≥ 2 hypotension requiring medical intervention), subsequent doses can be administered in appropriate outpatient ambulatory care setting. Patients should be observed for a minimum of 60 minutes following each infusion. For patients who have received outpatient treatment with KIMMTRAK for at least 3 months and have not experienced any interruptions greater than 2 weeks, outpatient monitoring following infusion may be decreased to a minimum of 30 minutes for subsequent doses.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Cytokine release syndrome (CRS)

Most patients experienced CRS following tebentafusp infusions. Diagnosis of CRS was most frequently based on pyrexia followed by hypotension and infrequently hypoxia. Other commonly observed symptoms with CRS included chills, nausea, vomiting, fatigue, and headache. CRS has been associated with organ dysfunction, including hepatic, renal, pancreatic, cardiac, and pulmonary dysfunction.

In the majority of cases, CRS started on the day of infusion with median time to resolution of 2 days. Pyrexia was noted in nearly all cases of CRS, and in these patients, an increase in body temperature generally occurred within the first 8 hours after tebentafusp infusion. CRS rarely (1.2 %) led to treatment discontinuation.

Patients should be monitored for signs or symptoms of CRS for at least 16 hours following first three infusions of tebentafusp in a hospital setting with immediate access to medicinal products and resuscitative equipment to manage CRS. If CRS is observed, prompt treatment with supportive care including antipyretics, intravenous fluids, tocilizumab, or corticosteroids should be initiated to avoid escalation to severe or life-threatening events and monitoring should be continued until resolution.

At subsequent doses, patients should be closely monitored after treatment for early identification of signs and symptoms of CRS (see section 4.2, Method of administration). Patients with co-morbidities, including cardiovascular disorders, may be at increased risk for sequalae associated with CRS.

Treatment with tebentafusp has not been studied in patients with clinically significant cardiac disease (see section 5.1). Depending on persistence and severity of CRS tebentafusp treatment should be withheld or discontinued (see section 4.2, Table 1).

Acute skin reactions

Acute skin reactions have been reported with tebentafusp infusion, which may be based on its mechanism of action and gp100 expression in normal melanocytes in the skin. Acute skin reactions mainly included rash, pruritus, erythema and cutaneous oedema (see section 4.8).

Acute skin reactions typically occurred following each of the first three tebentafusp infusions and decreased in severity and frequency over time. Majority of symptoms resolved without any systemic corticosteroid or any long term sequalae.

Acute skin reactions can be managed with antihistamine and topical corticosteroids. For persistent or severe symptoms, systemic steroids should be considered. Management of signs and symptoms of skin reactions may require temporary delays of subsequent tebentafusp treatments (see section 4.2, Table 2).

Cardiac disease

Cardiac events such as sinus tachycardia and arrhythmia have been observed in patients who have received tebentafusp treatment (see section 4.8). Patients with pre-existing cardiovascular disorders may be at increased risk for sequalae associated with CRS and should be monitored carefully. Any patient with signs or symptoms consistent with cardiac events should be evaluated and promptly treated. In addition, appropriate treatment should be administered for any underlying CRS as a precipitating factor.

Cases of QT interval prolongation were reported following tebentafusp treatment (see section 4.8). Tebentafusp treatment should be administered with caution in patients with history of or predisposition to QT interval prolongation and in patients who are taking medicinal products that are known to prolong QT interval.

An electrocardiogram (ECG) should be performed in all patients before and after tebentafusp treatment during the first 3 weeks of treatment and subsequently as clinically indicated. If QTcF exceeds 500 msec or increases by ≥ 60 msec from baseline value tebentafusp treatment should be withheld and patients should be treated for any underlying precipitating factors including electrolyte abnormalities. Tebentafusp treatment should be resumed once QTcF interval improves to <500 msec or is < 60 msec from baseline value. Depending on persistence and severity of the cardiac event and any associated CRS tebentafusp treatment should be withheld or discontinued (see section 4.2, Table 1).

Contraception

Women of childbearing potential have to use effective contraception during and for at least 1 week after last dose of tebentafusp treatment (see section 4.6)

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per mL, that is to say essentially ‘sodium-free’

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed with tebentafusp.

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. These patients should be monitored for toxicity (e.g., warfarin) or drug concentrations (e.g., cyclosporine). The dose of the concomitant medicines should be adjusted as needed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

Women of childbearing potential should use effective contraception during treatment with tebentafusp and for at least 1 week after last dose of tebentafusp.

