# Physician Survey to Assess the Effectiveness of the Additional Risk Minimisation Measures (aRMM) for KIMMTRAK® (tebentafusp)

# PASS Information

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| Title: | Physician Survey to Assess the Effectiveness of the Additional Risk Minimisation Measures (aRMM) for KIMMTRAK® (tebentafusp) |
| Study Identifier | IMCR-0001 |
| Version identifier: | Version 3.0 |
| Date of last version: | V2.0_31Oct2023 |
| European Union (EU) Post Authorisation Study (PAS) Register No: | Not yet assigned |
| Active substance: | Tebentafusp<br>Anatomical Therapeutic Chemical (ATC) Code: L01XX75 |
| Medicinal product(s): | KIMMTRAK |
| Product reference: | EMEA/H/C/004929 |
| Procedure number: | EMEA/H/C/004929/0000 |
| Marketing authorisation holder(s) (MAH): | Immunocore Ireland Ltd. |
| Joint Post Authorisation Safety Study: | No |
| Research question and objectives: | This study will assess:<br>a) Physicians' understanding of the important safety information detailed in the Treatment Guide for Healthcare Professionals to minimise the severity of cytokine release syndrome (CRS) with tebentafusp.<br>b) Healthcare Professionals' distribution of the Patient Guide to patients treated with tebentafusp |
| Countries of study: | At least 6 EU countries: Germany, France Austria, Belgium, Italy and Poland |
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# Marketing Authorisation Holder

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|---|---|
| Marketing Authorisation Holder(s) | Immunocore Ireland Limited<br>Unit 1, Sky Business Centre<br>Dublin 17,<br>D17 FY82<br>Ireland |
| MAH contact person | Daniel Sum PhD<br>Daniel.sum@immunocore.com<br>Immunocore Ireland Limited<br>Unit 1, Sky Business Centre<br>Dublin 17,<br>D17 FY82<br>Ireland |

## Approval

Name: Peter Psarologos MD

Title: EU Qualified Person for Pharmacovigilance

Signature:

*Electronically signed by:*
*Peter Psarologos*
*Reason: Approver*
*Date: Nov 14, 2023 18:11 GMT+1*

Date:

# 1. Table of Contents



## List of Tables

## List of Annexes

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# 2. List of Abbreviations

| Abbreviation | Definition |
|---|---|
| ATC | Anatomical Therapeutic Chemical (code) |
| aRMM | Additional Risk Minimisation Measure |
| CD | Cluster of Differentiation |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| CIOMS | Council for International Organisations of Medical Sciences |
| CRO | Contract Research Organisation |
| CRS | Cytokine Release Syndrome |
| ECG | Electrocardiogram |
| EDC | Electronic Data Capture |
| EMA | European Medicines Agency |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| EU | European Union |
| FDA | Food and Drug Administration |
| GEP | Good Epidemiological Practice |
| GPP | Good Pharmacoepidemiology Practices |
| GVP | Good Pharmacovigilance Practice |
| HCP | Healthcare Professional |
| HLA | Human Leukocyte Antigen |
| ICH | International Council for Harmonisation |
| IEA | International Epidemiological Association |
| ISPE | International Society for Pharmacoepidemiology |
| ISPOR | International Society for Pharmacoeconomics and Outcomes Research |
| KRM | Key Risk Message |
| MAH | Marketing Authorisation Holder |
| NCA | National Competent Authority |

| | |
|---|---|
| PAS | Post Authorization Study |
| PASS | Post Authorisation Safety Study |
| SAR | Suspected Adverse Reaction |
| TCR | T Cell Receptor |
| TLF | Tables, Listings and Figures |
| UM | Uveal Melanoma |

# 3. Responsible Parties

**Sponsor**

Immunocore Ireland Limited
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**Contract Research Organisation**

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# 4. Abstract

**Title:** Physician Survey to Assess the Effectiveness of the additional Risk Minimisation Measures (aRMM) for KIMMTRAK (tebentafusp).

**Rationale and Background:** The aRMM for KIMMTRAK include a Treatment Guide for Healthcare Professionals and a Patient Guide. These materials are distributed to all physicians who are expected to prescribe KIMMTRAK. The purpose of the Treatment Guide for Healthcare Professionals is to highlight the key measures for minimising the severity of cytokine release syndrome (CRS) associated with KIMMTRAK use. Healthcare professionals are required to provide the Patient Guide to patients when KIMMTRAK is prescribed in order that patients are informed as to what to expect following their KIMMTRAK infusion. The proposed assessment will evaluate the physicians' understanding of the important safety information in the Treatment Guide for Healthcare Professionals and whether healthcare professionals are providing patients with the Patient Guide.

**Research Questions and Objectives:** 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 KIMMTRAK.

b) Healthcare professionals' distribution of the Patient Guide to patients treated with KIMMTRAK.

**Study Design:** This study uses a multi-national, observational cross-sectional design. A survey will be administered to physicians who prescribe KIMMTRAK to treat human leukocyte antigen (HLA)-A*02:01-positive adult patients who have unresectable or metastatic uveal melanoma.

**Population:** The survey will be administered to physicians who prescribe KIMMTRAK to treat HLA-A*02:01-positive adult patients who have unresectable or metastatic uveal melanoma in at least six European Union ( EU) countries: Germany, France Austria, Belgium, Italy and Poland. Screening questions will be used to determine respondent eligibility for the survey. Individuals who currently work directly for, or whose immediate family members currently work directly for Immunocore or any of its affiliates, the European Medicines Agency (EMA) or any National Competent Authority (NCA) will not be considered for participation.

**Study Endpoints**: The additional Risk Minimisation Measure will be considered effective if at least 80% of respondents understand the key messages detailed in the Treatment Guide for Healthcare Professionals and 80% provide the Patient Guide to patients treated with KIMMTRAK.

**Variables:** The survey will collect responses to each question addressing each key risk message, in addition to demographic information (e.g., age, country of practice), and clinical experience (e.g., number of years working in medical oncology or dermato-oncology and the number of patients for whom they have prescribed KIMMTRAK).

**Data Sources**: Structured, self-administered surveys comprising closed-ended questions or statements with multiple-choice responses will be used to collect the data from prescribers of KIMMTRAK.

**Study Size**: The study will target completion of at least 40 surveys. With n=40 and a true proportion of 50%, this will provide a precision of +/- 16.2%.

**Data Analysis:** Data collected from the survey will be reported using descriptive statistics. Responses to each question relating to the understanding of risks will be categorised as “Correct” or “Incorrect”. Frequency distributions with 95% confidence intervals (CIs) will be calculated for responses to questions that address the survey objective (excluding demographic questions).

**Milestones:** Data collection will start 18 months after market launch in the relevant countries. Estimated start date in the first country is November 2023. Estimated start in last country is June 2025. The end of data collection is estimated in December 2025.
The final study report will be submitted six months after the end of data collection and estimated to be June 2026.

# 5. Amendments and Updates

| Date | Version | Reason for change |
|---|---|---|
| 31 Oct 2022 | 1.0 | Original |
| 20 Dec 2022 | 1.1 | Replacement of Appendix 1.3 as previous content did not display correctly |
| 17 Jan 2023 | 1.2 | Addition of 6th country: Poland<br>Updated timelines to reflect market launch in the 6 countries<br>Statement that survey will be extended if 40 completed surveys are not obtained<br>Option of "I do not know" for each of the Key Risk Message questions |
| 11 Sep 2023 | 1.3 | QC check, formatting changes |
| 31 Oct 2023 | 2.0 | Minor updates to the survey questions following recommendations from Survey User Testing. |
| 09 Nov 2023 | 3.0 | Minor update of question 6 following a recommendation from the User Acceptance Testing. |

# 6. Milestones

| Milestone | Planned Timeline |
|---|---|
| Start of data collection | 18 months after market launch in the relevant countries.<br>Estimated start in first country November 2023.<br>Estimated start in last country June 2025 |
| End of data collection | When at least 40 surveys have been completed, estimated December 2025 |
| Registration in the EU PAS Register | Prior to start of data collection |
| Final study report | 6 months after the end of data collection, estimated June 2026 |

# 7. Rationale and Background

Uveal melanoma (UM) is a rare and highly malignant subset of melanoma. The incidence varies by geography, race, and age, ranging from 5.3 to 10.9 cases per million (Singh, 2011). Despite its rare incidence, UM is the most frequent primary intraocular malignancy of the adult eye (85%) (Patel, 2011; Maio, 2013).

