***Text in red must be deleted/modified as applicable. Blue text is for guidance, delete once section is completed.***

**Development Safety Update Report**

|  |  |
| --- | --- |
| Investigational Drug(s) |  |
| DSUR Number |  |
| DIBD |  |
| Reporting Period |  |
| Date of Report |  |

|  |  |
| --- | --- |
| **Sponsor** | University College London (UCL)(Non-commercial) |
| **Address** | UCL Joint Research Office4th Floor West250 Euston RoadLondon NW1 2PG |
| **Contact** |  |
|  |  |

**Authorised by**: \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ *(signature)*

**This Development Safety Update Report (DSUR) contains confidential information.**

**This DSUR includes unblinded adverse event data** *(delete if not applicable)*

# Executive summary

*This section will be populated by the Sponsor after all the information has been collated and reviewed: It will include:*

*A concise summary of important information (can be used as a standalone document) covering the following areas:*

* *Report number and reporting period*
* *IMP(s) – modes of action, indication, therapeutic areas, dose, route and formulation*
* *Cumulative exposure of IMP to trial subjects*
* *Marketing approval – yes/no*
* *Actions taken for safety reasons including significant changes to RSI (IB/SPC) (based on sections 3 and 4)*
* *Summary of overall safety evaluation (based on section 18)*
* *Summary of Important risks (based on section 19)*
* *Conclusions (based on section 20)*

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# Introduction

This is the [add number] DSUR for the Investigational Medicinal Product (IMP) [add IMP name], covering the reporting period [add dates]. The Development International Birth Date (DIBD) for this DSUR is [add date].

|  |
| --- |
| **IMP name: [add here]** |
| Active Substance |  |
| Mode of Action |  |
| Therapeutic Class |  |
| Dose  |  |
| Route of Administration |  |
| Formulation |  |
| Indication and Population | *Brief description of Indication / patient population being studied* |
| Supplier | *Give details of supplier of the IMP (s) or state hospital stock* |

The scope of this DSUR is the[add trial title(s) (EudraCT number(s)]*. Provide the rationale here for submission of multiple DSURs for the investigational drug, if applicable.*

# Worldwide Marketing Approval Status

*Please give details if available (will be available on IMP boxes).*

The drug [add IMP name] has a marketing authorisation in the EU and is being used[inside/outside]its licenced indication and dosing ranges.

***OR***

The drug [add IMP name] does not have a marketing authorisation at this time.

UCL does not hold the manufacturing or marketing approval for the IMP(s) detailed in this DSUR and therefore UCL does not have access to some of the requested data. UCL is a non-commercial sponsor and where we cannot provide the requested data ‘Not applicable’ is provided.

# Actions Taken in the Reporting Period for Safety Reasons

Within the reporting period no actions were taken in regards to safety.

***OR***

The following actions were taken due to safety reasons: *(e.g. detail any Urgent Safety Measures and risk management activities such as changes to the protocol and other trial documents (dosage/formulation changes, eligibility criteria to minimise risks associated with IMP, updates to PIS in relation to safety issues), updates from trial committee meetings in relation to patient safety, suspension or early termination of an ongoing trial because of safety findings or lack of efficacy).*

# Changes to Reference Safety Information

The Reference Safety Information (RSI) for this trial is [add details].

*Example text:*

***The Reference Safety Information (RSI) for this trial is the Summary of Product Characteristics (SmPC) for Ketalar (ketamine hydrochloride) 10mg/ml Injection (Pfizer Ltd) PL 00057/0529 – Section 4.8: Undesirable Effects.***

***Investigator Brochure (IB) for ketamine hydrochloride (UCL) – Section 6.11: Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions.***

The version applicable at the start of the reporting period and used to assign expectedness of Serious Adverse Reactions (SARs) for this DSUR is [add version/date]. This version was approved with the Clinical Trial Authorisation / a substantial amendment *(delete as appropriate)* on [add date of approval].

***Where an SmPC is used as the RSI:***

The Marketing authorisation holder for [add IMP name]is responsible for updating the SmPC for this drug. The SmPC for [add IMP name]was updated on [add revision of text date]. The following has been updated:

*Add details here of updates.*

***Where an IB is used as the RSI (from commercial manufacturer):***

The IB for [add IMP name] is supplied by [add company name]to UCL for use in the [add trial short title]trial. [Company name] are responsible for updating the IB for this drug. The IB for [add IMP name]was updated on [add date]. The following has been updated:

*Add details here of any pertinent safety updates, or state there have been no pertinent changes applicable to the safety of the IMP.*

***OR***

The IB was not updated within the reporting period. *An IB should be updated annually, therefore the manufacturer will have to provide a reason why the update has not occurred which can be added here.*