Pregnancy

There are no data from the use of tebentafusp in pregnant women. Animal reproduction studies have not been conducted with tebentafusp (see section 5.3).

Tebentafusp is not recommended during pregnancy and in women of childbearing potential not using contraception. The pregnancy status in females of reproductive potential should be verified prior to initiating tebentafusp treatment.

Breast-feeding

There is insufficient information on the excretion of tebentafusp/metabolites in human milk. A risk to the newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with tebentafusp.

Fertility

No fertility studies have been conducted with tebentafusp (see section 5.3). The effect of tebentafusp on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

Tebentafusp has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

The most common adverse drug reactions in patients treated with KIMMTRAK were cytokine release syndrome (88 %), rash (85 %), pyrexia (79 %), pruritus (72 %), fatigue (66 %), nausea (56 %), chills (55 %), abdominal pain (49 %), oedema (49 %), hypo/hyperpigmentation (48 %), hypotension (43 %), dry skin (35 %), headache (32 %) and vomiting (34 %).
Adverse reactions led to permanent discontinuation in 4 % of patients receiving KIMMTRAK. The most common adverse reaction that led to discontinuation of KIMMTRAK was cytokine release syndrome.

Adverse reactions resulting in at least one dose interruption occurred in 26 % of KIMMTRAK-treated patients (dosed weekly) and resulted in a median of one skipped dose. Adverse reactions requiring dosage interruption in ≥ 2 % of patients included fatigue (3 %; Grade 1--3), pyrexia (2.7 %; Grade 1-3), alanine aminotransferase increase (2.4 %; Grade 1-4), aspartate aminotransferase increase (2.4 %; Grade 1-3) abdominal pain (2.1 %; Grade 1-3), and lipase increased (2.1 %; Grade 1-3).

Adverse reactions leading to at least one dose modification occurred in 4.2 % of patients in KIMMTRAK-treated group. Adverse reactions which required dose modification in ≥ 1 % of patients were cytokine release syndrome (1.9 %; Grade 1-3), and hypotension (1.1 %; Grade 2-4).

Tabulated list of adverse reactions

Table 3 summarizes adverse reactions that occurred in 378 metastatic uveal melanoma patients from two clinical studies (IMCgp100-102 and IMCgp100-202) that received the recommended dosing KIMMTRAK dosing regimen of 20 micrograms on Day 1, 30 micrograms on Day 8 and 68 micrograms on Day 15 and 68 micrograms weekly thereafter.

The adverse drug reaction frequency is listed by MedDRA System Organ Class (SOC) at the preferred term level. Frequencies of occurrence of adverse reactions are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 3: Adverse reactions in patients treated with KIMMTRAK monotherapy

	Adverse reactions
Infections and infestations	
Common	Nasopharyngitis
Immune system disorders	
Very common	Cytokine release syndrome[1]
Metabolism and nutrition disorders	
Very common	Decreased appetite, hypomagnesaemia, hyponatraemia, hypocalcaemia, hypokalaemia
Uncommon	Tumour lysis syndrome
Psychiatric disorders	
Very Common	Insomnia
Common	Anxiety
Nervous system disorders	
Very common	Headache[2] , dizziness, paraesthesia
Common	Taste disorder
Cardiac disorders	
Very common	Tachycardia[2]

Common	Arrhythmia[2], atrial fibrillation[2]
Uncommon	Angina pectoris[2], cardiac failure[2]
Vascular disorders	
Very common	Hypotension[2], flushing, hypertension
Respiratory, thoracic and mediastinal disorders	
Very common	Cough, dyspnoea
Common	Oropharyngeal pain, hypoxia[2]
Gastrointestinal disorders	
Very common	Nausea[2], vomiting[2], diarrhoea, abdominal pain, constipation, dyspepsia
Skin and subcutaneous tissue disorders	
Very common	Rash, pruritus, dry skin, hypo/ hyperpigmentation[4], erythema
Common	Alopecia, night sweats
Musculoskeletal and connective tissue disorders	
Very common	Arthralgia, back pain, myalgia, pain in extremity
Common	Muscle spasm
General disorders and administration site conditions	
Very common	Pyrexia[2], fatigue[3], chills[2], oedema[5], Influenza like illness
Investigations	
Very common	Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, lipase increased, anaemia, lymphocyte count decreased, blood phosphate decreased, blood creatinine increased
Common	Amylase increased, gamma glutamyltransferase increased, white blood cell count increased, blood alkaline phosphatase increased, blood glucose increased
Uncommon	Electrocardiogram QT prolonged