In Europe UM has had a stable incidence of approximately six per million since the 1970s, but there is a gradient from northern European countries to southern European countries, ranging from eight to nine per million in Scandinavia, four to six per million in Central Europe, to two per million in Spain and Italy (Piperno-Neumann, 2019; Jespersen, 2019; Virgili, 2007).

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 UV 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 UV 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 UV tumour cells.

KIMMTRAK (tebentafusp) received Marketing Authorisation from the European Commission on 1 April 2022 as monotherapy for the treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic UV.

Cytokine release syndrome (CRS) is an important identified risk of KIMMTRAK as it may be life-threatening if not appropriately managed. It is an expected adverse reaction of KIMMTRAK based on its mechanism of action of T cell activation leading to cytokine production.

In order to minimise the risk of CRS, additional risk minimisation measures (aRMM), consisting of a Treatment Guide for Healthcare Professionals and a Patient Guide, have been developed. These materials are distributed to all physicians who are expected to prescribe KIMMTRAK. The purpose of the Treatment Guide for Healthcare Professionals is to highlight the key measures for minimising the severity of CRS associated with KIMMTRAK use and for managing CRS should it occur. Healthcare professionals are required to provide the Patient Guide to patients when KIMMTRAK is prescribed in order that patients are informed as to what to expect following their KIMMTRAK infusion.

This survey will evaluate the physicians' understanding of the important safety information in the Treatment Guide for Healthcare Professionals and whether healthcare professionals are providing patients with the Patient Guide.

# 8. Research Question and Objectives

This 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 KIMMTRAK.

b) Healthcare professionals' distribution of the Patient Guide to patients treated with KIMMTRAK.

# 9. Research Methods

## 9.1. Study Design

This study uses a multi-national, observational cross-sectional design.

## 9.2. Setting

The assessment survey will be initiated 18 months after market launch of KIMMTRAK in Germany, France, Austria, Belgium, Italy and Poland.

The Treatment Guide for Healthcare Professionals and the Patient Guide will be sent to health care professionals (HCP)s who are expected to prescribe KIMMTRAK in each country in accordance with local distribution/communication plans as agreed by National Competent Authorities (NCAs). As unresectable or metastatic uveal melanoma is a rare disease, there are a very limited number of physicians per country who will prescribe KIMMTRAK

. These physicians will be medical oncologists or dermato-oncologists. The same survey will be used for all participating countries to ensure consistency in testing the target population. As such, variability of survey results based on geography is not anticipated. Start time for survey implementation will be staggered across countries, reflecting the staggered launch of KIMMTRAK in these countries due to reimbursement negotiations. It is anticipated that the survey will commence first in Germany and last in Belgium.

In the event that 40 completed surveys are not obtained after the survey has been implemented in these 6 countries, the Marketing Authorisation Holder (MAH) will extend the survey either to additional physicians in the existing countries if applicable and/or to additional countries, subject to market launch in order to reach 40 completed surveys.

The survey will be administered via the internet, which will allow respondents to participate at a time and location that is convenient for them. The survey includes questions that will assess physicians' understanding of the important safety information detailed in the Treatment Guide for Healthcare Professionals and assess HCP's distribution of the Patient Guide to patients treated with KIMMTRAK.

### *9.2.1. Survey Target Population*

Eligible medical oncologists and dermato-oncologists who respond to the survey invitation will make up the study population. Surveys will be sent to approximately 250 medical oncologists/dermato-oncologists in order to obtain at least 40 completed responses (see section 9.5 study size).

#### 9.2.1.1. Inclusion criteria

Medical oncologists and dermato-oncologists must meet the following criterion for inclusion in the survey:

- Must identify themselves having prescribed KIMMTRAK to treat HLA-A*02:01-positive adult patients who have unresectable or metastatic uveal melanoma.

#### 9.2.1.2. Exclusion criteria

Medical oncologists and dermato-oncologists meeting the following criterion will not be permitted to take the survey:

- Individuals who currently work directly for, or whose immediate family members

currently work directly for Immunocore or any of its affiliates, the EMA or any NCA.

## 9.3. Variables

The survey will collect responses to each question required to address the study objectives:

- Response to questions about important safety information detailed in the Treatment Guide for Healthcare Professionals
- Whether or not the Patient Guide is being distributed to patients treated with KIMMTRAK.

In addition, information on the following will be collected:

- Demographic information: age (years), geographic location (country), and
- Clinical experience: number of years working in medical oncology or dermato-oncology (years), number of patients for whom they have prescribed KIMMTRAK (count).
- Awareness of the Guide for HCPs and Patient Guide
- Source of safety information

## 9.4. Data Sources

In order to target the desired population, the data source will be a list of medical oncologists and dermato-oncologists (HCPs) who have been provided with the aRMM materials by Immunocore in Germany, France, Austria, Belgium, Italy and Poland.

The HCPs will receive an invitation letter to participate in the survey. The invitation letter (Appendix I.2) will include: an overview of the rationale for the survey, information on how to access the survey online and a unique invitation code to ensure that the invitation is used only once. Based on survey uptake within each respective country, reminder notices will be sent to those who have been invited but have not yet participated. Participating HCP's identifying information will be collected for the purposes of providing financial compensation, as allowed by local laws and country regulations.

A structured, self-administered questionnaire will be used to collect survey data (Appendix I.1). It is comprised of closed-ended questions or statements with multiple response choices.

Prior to finalisation of the questionnaire, User Testing will be performed with a sample HCPs. The User Testing procedure is designed to assess comprehension among HCPs regarding the words and phrases used in survey questions and response options. User Testing will also assess the clarity of the survey questions as presented to the HCPs and the flow and ease of completing the surveys. Findings and recommendations from the User Testing will be incorporated into the surveys.

The survey will be voluntary. The collection of any personal, identifying information (e.g., first name, last name, address) from respondents will only be used for processing of HCPs' financial compensation, as allowed by local laws and country regulations, and will be stored in a separate database.

Each individual will be randomly assigned a unique code to access the survey. Each unique code will be deactivated upon first use to prevent the code from being used to complete the survey multiple times. Individuals will not have to actively "decline to complete the survey".

Therefore, there will be no ability to track those who decline to participate. Participants who agree to respond to the survey will begin with a screening module with questions to confirm eligibility.

The internet survey will be self-administered and will include the following:

*Screening questions:*

- *Agreement to participate*
- *HCP having prescribed KIMMTRAK to treat HLA- A*02:01-positive adult patients who have unresectable or metastatic uveal melanoma*
- *Currently work directly for, or whose immediate family members currently work directly for Immunocore or any of its affiliates, the EMA or any NCA*

*Data on demographic characteristics:*

- *Age*
- *Geographical location*
- *Years working in medical oncology or dermato-oncology*
- *Number of patients prescribed KIMMTRAK*

*Data pertaining to evaluation of the HCPs' understanding of the important safety information in the Treatment Guide for Healthcare Professionals, and to evaluate whether or not the Patient Guide is being distributed to patients treated with KIMMTRAK.*

*Data pertaining to how HCPs obtained the safety information for KIMMTRAK.*

## 9.5. Study Size

The target sample size is at least 40 completed surveys. Approximately 250 invitations will be sent in order to obtain at least 40 completed surveys. The study size has been determined to take into account the rareness of the disease and the resulting small number of physicians who will prescribe KIMMTRAK and is not based upon statistical considerations. Depending upon the country population and healthcare organisation, it is estimated that there will typically be between 10 to 20 centres per country that will treat the majority of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. Thus, the potential pool of treating physicians eligible to participate in the survey is small. Whilst it is generally accepted that uptake to invitations for survey participation is generally low, it is anticipated that the response rate to the KIMMTRAK survey will be in the order of 15% to 20% for the following reasons: The MAH has well established relationships with the potential participants as a result of a prior expanded access program and field medical liaisons are in regular face-to-face contact with potential participants and these contacts will be used to encourage participation. However, as stated in section 9.2 above, survey invitations will be extended to additional physicians and/or countries if the target of 40 completed surveys is not reached.

Table 1 shows 2-sided 95% Confidence Intervals (CIs) based on the method of Clopper-Pearson for a sample size of 40.