***For IBs that are produced by UCL (or affiliate):***

The IB for [add IMP name] was updated in [add date]. The following has been updated:

*Add details here of any pertinent safety updates, or state there have been no pertinent changes applicable to the safety of the IMP.*

***OR***

The IB was not updated within the reporting period. *Provide a reason here why the update has not occurred.*

***State impact on trial documentation, and whether the RSI will be updated to the new version of the document. Include justification for not updating trial documentation or RSI if there have been updates to section of document used as RSI. Example text:***

After review by the Chief Investigator it was decided that no updates to trial documentation were required. The RSI will remain[add details of current version] for the next reporting period.

***OR***

After review by the Chief Investigator it was decided that updates were / will be made to the following trial documentation –[add details of updated documents]. The updated RSI will be / has been submitted to the MHRA as a substantial amendment. The RSI for the next reporting period will be [add details of updated version].

***OR***

After review by the Chief Investigator it was decided that no updates to trial documentation were required. However the updated RSI will be / has been submitted to the MHRA as a substantial amendment. The RSI for the next reporting period will be [add details of updated version].

***OR***

The RSI document has not been updated within the reporting period. The RSI will therefore remain the [add details of current version] for the next reporting period.

# Inventory of Clinical Trials Ongoing and Completed during the Reporting Period

This DSUR covers a single study: [add study here]. *Provide summary details of trial, e.g. .*

UCL is also sponsoring another study / other studies which is / are trialling this IMP: [add details on ongoing and completed trials during the reporting period] *(Delete if not applicable)*. Please refer to appendix 3.

# Estimated Cumulative Exposure

## 6.1 Cumulative Subject Exposure in the Development Programme

***For Blinded trials:***

The study remains blinded and the number of patients exposed to treatments is based on the randomisation scheme: [add details of treatment arms]. Appendix 4 contains estimated cumulative subject exposure in each treatment arm based on the randomisation scheme, all other demographic data is for the study as a whole.

***For Open Label trials:***

Appendix 4 contains a Cumulative Summary Tabulations of Demographic Data for the study.

*If the ethnicity is not available please add the following statement:*

The ethnicity is not available for the study as it is not being collected as part of the trial data.

## 6.2 Patient Exposure from Marketing Experience

Not Applicable. UCL does not hold the marketing approval for the IMP(s) detailed in this DSUR.

# Data in Line listings and Summary Tabulations

## Reference Information

Adverse Events are graded as per the National Cancer Terminology Criteria (CTCAE) v5.0 *(check version number used)*. The Medical Dictionary for Regulatory Activities (MedDRA) v23.1. *(check version number used)* was used for the coding of AEs in this DSUR.

The document(s) used to assess expectedness for Serious Adverse Reactions presented in this DSUR is / are shown below, and attached as part of the appendix.

|  |  |
| --- | --- |
| **IMP** | **Reference Safety Information** |
| Add drug name | *Examples:**SmPC for Ketalar (ketamine hydrochloride) 10mg/ml Injection (Pfizer Ltd),* ***03Jun2018*** *- Section 4.8: Undesirable Effects**IB for ketamine hydrochloride (UCL),* ***Version 2.0, 03Jun2018*** *– Section 6.11: Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions* |

## Line Listings of Serious Adverse Reactions during the Reporting Period

Please see Appendix 5.

***OR***

No Serious Adverse Reactions have been reported during the DSUR reporting period [add dates].

## Cumulative Summary Tabulations of Serious Adverse Events

Please see Appendix 6.

*Add details describing any adverse events excluded from these tables, e.g. events listed in protocol as exempt from reporting to sponsor.*

# Significant Findings from Clinical Trials during the Reporting period

UCL will complete this section if another study is sponsored trialling the same IMP, or include the statements below.

## Completed Clinical Trials

Not applicable. UCL is not sponsoring another study trialling this IMP.

## Ongoing Clinical Trials

Not applicable. UCL is not sponsoring another study trialling this IMP.

## Long-term Follow-up

Not applicable. UCL is not sponsoring another study trialling this IMP.

## Other Therapeutic Use of Investigational Drug

Not applicable. UCL is not sponsoring another study trialling this IMP.

## New Safety Data Related to Combination Therapies

Not applicable. UCL is not sponsoring another study trialling this IMP.

# Safety Findings from Non-interventional Studies

UCL will complete this section if we are sponsoring another study trialling the same IMP, or include the statement below.

UCL is not sponsoring any non-interventional studies trialling this IMP.

# Other Clinical Trial/Study Safety Information

Not Applicable. No information from clinical trials/studies has become available to UCL during the reporting period [add dates].