[1] CRS was adjudicated using the ASTCT consensus grading of CRS criteria (Lee et.al 2019). Adjudicated CRS is provided in lieu of investigator reported CRS.
[2] Some of the events may be associated with CRS or may be isolated reported events.
[3] Includes fatigue and asthenia.
[4] Includes achromotrichia acquired, ephelides, eyelash discolouration, eyelash hypopigmentation, hair colour changes, lentigo, pigmentation disorder, retinal depigmentation, skin depigmentation, skin discolouration, skin hyperpigmentation, skin hypopigmentation, solar lentigo, vitiligo.
[5] Includes eye oedema, eye swelling, eyelid oedema, periorbital swelling, periorbital oedema, swelling of eyelid, pharyngeal oedema, lip oedema, lip swelling, face oedema, generalized oedema, localized oedema, oedema, oedema peripheral, peripheral swelling, swelling, swelling face.

Description of selected adverse reactions

Cytokine release syndrome (CRS)

In clinical study IMCgp100-202, cytokine release syndrome (adjudicated based on ASTCT consensus grading 2019) occurred in 89 % of KIMMTRAK treated patients. The overall incidence of CRS included 12 % Grade 1, 76 % Grade 2 and 0.8 % Grade 3 events. Most commonly observed symptoms with CRS included chills, nausea, vomiting, fatigue, hypotension, and headache. Grade 3 events that may be observed in association with CRS include tachycardia, hypoxia, angina pectoris, atrial flutter, and left ventricular dysfunction.

The majority (84 %) of episodes of CRS started the day of infusion. The median time to resolution of CRS was 2 days. CRS rarely (1.2 %) led to treatment discontinuation. All CRS symptoms were reversible and were mostly managed with intravenous fluids, antipyretics, or a single dose of

corticosteroid. Two patients (0.8 %) received tocilizumab.

For clinical management of CRS, see section 4.2, Table 1.

Acute skin reactions

In Study IMCgp100-202, acute skin reactions occurred in 91 % of patients treated with KIMMTRAK. including any grade rash (83 %), pruritis (69 %), erythema (25 %) and cutaneous oedema (27 %). Most skin reactions were Grade 1 (28 %) or 2 (44 %) and some KIMMTRAK treated patients experienced Grade 3 (21 %) events. Among patients with observed rash, patients commonly experienced rash (55 %), rash maculo-papular (31 %) and skin exfoliation (21 %). Grade 3 adverse reactions of rash were reported in 5 % of patients and included rash (2.4 %) and rash maculopapular (1.6 %).

Acute skin reactions typically occurred following each of the first three KIMMTRAK infusions, with decreasing frequency of ≥ Grade 3 reactions (dose 1; 17 %, dose 2; 10 %, dose 3; 8 %, dose 4; 3 %). The median time to onset of acute skin reactions was 1 day in the KIMMTRAK treated patients and median time to improvement to ≤ Grade 1 was 6 days.

For clinical management of acute skin reactions, see section 4.2, Table 2.

Elevated liver enzymes

In Study IMCgp100-202 where 95 % of patients had preexisting liver metastasis, ALT/AST increase to ≥ Grade 1 were observed in 65 % of patients treated with KIMMTRAK. Elevations in bilirubin have been reported in 27 % of patients and these were primarily associated with increase in size of liver metastasis. The majority Grade 3 or 4 ALT/AST elevations generally occurred within the first 3 KIMMTRAK infusions. Most patients experiencing Grade 3 or 4 ALT/AST elevations had improvement to ≤ Grade 1 within 7 days.

Immunogenicity

Treatment-emergent anti-drug antibodies (ADA) against tebentafusp were detected in 33 % and 29 % of patients receiving tebentafusp across all doses in study IMCgp100-102 and study IMCgp100-202, respectively. The median onset time to ADA formation was 6 to 9 weeks after start of tebentafusp treatment.

There was no evidence of ADA impact on safety or efficacy of tebentafusp, although the small number of patients who developed high titer ADA precludes firm conclusions regarding their clinical impact.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

There is no information on overdose with tebentafusp. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, other antineoplastic agents, ATC code: L01XX75

Mechanism of action

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 tumour 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.