**Table 1 Estimated Precision, by Sample Size and Proportion**

| Sample size | Proportion of Correct Responses Observed (%) | Precision or Margin of Error* (±%) |
|---|---|---|
| 40 | 20 | -10.9%; +15.6% |
| | 40 | -15.1%; +16.7% |
| | 60 | -16.7%; +15.1% |
| | 80 | -15.6%; +10.9% |
| | 90 | -13.7%; +7.2% |
| | 100 | -8.8%; + 0% |

*95% confidence interval, two-sided (Clopper-Pearson method).

## 9.6. Data Management

All data collected during the survey will be confidential. The electronic data capture (EDC) system used for data collection does not include any respondent-identifying information. Respondent identifiers are stored in a separate encrypted electronic database from the survey responses and are used solely for the purposes of payment to respondents where allowed by local regulations. No respondent contact information will be included in the tables or in the final report.

The survey is programmed to ensure that respondents cannot go back or skip ahead. Where possible, statements requiring response and response options are presented in a list and are randomised to minimise positional bias. There will be no follow-up questions to respondents for this project.

Throughout the course of the study, a full back-up of the data will be performed on a nightly basis and cumulative back-ups will also be performed on a weekly basis. Back-up files will be stored at a secure off-site location.

Testing and production data extracted from the EDC database-derived analysis datasets, and generated tables, listings, and figures (TLFs), will be validated, documented, and retained after the data is exported from the EDC system.

## 9.7. Data Analysis

Data collected from the survey will be reported as descriptive statistics. Frequency distributions with 95% CIs will be calculated for responses to questions that address the survey objectives (i.e., excluding demographic questions).

Survey data will be analysed overall and stratified by country. Responses will be categorised as “Correct response” and “Incorrect response”.

The aRMM will be considered successful if at least 80% of physicians understand each of the 7 key risk messages (KRM) (Table 2). Table 2 outlines the 7 KRM, the individual questions within each message, and the criteria for success of each message.

## Table 2 Key Risk Messages and Criteria for Success

| Key Risk Message (KRM) | Desired Response | Demonstrated Understanding of Message* |
|---|---|---|
| **KRM 1: Description of CRS** | | Correctly responding to all 3 elements of KRM1. |
| Question 8: Which of the following statements is correct? *Please select one option*<br>a) CRS has <u>not</u> been observed in clinical trials with KIMMTRAK<br>b) KIMMTRAK commonly causes mild to moderate Cytokine Release Syndrome (CRS)<br>c) CRS following KIMMTRAK only occurs in patients who have other risk factors<br>d) I do not know | b | |
| Question 9. Which of the following statements is correct? *Please select one option*<br>a) Patients are more likely to experience CRS within the first three KIMMTRAK infusions<br>b) CRS is typically not seen until after six KIMMTRAK infusions<br>c) The severity of CRS increases with each infusion<br>d) I do not know | a | |
| Question 10. Which of the following statements is correct? *Please select one option*<br>a) The majority of episodes of CRS are delayed reactions starting seven days after infusion of KIMMTRAK<br>b) The majority of episodes of CRS start on the day of infusion of KIMMTRAK<br>c) The majority of CRS occurs three days after infusion of KIMMTRAK<br>d) I do not know | b | |

| Key Risk Message (KRM) | Desired Response | Demonstrated Understanding of Message* |
|---|---|---|
| **KRM 2: Monitoring** | | Correctly responding to all 2 elements of KRM2. |
| Question 11. Which of the following statements is correct regarding KIMMTRAK administration and monitoring? *Please select one option*<br>a) For at least the first three infusions, patients should be monitored for 16 hours in a hospital<br>b) The first three infusions can be administered in an outpatient setting<br>c) There is no requirement to monitor patients for CRS following administration<br>d) I do not know | a | |
| Question 12. Which of the following statements is correct? *Please select one option*<br>a) For the first three infusions, vital signs should be checked only once at 16 hours after the infusion<br>b) For the first three infusions, vital signs should be checked before dosing and at a minimum interval of every four hours for at least 16 hours<br>c) If vital signs are normal following the first infusion, there is no requirement to monitor for subsequent infusions<br>d) I do not know | b | |
| **KRM 3: Management of CRS** | | Correctly responding to all 2 elements of KRM3. |
| Question 13. Which of the following statements is correct? *Please select one option*<br>a) Intravenous steroids are never required for CRS associated with KIMMTRAK administration<br>b) All patients should receive intravenous steroids prophylactically prior to each infusion of KIMMTRAK<br>c) For Grade 3 CRS, or for persistent or recurrent Grade 2 CRS associated with KIMMTRAK, | c | |

| Key Risk Message (KRM) | Desired Response | Demonstrated Understanding of Message* |
|---|---|---|
| steroids should be administered at least 30 minutes before the next dose<br>d) I do not know | | |
| Question 14. Which of the following statements is correct? *Please select one option*<br>a) KIMMTRAK may be restarted once the patient recovers from Grade 4 CRS<br>b) KIMMTRAK should be permanently discontinued if a patient experiences CRS of any grade.<br>c) KIMMTRAK should be permanently discontinued if a patient experiences Grade 4 CRS<br>d) I do not know | c | |
| **KRM 4: Minimise the risk of hypotension** | | Correctly responding to the single element of KRM4. |
| Question 15. Which of the following statements is correct? *Please select one option*<br>a) For patients with pre-existing adrenal insufficiency on maintenance systemic steroids, there is no need to adjust corticosteroid dose<br>b) For patients with pre-existing adrenal insufficiency on maintenance systemic steroids, the corticosteroid dose should be adjusted in order to manage the risk of hypotension<br>c) For patients with pre-existing adrenal insufficiency on maintenance systemic steroids, patients should have corticosteroids held<br>d) I do not know | b | |

| Key Risk Message (KRM) | Desired Response | Demonstrated Understanding of Message* |
|---|---|---|
| **KRM 5: Electrocardiogram (ECG) monitoring** | | Correctly responding to a single element of KRM5. |
| Question 16. Which of the following statements is correct? *Please select one option*<br>a) During the first three infusions, an ECG should be performed in all patients before and after KIMMTRAK treatment<br>b) There is no requirement to undertake ECGs in patients being treated with KIMMTRAK<br>c) Patients should have an ECG only if cardiac symptoms are observed<br>d) I do not know | a | |
| **KRM 6 Cardiac Disease** | | Correctly responding to the single element of KRM6. |
| Question 17. Which of the following statements is correct? *Please select one option*<br>a) Patients with pre-existing cardiac disorders are <u>not</u> expected to be at any increased risk for sequelae associated with CRS<br>b) Patients with pre-existing cardiac disorders should not be treated with KIMMTRAK<br>c) Patients with cardiac disease, including QT prolongation and risk factors for cardiac failure, should be monitored carefully<br>d) I do not know | c | |
| **KRM 7 Patient Counselling** | | Correctly responding to the single element of KRM7 |
| Question 18. Patients treated with KIMMTRAK should be advised that if they develop symptoms of CRS they should do the following: *Please select one option*<br>a) Alert their doctor or nurse immediately<br>b) Make an appointment to see the doctor within the next seven days<br>c) Manage their symptoms with anti-pyretics and non-steroidal anti-inflammatory agents<br>d) None of the above<br>e) I do not know | a | |

Among prescribers, the proportion who report distributing, or instructing another healthcare professional to distribute the Patient Guide to patients prescribed KIMMTRAK for the first time will be assessed.

Among prescribers, the proportion who correctly identify the indication for KIMMTRAK will be assessed.

Among prescribers, the source of knowledge of the safety information will be summarised.

The following information will be reported as part of the analysis:

Physicians :

- *Survey administration will be performed by country and overall:*
  - *The number of survey invitations*
  - *The number of survey invitations/reminders returned due to incorrect mailing/emailing address of physicians invited to participate in the survey*
  - *The number of physicians who responded to the invitation to participate in the survey*
  - *The number of physicians who meet the inclusion criteria for participation in the survey*
  - *The number of physicians who do not meet the inclusion criteria along with the reasons for ineligibility*
  - *The number of physicians who meet the inclusion criteria who completed the survey*
- *Demographic characteristics of participants by country*
  - *Distribution of participants by age groups*
  - *Distribution of participants by number of patients treated with KIMMTRAK*
- *Responses to questions pertaining to the KRM (Question 8 to Question 18)*
  - *Demonstrated understanding of each KRM as defined in Table 2 presented with 95% CI.*
- *Response to question as to whether participant or colleague provides the Patient Guide to the patient?*

## 9.8. Quality Control

Data will be collected using a secure and validated online EDC system. The Information Technology applications are governed by a development approach to ensure compliance to Food and Drug Administration (FDA)'s guidance for Industry -Computerized Systems Used in the Guidance for Industry 21 Code of Federal Regulations (CFR) Part 11, Electronic Records; Electronic Signatures, and EudraLex Annex 11: Computerized Systems, and international regulations and standards (e.g., EU Good Pharmacovigilance Practices (GVP), International Conference for Harmonisation ( ICH)) and relevant EMA guidelines. The system is compliant for the entry, storage, handling, analysis and transmission of electronic information.
Respondent-identifying information will be stored separately from the survey responses.