Pharmacodynamic effects

Transient and clinically nonsignificant reduction in lymphocyte counts in blood was observed after treatment with tebentafusp. Lymphocytes decreased the day after the first 3 doses and returned to baseline prior to subsequent doses.

After treatment with tebentafusp, transient increases in serum levels of proinflammatory cytokines and chemokines were observed in samples collected after the first three doses. Peak levels were observed between 8 to 24 hours after treatment with tebentafusp and levels returned to baseline prior to subsequent doses.

Clinical efficacy and safety

Study IMCgp100-202: Previously untreated metastatic uveal melanoma

Study IMCgp100-202 was a randomised, open label, multicentre study that enrolled HLA-A*02:01 positive metastatic uveal melanoma patients who were naïve to systemic therapy. Patient could not have received previous systemic treatment or localized (liver--directed) therapy for metastatic uveal melanoma except for a prior surgical resection of oligometastatic disease. Patient were excluded for presence of symptomatic or untreated brain metastasis, symptomatic congestive heart failure, QT interval corrected by Fridericia's formula (QTcF) > 470 msec or congenital long QT syndrome, acute myocardial infarction, or unstable angina pectoris less than 6 months prior to treatment initiation.

Patients were randomised (2:1) to receive tebentafusp weekly by intravenous infusion according to the recommended intra-patient dosing regimen section 4.2 or investigator's choice treatment (pembrolizumab, ipilimumab, or dacarbazine) at the approved doses of these agents until disease progression or unacceptable toxicity.

Patients could receive tebentafusp, pembrolizumab, or ipilimumab treatment beyond disease progression if the patients were clinically stable, deriving clinical benefit and showed no signs of unacceptable toxicity as determined by the investigator. Treatment breaks for up to 2 consecutive weeks were allowed. Randomisation was stratified by lactate dehydrogenase (LDH) status, a known prognostic factor for unresectable or metastatic UM.

The primary efficacy outcome was overall survival (OS) in all patients randomised in the study. Tumour assessments were conducted every 12 weeks. Additional efficacy outcomes were investigator assessed progression free survival (PFS) A total of 378 patients were randomised; 252 to tebentafusp-treated group and 126 to the investigator's choice treated group (pembrolizumab: 82 %; ipilimumab: 12 %; or dacarbazine: 6 %). The median age was 64 years (range 23 to 92 years); with

49.5 % of patients ≥ 65 years, 87 % were white, 50 % were female. Baseline ECOG performance status was 0 (72 %) or 1 (20.4 %) or 2 (0.3 %), 36 % had elevated LDH level, and 95 % had liver metastasis.

In this study IMCgp100-202, 43 % of patients received treatment beyond progression with tebentafusp with no new safety signals identified. Median duration of tebentafusp treatment beyond progression was 8 weeks. Of the total tebentafusp infusions during the study, 21.5 % was administered after progression.

After completion of the primary efficacy analysis, patients from the investigator's choice arm were permitted to crossover to the tebentafusp treatment. With a median duration of follow up of 22.4 months, the updated OS continued to favour the tebentafusp arm (HR= 0.58; 95% CI: 0.44, 0.77). At the time of analysis, 16 patients had crossed over to tebentafusp treatment.

The efficacy results are summarized in Table 4 and Figure 1. Figure 1 represents an analysis with 3 years of follow-up. At the time of this analysis 16 patients from the control group have crossed-over to the tebentafusp treatment.

Table 4: Efficacy results in study IMCgp100-202

Primary and secondary endpoints	**KIMMTRAK (N = 252)**	**Investigator`s choice therapy (N = 126)**
Overall survival (OS) [1]		
Number of deaths	87 (34.5 %)	63 (50 %)
Median months (95 % CI)	21.7 (18.6, 28.6)	16.0 (9.7, 18.4)
HR (95 % CI)[2, 4]	0.51 (0.37, 0.71)	
Stratified log-rank p-value[2]	p = <0.0001	
Progression free survival (PFS)[3, 4]		
Number (%) of patients with event	198 (78.6 %)	97 (77 %)
Median in months (95 % CI)	3.3 (3.0, 5.0)	2.9 (2.8, 3.0)
HR (95 % CI)[4]	0.73 (0.58, 0.94)	
Stratified log-rank p-value[2]	p = 0.0139	
Objective response rate (ORR)[6]		
n (%)	26 (10.3)	6 (4.8)
95% CI	6.9, 14.8	1.8, 10.1
Complete Response (CR)	1 (0.4)	0
Partial Response (PR)	25 (9.9)	6 (4.8)
Stable Disease (SD)[5]	52 (20.6)	16 (12.7)
Median duration of response		
Months (95% CI)	9.9 (5.6, 22.1)	9.7 (2.7, --)

CI = Confidence interval, HR = Hazard ratio

[1] At a prespecified interim analysis, 150 OS events were observed, and a p-value boundary for declaring efficacy (0.006) was determined by a Lan-Demets alpha spending function with O'Brien Fleming type boundary.

[2] Two-sided p-value based on log rank test stratified by LDH.

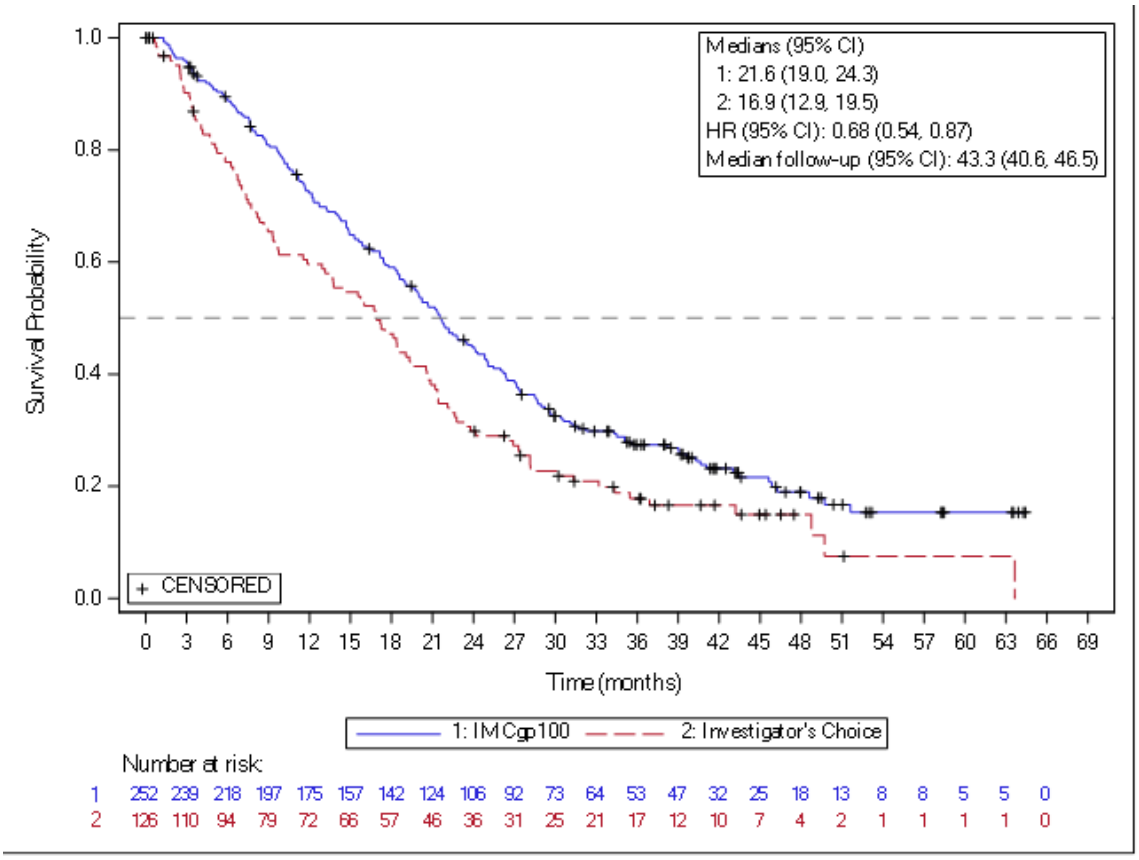
[3] As assessed by investigator using RECIST v1.1 criteria.

[4] Hazard ratio is from a proportional hazards model stratified by LDH status

[5] Based on ≥24 weeks.

[6] Updated based on all patients having opportunity for at least 3 radiological assessments

Figure 1: Kaplan-Meier curves of overall survival in the study IMCgp100-202 (3-Year Follow-up Analysis) – ITT Population



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

After 3 years of follow-up, tebentafusp continues to provide a substantial survival benefit compared with investigator's choice.