## 9.9. Limitations of the Research Methods

Participants will be self-selected since they will voluntarily respond to the invitation to participate, so the potential exists that those who choose to respond to the survey may differ in their understanding of the important safety information from those who elect not to participate. This is a common limitation of all studies that rely on voluntary participation.

It is also possible that the respondents have acceptable understanding of the important safety information despite not reading the Treatment Guide for Healthcare Professionals. The survey can assess the HCPs' understanding of the important safety information but cannot clearly determine via which channel they gained the information.

All data from the survey are self-reported and therefore susceptible to possible reporting bias.

A further limitation is in the design and analysis of these types of surveys. When a threshold is applied for determining success (as is described in the current protocol where 80% of HCPs are required to demonstrate understanding of each key risk message), the more questions asked, the more opportunities for an HCP to answer incorrectly and therefore not meet criteria towards success.

### *9.9.1. Controls to minimise bias*

A number of controls will be in place to ensure that the survey is conducted to minimise bias, including the following:

- Lists of response options will be randomised to minimise the potential for positional bias.
- Respondents cannot skip ahead or go back to a question once the question has been answered. All questions presented must be answered in order to complete a survey.
- Respondents will be provided with a unique code during the recruitment process in order to gain access to the internet-based systems. The code will be inactivated after use to minimise exposure bias and fraud.

## 9.10. Other Aspects

Not applicable.

# 10. Protection of Human Subjects

## 10.1. Personal Information and Consent

All data collected during the survey will be kept confidential and used only for the purposes stated in the survey instructions. The collection of any personal, identifying information (first name, last name, address) from respondents will only be used for the processing of the HCPs' financial compensation. Respondent identifiers will be stored in a separate encrypted electronic database from the survey responses. The EDC system used for data collection of the survey responses does not collect any identifiable information. The sponsor will not have access to any personal information collected in relation to this survey.

By answering the first question of the survey ("*Do you agree to participate in this survey?*"), respondents are providing informed consent for participation in the research study.

## 10.2. Respondent withdrawal

Respondents can decline to participate or stop taking the survey at any time. Only complete surveys will be included in the analysis.

## 10.3. Ethics Committee

Approval of this protocol by the respective local Ethics Committee will be sought prior to initiating the survey in each country, where applicable.

## 10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor, and follow generally accepted research practices described in the *Guideline on Good Pharmacovigilance Practices* (GVP) Module XVI- RMM: Selection of Tools and Effectiveness Indicators, *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), *Good Epidemiological Practice* (GEP) guidelines issued by the International Epidemiological Association (IEA), *Good Outcomes Research Practices* issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), *International Ethical Guidelines for Epidemiological Research* issued by the Council for International Organisations of Medical Sciences (CIOMS), EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology*, and the United States FDA Guidance for Industry: *Good Pharmacovigilance and Pharmacoepidemiologic Assessment*.

# 11. Management and Reporting of Adverse Events/Adverse Reactions

Adverse events will not be actively collected as this study is assessing HCPs' understanding of the important safety information detailed in the Treatment Guide for Healthcare Professionals and the distribution of the Patient Guide to patients being treated with KIMMTRAK.

Study personnel and survey respondents are requested to report any suspected adverse reactions (SARs) with any drug to the appropriate party as required in normal practice.

# 12. Plans for Disseminating and Communicating Study Results

The final report will be submitted to regulatory agencies. The study, including the final report, will also be registered in the PAS Register. The study findings may be submitted to a scientific congress and/or to a peer-reviewed journal.

# 13. References

Council for International Organisations of Medical Sciences. *International Ethical Guidelines for Epidemiological Research*.

Clopper CJ, Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika* 1934;26(4):404–413.

European Medicines Agency European Network of Centres for Pharmacoepidemiology and Pharmacovigilance. *Guide on Methodological Standards in Pharmacoepidemiology.*

Guideline on Good Pharmacovigilance Practices Module XVI- RMM: Selection of Tools and Effectiveness Indicators.

International Epidemiological Association. *Good Epidemiological Practice*.

International Society for Pharmacoepidemiology. *Good Pharmacoepidemiology Practices.*

International Society for Pharmacoeconomics and Outcomes Research. *Good Outcomes Research Practices.*

Jespersen H, Bagge RO, Ullenhag G, et al. Concomitant use of pembrolizumab and entinostat in adult patients with metastatic uveal melanoma (PEMDAC study): protocol for a multicenter phase II open label study. *BMC Cancer*. 2019 May 2;19(1):415.

Maio M, Danielli R, Chiarion-Sileni V, et al. Efficacy and safety of ipilimumab in patients with pre-treated, uveal melanoma. *Ann Oncol*. 2013 Nov;24(11):2911-5.

Patel M, Smyth E, Chapman PB, et al. Therapeutic implications of the emerging molecular biology of uveal melanoma. *Clin Cancer Res*. 2011;17(8):2087-100.

Piperno-Neumann S, Piulats JM, Goebeler M, et al. Uveal Melanoma: A European Network to Face the Many Challenges of a Rare Cancer. Cancers (Basel). 2019 Jun 13;11(6):817.

Singh AD, Turell ME, Topham AK. Uveal melanoma: Trends in incidence, treatment, and survival. *Ophthalmology*. 2011 Sep;118(9):1881-5.

United States Food and Drug Administration. Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment.

Virgili G, Gatta G, Ciccolallo L, et al; EUROCARE Working Group. Incidence of uveal melanoma in Europe. *Ophthalmology*. 2007 Dec;114(12):2309-15.

# Annex 1. List of Standalone Documents

| Number | Document Reference Number | Date | Title |
|---|---|---|---|
| 1 | Appendix I.1 | | Proposed Physician Survey |
| 2 | Appendix I.2 | | Sample Draft Survey Invitation Letter for Physicians |
| 3 | Appendix I.3 | | Healthcare Professional Educational Material and the Patient Guide |

## APPENDIX I.1. PHYSICIAN SURVEY

### INTRODUCTION

Thank you for your interest in this voluntary research survey about KIMMTRAK® (tebentafusp) which is being conducted by [Contract Research Organisation (CRO)] on behalf of the sponsor, Immunocore Ireland Ltd, the marketing authorisation holder of KIMMTRAK. Taking part in this survey is voluntary; you are under no obligation to participate. You may refuse to take the survey or stop taking the survey at any time.

This survey should take approximately 20 minutes to complete. If you cannot complete the survey at this time, please come back when you can. Once you begin the survey, you will need to answer all questions during the same sitting; you will not be able to access the survey again if you exit the survey before answering all survey questions.

**How We Use Your Information**

This survey is part of a post marketing commitment between Immunocore Ireland Ltd and the EMA to assess the effectiveness of the material sent to you to minimise the risk of cytokine release syndrome associated with KIMMTRAK use. Your answers to the survey questions will be combined with those from other respondents and reported in anonymous form to Immunocore, the EMA, and any other locally applicable regulatory organisations. Your name will not be used in any report. If you are able to complete all inclusion questions as presented, complete all the important safety information questions, and provide your contact information; you will receive financial compensation based on your local rules and regulations. This financial compensation represents the fair market value for your time in connection with completion of the survey. The amount of the financial compensation was not determined by the volume or value of any referrals or business otherwise generated by you. Your name and address will only be used to send the financial compensation to you once you complete the survey. This survey is voluntary; you are under no obligation to participate.

**How We Protect Your Privacy**

We respect that the privacy of your personal information is important to you. All the information you provide will be kept strictly confidential. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Your privacy will be protected; however, research survey records may be inspected by the EMA or other regulatory agencies. Your choice to allow Immunocore to use your answers to the survey questions is entirely voluntary but necessary to participate.

**How to Learn More about the Online Survey**

If you have questions about or problems with the survey, please contact the Help Desk at: [country specific phone number to be added]

**SCREENING QUESTIONS**

1. Do you agree to take part in this survey about KIMMTRAK (tebentafusp)?
    a) Yes
    b) No (terminate)

2. Have you prescribed KIMMTRAK to treat human leukocyte antigen (HLA)-A*02:01-positive adult patients who have unresectable or metastatic uveal melanoma.
    a) Yes
    b) No (terminate)

3. Do you or any of your immediate family members work for Immunocore or its affiliates, the European Medicines Agency (EMA), or any National Competent Authority (NCA)?
    a) Yes (terminate)
    b) No

**DEMOGRAPHIC QUESTIONS**

4. Which of the following groups best describes your age?
    a) Less than 40
    b) 40 to 59
    c) 60 or older
    d) Prefer not to answer

5. Which of the following best describes your clinical specialty?
    a) Medical oncologist
    b) Dermato-oncologist
    c) Other *Please specify*
    d) Prefer not to answer

6. For how many years have you been practicing in the specialty you previously identified?
    a) Less than 5 years
    b) 5 to 10 years
    c) 11 to 15 years
    d) More than 15 years
    e) Prefer not to answer

7. For how many patients have you prescribed KIMMTRAK to treat human leukocyte antigen (HLA)-A*02:01-positive adult patients who have unresectable or metastatic uveal melanoma?
    a) 1 to 5
    b) 6 to 10
    c) More than 10
    d) Prefer not to answer

**KEY RISK MESSAGE QUESTIONS**

8. Which of the following statements is correct? *Please select one option*
    a. CRS has <u>not</u> been observed in clinical trials with KIMMTRAK
    b. KIMMTRAK commonly causes mild to moderate Cytokine Release Syndrome (CRS) √
    c. CRS following KIMMTRAK only occurs in patients who have other risk factors
    d. I do not know

9. Which of the following statements is correct? *Please select one option*
    a. Patients are more likely to experience CRS within the first three KIMMTRAK infusions √
    b. CRS is typically not seen until after six KIMMTRAK infusions
    c. The severity of CRS increases with each infusion
    d. I do not know

10. Which of the following statements is correct? *Please select one option*
    a. The majority of episodes of CRS are delayed reactions starting seven days after infusion of KIMMTRAK
    b. The majority of episodes of CRS start on the day of infusion of KIMMTRAK √
    c. The majority of CRS occurs three days after infusion of KIMMTRAK
    d. I do not know

11. Which of the following statements is correct regarding KIMMTRAK administration and monitoring? *Please select one option*
    a. For at least the first three infusions, patients should be monitored for 16 hours in a hospital √
    b. The first three infusions can be administered in an outpatient setting
    c. There is no requirement to monitor patients for CRS following administration
    d. I do not know

12. Which of the following statements is correct? *Please select one option*
    a. For the first three infusions, vital signs should be checked once at 16 hours after the infusion.
    b. For the first three infusions, vital signs should be checked before dosing and at a minimum interval of every four hours, for at least 16 hours √
    c. If vital signs are normal following the first infusion, there is no requirement to monitor for subsequent infusions
    d. I do not know

13. Which of the following statements is correct? *Please select one option*
    a. Intravenous steroids are never required for CRS associated with KIMMTRAK administration
    b. All patients should receive intravenous steroids prophylactically prior to each infusion of KIMMTRAK
    c. For Grade 3 CRS, or for persistent or recurrent Grade 2 CRS associated with KIMMTRAK, steroids should be administered at least 30 minutes before the next dose √
    d. I do not know

14. Which of the following statements is correct? *Please select one option*
    a. KIMMTRAK may be restarted once the patient recovers from Grade 4 CRS
    b. KIMMTRAK should be permanently discontinued if a patient experiences CRS of any grade.
    c. KIMMTRAK should be permanently discontinued if a patient experiences Grade 4 CRS √
    d. I do not know

15. Which of the following statements is correct? *Please select one option*
    a. For patients with pre-existing adrenal insufficiency on maintenance systemic steroids, there is no need to adjust corticosteroid dose
    b. For patients with pre-existing adrenal insufficiency on maintenance systemic steroids, the corticosteroid dose should be adjusted in order to manage the risk of hypotension √
    c. For patients with pre-existing adrenal insufficiency on maintenance systemic steroids, patients should have corticosteroids held
    d. I do not know

16. Which of the following statements is correct? *Please select one option*
    a. During the first three infusions, an ECG should be performed in all patients before and after KIMMTRAK treatment √
    b. There is no requirement to undertake ECGs in patients being treated with KIMMTRAK
    c. Patients should have an ECG only if cardiac symptoms are observed
    d. I do not know

17. Which of the following statements is correct? *Please select one option*
    a. Patients with pre-existing cardiac disorders are <u>not</u> expected to be at any increased risk for sequelae associated with CRS
    b. Patients with pre-existing cardiac disorders should not be treated with KIMMTRAK
    c. Patients with cardiac disease, including QT prolongation and risk factors for cardiac failure, should be monitored carefully √
    d. I do not know

18. Patients treated with KIMMTRAK should be advised that if they develop symptoms of CRS they should do the following: *Please select one option*
    a. Alert their doctor or nurse immediately (√)
    b. Make an appointment to see the doctor within the next seven days
    c. Manage their symptoms with anti-pyretics and non-steroidal anti-inflammatory agents
    d. None of the above
    e. I do not know

**KIMMTRAK INDICATION**

19. Which is the correct indication for KIMMTRAK *Please select one option*
    a) Treatment of HLA-A*02:01-positive adult patients with uveal melanoma which is resectable and not metastatic
    b) Treatment of adult patients with unresectable or metastatic uveal melanoma who are not HLA-A*02:01-positive
    c) Treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma (√)
    d) I do not know

**EDUCATIONAL MATERIALS**

20. Have you received and read the Treatment Guide for Healthcare Professionals?
    a) Yes
    b) No

21. Were you aware (prior to today) of the Patient Guide?
    a) Yes
    b) No

22. Have you received copies of the Patient Guide?
    a) Yes
    b) No

23. When administering KIMMTRAK for the first time to a patient, do you or a colleague provide the Patient Guide to the patient? *Please select one option*
    a. Always
    b. Sometimes
    c. Never

24. When administering KIMMTRAK for the first time to a patient, do you or a colleague discuss the content of the Patient Guide with the patient? *Please select one option*
    a) Always
    b) Sometimes
    c) Never

25. From where did you obtain information regarding the safe use of KIMMTRAK?
    a) Summary of Product Characteristics
    b) KIMMTRAK Educational Materials
    c) Professional meetings
    d) Professional societies
    e) Immunocore staff
    f) Other
    g) I do not know

## APPENDIX I.2. SAMPLE DRAFT INVITATION LETTER FOR PHYSICIANS

[Date]
[Addressee's name]
[Title]
[Street address]
[City, State, Post code]
[Country]

**Re: Invitation to Participate in KIMMTRAK® (tebentafusp) Survey**

Dear Dr. [insert physician's LAST NAME],

On behalf of Immunocore Ireland Ltd, we would like to invite you to participate in a voluntary safety survey about KIMMTRAK (tebentafusp), indicated for KIMMTRAK as monotherapy for the treatment of human leukocyte antigen (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma.

The safety survey is part of a Risk Management Plan (RMP) commitment between Immunocore and the European Medicines Agency (EMA) to assess the effectiveness of the Treatment Guide for Healthcare Professionals to minimise the risk of cytokine release syndrome associated with use of KIMMTRAK. The safety survey should take approximately 20 minutes to complete. If you complete the safety survey and provide your contact information, you have the opportunity to receive [**€XX**] as fair compensation of your time, subject to local rules and regulations.

You are only able to participate if you are currently treating or have treated (HLA)-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma with KIMMTRAK.

For your convenience, the survey can be completed online at

You will need the following code when completing the survey: **[UNIQUE CODE]**.

**Why is this important?**

In accordance with European regulations, Immunocore develops RMPs for its medications. The RMP for KIMMTRAK outlines the identified and potential risks associated with use of KIMMRAK, how these are monitored and what steps are taken to minimise them. In addition to the product labelling, a Treatment Guide for Healthcare Professional and a Patient Guide were developed as additional risk minimisation measures. As part of its regulatory commitment, Immunocore is required to assess the effectiveness of these additional risk minimisation measures and report back to the regulatory authorities.