Study IMCgp100-102: Previously treated metastatic uveal melanoma

Study IMCgp100-102 was an open-label, Phase 2 multicentre study conducted in 127 patients, who were treated with the dosing scheme recommended in section 4.2. Patients were required to be HLA-A*02:01 positive. Patients were eligible if they had experienced disease progression following at least 1 or more prior lines of liver directed therapy or systemic therapy including immune check point inhibitors in the metastatic setting. Patients were excluded for clinically significant cardiac disease and presence of symptomatic or untreated brain metastasis.

Major efficacy outcome measures included confirmed ORR as assessed by Independent Central Review (ICR) using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1. Secondary efficacy outcomes included PFS, DCR, DOR and OS.

The median age was 61 years, 50 % were female, 99 % were white, the ECOG performance score was 0 (70 %) or 1 (30 %) and 96 % of patients had liver metastasis. Prior treatments included immunotherapy (73 % of patients) including immune checkpoint inhibitors (PD-1/PD-L1; 65 %; CTLA-4; 31 %) and liver directed therapy 45%. Efficacy results from study IMCgp100-102 are summarised in Table 5.

Table 5: Efficacy results in study IMCgp100-102

Primary and secondary endpoints	**KIMMTRAK (N = 127)**
Confirmed objective response rate[1]	6 (4.7 %)

(95% CI)	(1.8 %, 10 %)
Complete response (CR)	0
Partial Response (PR)	6 (4.7 %)
Stable Disease (SD) [2]	23 (18.1 %)
Median duration of response	
Months (95% CI)	8.7 (5.6, 24.5)

[1] As assessed by independent central review using RECIST v1.1 criteria.
[2] Based on ≥24 weeks

5.2 Pharmacokinetic properties

Absorption

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.

Distribution

Tebentafusp did not distribute extensively and displayed a volume of distribution comparable to blood volume (5.25 L).

Biotransformation

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.

Elimination

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.

Special populations

Population pharmacokinetic analysis indicated that there was no significant effect of weight (43 to 163 kg), gender, race, and age (23 to 91 years) on tebentafusp clearance.

Renal impairment

No formal pharmacokinetic studies of tebentafusp have been conducted in patients with renal impairment.

No impact on safety or efficacy parameters was identified in patients with mild (creatinine clearance [CrCL] ranging 60 to 89 mL/min) to moderate (CrCL ranging 30 to 59 mL/min) renal impairment and no dose adjustments are recommended. There are limited data from patients (< 5%) with moderate renal impairment and there is no information available from patients with severe renal impairment (CrCL < 30 mL/min).

Hepatic impairment

No formal pharmacokinetic studies of tebentafusp have been conducted in patients with hepatic 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.

5.3 Preclinical safety data

Tebentafusp is a human--specific protein and there are no relevant animal species in which nonclinical toxicology of tebentafusp could be tested.

No carcinogenicity, genotoxicity, or developmental and reproductive toxicity studies have been conducted with tebentafusp.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose
D (-) -Mannitol
Di-sodium hydrogen phosphate
Citric acid monohydrate
Polysorbate 20
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

The expiry date of the product is indicated on the packaging materials.

After opening

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 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.

6.4 Special precautions for storage

Store and transport refrigerated (2 °C – 8 °C).
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I glass vial with a bromobutyl rubber stopper and an aluminium/plastic flip-off seal, containing 0.5 mL concentrate.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

General precautions

The solution for infusion should be prepared by a healthcare professional using proper aseptic technique throughout the handling of this medicinal product.

Use aseptic technique for dilution and preparation of dosing solutions.

Closed system transfer devices (CSTDs) must not be used for dose preparation of KIMMTRAK solution for infusion.

Parenteral medicinal products and infusion bags should be inspected visually for particulate matter and discolouration prior to administration, whenever solution and container permit.

Preparation

KIMMTRAK must be diluted prior to intravenous administration.
Ensure the following supplies are available prior to preparing KIMMTRAK for administration:

- 1 mL sterile syringes with graduations of 2 decimal places.
- Sterile needles.
- Human albumin; use concentration as per local availability. Local concentrations include but not restricted to 4 % (40 g/L), 5 % (50 g/L), 20 % (200 g/L), 25 % (250 g/L).
- A 100 mL infusion bag containing sodium chloride 9 mg/mL (0.9 %) solution for injection:
  - The infusion bag should be constructed of polyolefins (PO) [such as polyethylene (PE) and polypropylene (PP)] or polyvinyl chloride (PVC).
- A sterile, nonpyrogenic, low protein binding 0.2 micron in-line filter infusion set for administration of the final infusion bag.