Participating in this safety survey is entirely voluntary. All information that is collected during the course of the safety survey will be kept strictly confidential. Results will be

reported in aggregate only. Your participation in the safety survey and your answers to the survey questions will not affect your ability to prescribe or currently treat patients with KIMMTRAK. You will not be contacted for marketing purposes. Neither Immunocore nor its contractors will sell, transfer, or rent your information.

Your assistance with this safety survey is greatly appreciated. Thank you for your participation in this important research.

Sincerely,

# APPENDIX I.3 ADDITIONAL RISK MINIMISATION MATERIALS

PLACEHOLDER·for·national·logo·of·educational·material·(place·it·left·or·right·side·depending·on·national·requirements)¶

¶
¶
¶

# Treatment·Guide·for·Healthcare·Professionals·¶

## Important·information·about·▼KIMMTRAK®·(tebentafusp)¶

¶

[ADD·any·national·required·statement·here]¶

¶

**Information·to·assist·healthcare·professionals·in:·¶**

- →Description·of·the·symptoms·of·CRS,·including·severity,·frequency,·time·to·onset,·treatment·and·resolution,·in·patients·treated·with·KIMMTRAK.·¶
- →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.·¶
- →How·to·monitor·patients·for·the·first·three·infusions·and·for·subsequent·infusions.¶
- →How·to·minimise·the·risk·of·hypotension·associated·with·Cytokine·Release·Syndrome·(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.·¶

¶

**▼·This·medicinal·product·is·subject·to·additional·monitoring.·The·additional·risk·minimisation·material·is·provided·by·Immunocore·(Ireland)·Limited·as·a·condition·of·the·KIMMTRAK·marketing·authorisation.¶**

.....Page Break.....¶

# Table of Contents

# About this brochure

This brochure is intended to summarise important safety information about KIMMTRAK with patient monitoring, medical management of Cytokine Release Syndrome (CRS), management of ECG schedule and handling of patients with cardiac risk factors.

This information is intended to assist healthcare professionals in communicating key safety messages to patients receiving KIMMTRAK therapy and in caring for patients receiving KIMMTRAK therapy.

It does not contain all the information about this product. Please always consult the Summary of Product Characteristics (SmPC) before prescribing, preparing or administering KIMMTRAK.

# KIMMTRAK is indicated for:

Treatment of HLA-A*02:01-positive adult patients with unresectable or metastatic uveal melanoma. It 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.

# Cytokine Release Syndrome (CRS):

**In clinical trials CRS, which may be serious or life threatening, have occurred following KIMMTRAK infusion. It decreased in frequency and severity following each subsequent KIMMTRAK infusion. Monitor for at least 16 hours following the first three infusions and then as clinically indicated.**

## Symptoms of CRS:

- Pyrexia
- Hypotension
- Hypoxia
- Chills
- Nausea
- Vomiting
- Fatigue
- Headache

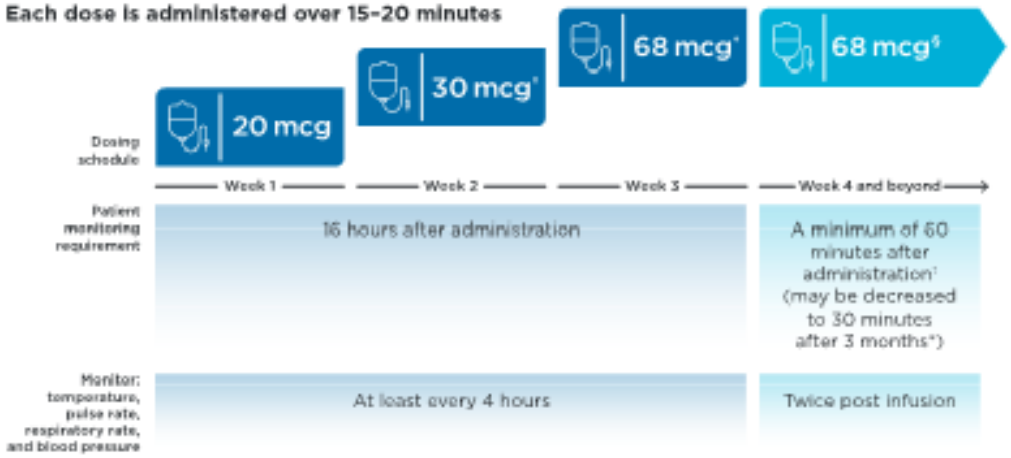
## Clinical manifestation of CRS (severity, frequency, onset time, treatment options):

- In clinical trials it was seen, that KIMMTRAK commonly causes mild to moderate CRS, which if not identified and treated appropriately may become life-threatening or fatal.

- Most of patients typically experienced CRS following each of the first 3 KIMMTRAK infusions with decreasing severity and frequency.
  - The majority of episodes of CRS started at the day of infusion
  - CRS led to permanent discontinuation in 1.2% of patients
  - All CRS symptoms were reversible and were mostly managed with IV fluids, antipyretics, or a single dose of systemic corticosteroids
  - Pyrexia was noted in nearly all cases of CRS

An increase in body temperature generally occurred within the first 8 hours after KIMMTRAK infusion.

## KIMMTRAK Patient Monitoring & Dosing:




The starting dose is 20 mcg for week 1. The dose increases to 30 mcg for week 2 and 68 mcg for weeks 3 and beyond.
One 0.5 mL KIMMTRAK vial contains 100 micrograms of tebentafusp, corresponding to a concentration before dilution of 200 mcg/mL.

† Do not escalate dose level if Grade 3 CRS or skin reactions occurred; resume escalation once dosage is tolerated. Kimmtrak treatment should be permanently discontinued if Grade 4 CRS or skin reactions are experienced at any time during treatment.
§ After 68 mcg dose level is tolerated (i.e., absence of Grade ≥2 hypotension requiring medical intervention), subsequent doses can be administered in appropriate out-patient ambulatory care setting.
‡ 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. If the third infusion was not well tolerated (Grade ≥ 2 hypotension requiring medical intervention), follow monitoring guide as for the first 3 infusions.
* 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.

**Adjustment on what to monitor and at what frequency should be made using clinical judgment or by institutional standards.**

**For at least the first 3 infusions, patients should be monitored during infusion and at least for 16 hours after infusion is complete in a hospital setting with overnight monitoring.**

- Based on clinical trials, 16 hours is the likely time frame for presentation of cytokine release syndrome (CRS) symptoms.
- Ensure that healthcare providers administering KIMMTRAK have immediate access to medications and resuscitative equipment to manage CRS.
- After infusion 3, and once the patient tolerates the most recent infusion without hypotension requiring medical intervention (e.g. giving IV fluids), subsequent doses can be administered in appropriate out-patient ambulatory care setting.

**First 3 Infusions of KIMMTRAK: during infusions and 16-hour monitoring post-infusion**

Before dosing and every 4 hours (at a minimum) thereafter, check vital signs:

- temperature
- pulse rate
- respiratory rate
- blood pressure
- oxygenation level

*If clinically indicated, more frequent monitoring or prolongation of hospitalization should occur.*

*In cases of hypotension (Grade 3 or 4), consider vital sign monitoring at least every hour for at least 4 hours for the next three infusions.*

**Starting with the 4th Infusion: Minimum 60-minute monitoring following each infusion**

*If the third infusion was well tolerated (i.e., absence of Grade ≥ 2 hypotension requiring medical intervention):*

- Observe patient for a minimum of 60 minutes following each infusion for 3 months.

*If the third infusion was not well tolerated (Grade ≥ 2 hypotension requiring medical intervention):*

- Follow monitoring guide as for the first 3 infusions
- Check vital signs before dosing and every 4 hours, or as clinically indicated
- 16-hour monitoring post-infusion in a hospital setting with overnight monitoring

*If infusions were given in an outpatient setting for at least 3 months and patient has not experienced any interruptions greater than 2 weeks:*

- Outpatient monitoring following infusion may be decreased to a minimum of 30 minutes for subsequent doses.

## CRS Management Guidance:

No dosage reduction for KIMMTRAK is recommended. Dosage modifications for KIMMTRAK for CRS are summarized below.

Table 1: CRS Grading and CRS Treatment guide

| CRS grade* | Management |
|---|---|
| **Grade 1**<br>Temperature ≥ 38 °C<br><br>No hypotension or hypoxia | • Continue treatment and provide symptomatic support. Monitor for escalation in CRS severity. |
| **Grade 2**<br>Temperature ≥ 38 °C<br><br>Hypotension that responds to fluids and does not require vasopressors.<br><br>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.<br><br>• 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).<br><br>• 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 |

| CRS grade* | Management |
|---|---|
| **Grade 3**<br>Temperature ≥ 38 °C<br><br>Require a vasopressor with or without vasopressin.<br><br>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<br><br>• Administer high-dose intravenous corticosteroid (e.g. 2 mg/kg/day methylprednisolone or equivalent).<br><br>• Administer tocilizumab as needed<br>- Patient weight ≤ 30 kg: 12 mg/kg intravenously over 1 hour<br>- Patient weight ≥ 30 kg: 8 mg/kg intravenously over 1 hour (maximum dose 800 mg)<br><br>• 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)<br><br>• For Grade 3 CRS, administer corticosteroid premedication (e.g. dexamethasone 4 mg or equivalent) at least 30 minutes prior to next dose |
| **Grade 4**<br>Temperature ≥ 38 °C<br><br>Require multiple vasopressors (excluding vasopressin)<br>Requiring positive pressure (e.g. CPAP, BiPAP, intubation and mechanical ventilation). | • Permanently discontinue KIMMTRAK<br><br>• Administer intravenous corticosteroid (e.g., 2 mg/kg/day methylprednisolone or equivalent) |

*Based on ASTCT consensus grading of CRS criteria (Lee DW, Santomasso BD, Locke FL, et al. ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. Biol Blood Marrow Transplant 2019 Apr;25(4):625-638.)

## How to minimise the risk of hypotension associated with CRS

- Administering i.v. fluids prior to starting KIMMTRAK infusion based on clinical evaluation and the volume status of the patient.

For patients with pre-existing adrenal insufficiency on maintenance systemic corticosteroids:

- Adjusting the corticosteroid dose to manage the risk of hypotension as needed.

## ECG schedule and management requirements based on ECG results

- ECG before and after tebentafusp treatment during the first 3 weeks of treatment and subsequently as clinically indicated.
- Stop KIMMTRAK infusion if QTcF interval exceeds 500 ms or increases by ≥ 60 msec from baseline value and treat any underlying precipitating factors including electrolyte abnormalities.
- Re-start treatment once QTcF interval improves to < 500 ms or is < 60 msec from baseline value.
- Stop or discontinue KIMMTRAK treatment depending on persistence and severity of cardiac event and any associated CRS.

## Monitoring requirements of patients with cardiac diseases, QT prolongation and risk factors for cardiac failure

KIMMTRAK has not been studied in patients with clinically significant cardiac diseases or impaired cardiac function. Some cardiac events (e.g. sinus tachycardia and arrhythmia) and cases of QT interval prolongation have been observed in patients under KIMMTRAK treatment. It might be that patients with pre-existing cardiovascular disorders may be at increased risk for sequelae associated with CRS. As CRS occurs frequently under treatment with KIMMTRAK with associated hypotension, the hypotension may not be tolerated in some patients with cardiovascular disease.

- Carefully monitor patients with cardiac disease, QT prolongation and risk factors for cardiac failure.
- Administer carefully KIMMTRAK in:
  - patients with history of or predisposition to QT interval prolongation
  - patients who are taking medicinal products that are known to prolong QT interval.
- Any patient with signs or symptoms consistent with cardiac events should be evaluated and promptly treated.

# Important Information for Patients

- Most patients treated with KIMMTRAK have developed Cytokine Release Syndrome called CRS, which can become life-threatening if not promptly treated.
- Discuss with patients the frequency and way of monitoring and the possible side effects that can occur.
- **Remind the patient to alert their doctor or nurse immediately if they experience any of the following signs or symptoms suggestive of CRS:**
  - Fever

- Tiredness or weakness
- Vomiting
- Chills
- Nausea
- Low blood pressure
- Dizziness and light headedness
- Headache

- To report any side effects to doctor or nurse.
- To hand-over the Patient Guide and PIL

## Reporting of suspected adverse events or reactions

Reporting suspected adverse events or reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions (see details below).

Where possible, healthcare professionals should report adverse events or reactions by brand name and batch number.

**In the event of a suspected adverse event, please report it to:**

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

Phone: +44 (0) 2076645100
Toll Free Number: +00 800-74451111
e-mail: medinfo.eu@immunocore.com
http://www.immunocore.com

**Alternatively, suspected adverse reactions should be reported to:**

**[ENTER NATIONAL HEALTH AUTHORITY NAME]**

**[ENTER Website of NATIONAL HEALTH AUTHORITY]**

# Further Information

**For electronic copies of the Treatment Guide for HCPs and Patient Guide**, visit:

**[Enter website of educational materials of NATIONAL HEALTH AUTHORITY]**

Or

www.kimmtraksupport.eu

**For Questions and medical enquiries**

For more information, contact the Immunocore Medical Information Center at +44 (0)1235 438600 or via email info@immunocore.com.

IMMUNOCORE

PLACEHOLDER for national logo of educational material (place it left or right side depending on national requirements)

# Patient Guide

## What you should know about ▼KIMMTRAK® (tebentafusp)

[ADD any national required statement here]

**Important safety information for patients receiving KIMMTRAK therapy:**

- This brochure contains important safety information only.
- See the KIMMTRAK Package Leaflet for more information.

**▼ This medicinal product is subject to additional monitoring. The additional risk minimisation material is provided by Immunocore (Ireland) Limited as a condition of the KIMMTRAK marketing authorisation.**

# Table of Contents

# About this brochure

The information in this brochure is for patients who are being given KIMMTRAK.

It is administered by your doctor. Your doctor will also talk with you about this brochure and important information for you like the benefits and the risks of KIMMTRAK therapy and what to expect regarding your monitoring schedule.

This brochure will:

- Tell you about KIMMTRAK
- Tell you about KIMMTRACK therapy and what kind of clinical monitoring you can expect
- Tell you about important side effect that you need to be aware of –the risk of 'Cytokine Release Syndrome' or CRS
- Tell you what the signs and symptoms of CRS are
- Tell you what to do if you think you are getting CRS
- Provide you with information on how to report side effects

# What you should know about KIMMTRAK

## What is KIMMTRAK?

KIMMTRAK is a prescription medicine used to treat HLA-A*02:01-positive adults with uveal melanoma that cannot be removed by surgery or has spread. Your doctor will give you a blood test to see if you are HLA-A*2:01 positive and determine if KIMMTRAK is right for you.

## How will I receive KIMMTRAK?

KIMMTRAK will be given to you by intravenous (IV) infusion into your vein for 15 to 20 minutes.

## How often will I receive KIMMTRAK?

KIMMTRAK is usually given every week. Your dose should increase over the first three visits then remain consistent. Your doctor will decide how many treatments you need.

# What can I expect when I receive my infusion of KIMMTRAK?

- You will have an overnight stay in the hospital and will need to be monitored for side effects during and after receiving KIMMTRAK

- For at least your first 3 infusions, you will be monitored during your infusion and for at least **16 hours** after. This is the period of time that it would be likely that certain serious side effects may be seen.
  - Your vital signs (temperature, pulse rate, respiratory rate, and blood pressure) will be taken at least every 4 hours
- After the first 3 infusions:
  - *If you tolerated KIMMTRAK well and you didn't have significant side effects:*
    - You will be monitored during your infusions and typically for a minimum of **60 minutes** after your infusions for at least 3 months
    - In case you tolerated the infusions well for at least 3 months, your monitoring might be decreased to a minimum of 30 minutes.
    - Your vital signs (temperature, pulse rate, respiratory rate, and blood pressure) will be taken at least twice after infusion
  - *If you did have significant side effects,* you may need to be monitored longer like for the first 3 infusions and your treatment may be delayed

**Before your infusion, your doctor may adjust your other medications.**
**Before receiving KIMMTRAK, tell your doctor about all of your medical conditions**
**Tell your doctor about all medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.**

## Why do I need to be monitored when I receive KIMMTRAK?

KIMMTRAK can cause side effects that can be severe or life threatening. One of these side effects might be 'Cytokine release syndrome' (CRS) – an expected adverse reaction related to immune cell activation caused by KIMMTRAK. When immune cells are activated, they produce proteins called cytokines. This can cause some of the below listed signs:

| | |
|---|---|
| o fever | o headache |
| o tiredness or weakness | o nausea |
| o vomiting | o low blood pressure |
| o chills | o dizziness and light-headedness |

**Call or see your doctor right away if you develop any symptoms.**
Side effects such as CRS are most likely to occur during the first 3 infusions.