Dilution and Administration

A 2-step process is required for preparation of the final KIMMTRAK dose:

Step 1: Prepare the infusion bag

Using aseptic technique, prepare the infusion bag as follows:

a. Using a 1 mL syringe and a sterile needle, withdraw the calculated volume of human albumin into the syringe (see Table 6 below) and add to the 100 mL infusion bag containing sodium chloride 9 mg/mL (0.9 %) solution for injection to make a final human albumin concentration between 225 mcg/mL and 275 mcg/mL.

Table 6: Examples of human albumin concentration and acceptable withdrawal volumes

Human albumin concentration	Acceptable volume range for addition to 100 mL infusion bag for human albumin concentration between 225 mcg/mL to 275 mcg/ mL
4 % (40 g/L)	0.63 mL (0.57 mL to 0.69 mL)
5 % (50 g/L)	0.50 mL (0.45 mL to 0.55 mL)
20 % (200 g/L)	0.13 mL (0.12 mL to 0.14 mL)
25 % (250 g/L)	0.10 mL (0.09 mL to 0.11 mL)

b. Gently homogenize the diluted solution by completing the following steps:
   i. Invert the infusion bag so that the entry port is positioned at the top of the bag and tap the

side of port tubing to ensure that any residual solution is released into the bulk solution.

ii. Mix by gently rotating the bag lengthwise 360 degrees from the inverted position at least 5 times. Do NOT shake the infusion bag.

iii. Repeat (i) and (ii) an additional three times.

Step 2: Preparation of KIMMTRAK solution for infusion

c. Using a 1 mL syringe and a sterile needle, withdraw the required volume of KIMMTRAK 100 micrograms/ 0.5 mL as per the dose required (shown in Table 7 below) and add to the prepared 100 mL infusion bag containing sodium chloride 9 mg/mL (0.9 %) solution for injection, plus human albumin.

d. Do NOT flush the needle and syringe on transfer. Discard the vial containing the unused portion of KIMMTRAK in accordance with local requirements. Do not prepare more than one dose from the vial.

Table 7: KIMMTRAK volumes required for addition to infusion bag

Day of treatment	Dose (mcg) of KIMMTRAK	Volume (mL) of KIMMTRAK
Day 1	20	0.10
Day 8	30	0.15
Day 15 and weekly thereafter	68	0.34

e. Mix the infusion bag by following the same procedure outlined in Step 1b.

Administration

- Administer KIMMTRAK as intravenous infusion only.
- Immediately administer the infusion over 15 to 20 minutes through a dedicated intravenous line. A sterile, nonpyrogenic, low protein binding 0.2 micron in line filter infusion set should be used. Administer the entire contents of the KIMMTRAK infusion bag to the patient.
- Upon completion of KIMMTRAK infusion, flush the infusion line with adequate volume of sterile sodium chloride 9 mg/mL (0.9 %) solution for injection, to ensure that the entire contents of the infusion bag are administered. Do not administer KIMMTRAK as an intravenous push or bolus. Do not mix KIMMTRAK with other drugs or administer other drugs through the same intravenous line.

Storage of prepared infusion bag

- KIMMTRAK does not contain a preservative. The prepared infusion bag should be administered within 4 hours from the time of preparation including the duration of infusion. During the 4 hour window, the KIMMTRAK infusion bag should remain below 30 °C.
- If not used immediately, store the KIMMTRAK infusion bag in a refrigerator at 2 °C to 8 °C for up to 24 hours from the time of preparation which includes the time allowed for equilibration of the infusion bag to room temperature and the duration of the infusion.
- Once removed from the refrigerator, KIMMTRAK infusion bag must not be refrigerated again. Discard unused KIMMTRAK solution beyond the recommended storage time.

7. MANUFACTURER

Immunocore Ireland Limited
Unit 1, Sky Business Centre
Dublin 17, D17 FY82
Ireland

8. LICENSE HOLDER

Medison Pharma Ltd.

10 Hashiloach Street, P.O.B. 7090
Petach Tikva
Israel

9. REGISTRATION NUMBER:

173-92-37400

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