## What happen when I experience side effects?

Treatment-related side effects were generally:

- predictable,
- manageable with appropriate treatment, and
- typically occurred during the first 3 doses.

To manage potential side effects your doctor may give you IV fluids, medicine, or supplemental oxygen.

You will be monitored during and after your infusion so any side effects can be treated as soon as possible.

Your healthcare provider will:

- perform heart tests, check heart rhythm, body temperature and relevant vital signs
- check for any problems during treatment with KIMMTRAK.
- may temporarily stop or completely stop your treatment with KIMMTRAK if you have severe side effects.

## What should I do if I develop a side effect when I go home after my infusion?

**Call your healthcare provider right away if you develop any symptoms.**
**Do not wait until your next infusion or doctor's appointment. If you experience Cytokine Release Syndrome (CRS) symptoms seek medical attention immediately.**

# Reporting of suspected adverse events or reactions

If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in the Package Leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

**In the event of a side effect, please report it to:**

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

Phone: +44 (0) 2076645100
Toll Free Number: +00 800-74451111
e-mail: medinfo.eu@immunocore.com
http://www.immunocore.com

**Alternatively, side effects should be reported to:**

**[ENTER NATIONAL HEALTH AUTHORITY NAME]**

**[ENTER Website of NATIONAL HEALTH AUTHORITY]**

# Further Information

**Talk to your doctor or nurse if you have any questions or concerns.**

**For electronic copies of the Patient Guide**, visit:

**[Enter website of educational materials of NATIONAL HEALTH AUTHORITY]**

Or

www.kimmtraksupport.eu

**For Questions and medical enquiries**

For more information, contact the Immunocore Medical Information Center at +44 (0)1235 438600 or via email info@immunocore.com.

IMMUNOCORE

# Annex 2. ENCePP Checklist for Study Protocols

| **Study title:** |
|---|

| **EU PAS Register® number:**<br>**Study reference number (if applicable):** |
|---|

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[1] | ☒ | ☐ | ☐ | 6 |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | 6 |
| 1.1.3 Progress report(s) | ☐ | ☐ | ☒ | |
| 1.1.4 Interim report(s) | ☐ | ☐ | ☒ | |
| 1.1.5 Registration in the EU PAS Register® | ☒ | ☐ | ☐ | 6 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 6 |

Comments:

| |
|---|
| |

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | ☒ | ☐ | ☐ | 8 |
| 2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | 7 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | 8 |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | 9.2.1 |
| 2.1.4 Which hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| The study will be descriptive and there will not be hypothesis testing |

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

| **Section 3: Study design** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 3.1 | Is the study design described? (e.g. cohort, case-control, cross-sectional, other design) | ☒ | ☐ | ☐ | 9.1 |
| 3.2 | Does the protocol specify whether the study is based on primary, secondary or combined data collection? | ☒ | ☐ | ☐ | 9.2 |
| 3.3 | Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence) | ☐ | ☐ | ☒ | |
| 3.4 | Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH)) | ☐ | ☐ | ☒ | |
| 3.5 | Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 11 |

Comments:

| |
|---|
| |

| **Section 4: Source and study populations** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 4.1 | Is the source population described? | ☒ | ☐ | ☐ | 9.2 |
| 4.2 | Is the planned study population defined in terms of: | | | | |
| | 4.2.1 Study time period | ☒ | ☐ | ☐ | 9.6 |
| | 4.2.2 Age and sex | ☒ | ☐ | ☐ | 9.3 |
| | 4.2.3 Country of origin | ☒ | ☐ | ☐ | 9.3 |
| | 4.2.4 Disease/indication | ☐ | ☐ | ☒ | |
| | 4.2.5 Duration of follow-up | ☐ | ☐ | ☒ | |
| 4.3 | Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 9.4 |

Comments:

| |
|---|
| Age will be collected. Sex will not be collected |

| **Section 5: Exposure definition and measurement** | | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|---|
| 5.1 | Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure) | ☐ | ☐ | ☒ | |

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☐ | ☐ | ☒ | |
| 5.3 Is exposure categorised according to time windows? | ☐ | ☐ | ☒ | |
| 5.4 Is intensity of exposure addressed? (e.g. dose, duration) | ☐ | ☐ | ☒ | |
| 5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☐ | ☐ | ☒ | |
| 5.6 Is (are) (an) appropriate comparator(s) identified? | ☐ | ☐ | ☒ | |

Comments:

| **Section 6: Outcome definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated? | ☒ | ☐ | ☐ | 8 |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 9.7 |
| 6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study) | ☒ | ☐ | ☐ | 9.7 |
| 6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management) | ☐ | ☐ | ☒ | |

Comments:

| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication) | ☐ | ☐ | ☒ | |
| 7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias) | ☒ | ☐ | ☐ | 9.9 |
| 7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias) | ☐ | ☐ | ☒ | |

Comments:

| | |
|---|---|
| | |

| **Section 8: Effect measure modification** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect) | ☐ | ☐ | ☒ | |

Comments:

| | |
|---|---|
| | |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | ☐ | ☐ | ☒ | |
| 9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☐ | ☐ | ☒ | |
| 9.1.3 Covariates and other characteristics? | ☐ | ☐ | ☒ | |
| 9.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☐ | ☐ | ☒ | |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | ☐ | ☐ | ☒ | |
| 9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☐ | ☐ | ☒ | |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☐ | ☐ | ☒ | |
| 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA)) | ☐ | ☐ | ☒ | |
| 9.3.3 Covariates and other characteristics? | ☐ | ☐ | ☒ | |
| 9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other) | ☐ | ☐ | ☒ | |

Comments:

| | |
|---|---|
| | |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Are the statistical methods and the reason for their choice described? | ☒ | ☐ | ☐ | 9.7 |
| 10.2 Is study size and/or statistical precision estimated? | ☒ | ☐ | ☐ | 9.5 |
| 10.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | 9.8 |
| 10.4 Are stratified analyses included? | ☒ | ☐ | ☐ | 9.8 |
| 10.5 Does the plan describe methods for analytic control of confounding? | ☐ | ☐ | ☒ | |
| 10.6 Does the plan describe methods for analytic control of outcome misclassification? | ☐ | ☐ | ☒ | |
| 10.7 Does the plan describe methods for handling missing data? | ☐ | ☐ | ☒ | |
| 10.8 Are relevant sensitivity analyses described? | ☐ | ☐ | ☒ | |

Comments:

Study size is not based upon statistical considerations but based upon the number of available physicians. Only completed surveys will be included in the analysis, therefore there would not be missing data

| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 9.6 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 9.8 |
| 11.3 Is there a system in place for independent review of study results? | ☐ | ☐ | ☒ | |

Comments:

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.1 Does the protocol discuss the impact on the study results of: | | | | |
| 12.1.1 Selection bias? | ☒ | ☐ | ☐ | 9.9 |
| 12.1.2 Information bias? | ☒ | ☐ | ☐ | 9.9 |
| 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods). | ☐ | ☐ | ☒ | |

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates) | ☒ | ☐ | ☐ | 9.5 |

Comments:

| **Section 13: Ethical/data protection issues** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/ Institutional Review Board been described? | ☒ | ☐ | ☐ | 10.3 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☐ | ☒ | |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | 10.1 |

Comments:

| **Section 14: Amendments and deviations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document amendments and deviations? | ☒ | ☐ | ☐ | 5 |

Comments:

| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (e.g. to regulatory authorities)? | ☒ | ☐ | ☐ | 12 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 12 |

Comments:

Name of main author of protocol

Date: dd/Month/year

Daniel Sum *Electronically signed by: Daniel Sum*
*Reason: Reviewer*
*Date: Nov 14, 2023 10:40 EST*

Signature: _____

# Annex 3. Additional Information

Not applicable.

# Physician_survey_Kimmtrak_RMP_v_3.0_09Nov 2023

Final Audit Report 2023-11-14

| | |
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| Created: | 2023-11-14 |
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