# Safety Findings from Marketing Experience

Not Applicable. No information regarding safety findings have become available to UCL during the reporting period [add dates].

***OR*** *if the product is in development only please state the following:*

Not Applicable. This product is not marketed and is in the development phase only.

# Non-clinical Data

Not Applicable. No information from non-clinical studies has become available to UCL during the reporting period.

# Literature

*Please perform literature search relevant to disease group and IMP using the period reporting dates. Copy and paste relevant abstract into this section and provide precise reference (i.e., Gilani, Farhat F. "The Wonders of Pharmacovigilance." Journal of clinical Trials 58.2 (2011): 265. If no relevant articles published please state:*

No new relevant literature articles have become available to UCL during the reporting period.

*(Please provide printout of copy of literature search for TMF)*

# Other DSURs.

*The Sponsor will complete this section.*

UCL have not submitted any other DSURs detailing the IMP.

# Lack of Efficacy.

*This section should contain data indicating lack of efficacy, or lack of efficacy relative to established therapies. Update this section if applicable or state:*

No data have been obtained by UCL during the reporting year that indicates a lack of efficacy.

# Region specific Information

## Cumulative Summary Tabulation of Suspected Unexpected Serious Adverse Reactions

A total of XX SUSARs have been reported for the IMP [add name] since the DIBD. Please See Appendix 8 (R1) for details.

***OR***

No SUSARs have been reported for the IMP [add name] since the DIBD.

## List of Subjects who Died During the Reporting Period

A total of XX subjects died during the reporting period. Please see appendix 8 (R2) for details.

***OR***

No subjects died during the reporting period.

## List of Subjects who Dropped out of Clinical Trials in Association with an Adverse Event during the Reporting Period

A total of XX subjects dropped out of the clinical trial(s) in association with an adverse event during the reporting period. Please see appendix 8 (R3) for details.

***OR***

No subjects dropped out of the clinical trial(s) in association with an adverse event during the reporting period.

## Significant Phase 1 Protocol Modifications With Respect to a US Investigational New Drug Application

Please see Appendix 8 (R4). *(US trials only)*

*Or state:*

Not Applicable.

## Significant Manufacturing Changes

*Add any details here, (e.g. new source of IMP).* See appendix 8 (R5) for details.

*Or state:*

UCL is a non-commercial sponsor and does not have access to information concerning changes to the manufacturing of [add IMP].

## Description of the General Investigation Plan for the Coming Year With Respect to a US Investigational New Drug Application

Please see Appendix 8 (R6). *(US trials only)*

*Or state:*

Not Applicable.

## Log of Outstanding Business With Respect to a US Investigational New Drug Application

Please see Appendix 8 (R7). *(US trials only)*

*Or state:*

Not Applicable.

# Late Breaking Information.

*If new safety information is highlighted from the production of this DSUR or new information is made available please add it here (e.g. clinically significant new case reports, action from DMC or sponsor occurring after the data lock point). Or state:*

There is no late breaking information applicable for this DSUR.

# Overall Safety Assessment.

*Possible wording (amend as appropriate).* *Take into account all new information, interpret the information and details its implication of the trial population.*

As of the data at data lock point [add date], XX number of SAEs have been reported of which XX were SARs. There have been no SUSARs. The trial safety profile remains unchanged and is in line with the current information available in the IB/SmPC. The have been no safety issues highlighted to the Trial Management Group (TMG) or Independent Data Monitoring Committee (IDMC) *(add dates of recent meetings and any findings as appropriate)*.

## Evaluation of Risks.

*Evaluation of risks to trial subjects: Take into account data related to newly identified safety concerns or providing significant new information relative to previously identified safety concerns. Interpretation of safety data from this specific trial, literature searches, changes to safety reference documents and other trial information supplied by sponsor. Or state:*

Overall [add IMP] has been well tolerated. No new risks to trial subjects have been identified.

## Benefit-Risk Considerations.

Take into account information from this specific trial, literature searches, changes to safety reference documents and other trial information supplied by sponsor. Provide a succinct statement and note whether there have been any changes in this balance since the previous DSUR. If the benefit-risk has not changed in the reporting year state:

The benefit-risk balance for subjects receiving [add IMP] on this/these trial(s) remains unchanged.

# Summary of Important risks.

*Detail the most important risks to trial participants and how they are mitigated, can be narrative or tabular format. Refer to protocol and PIS.*

# Conclusions.

*Briefly describe any changes to the previous knowledge of efficacy and safety resulting from information gained since the last DSUR. The conclusion should outline actions that have been or will be taken to address emerging safety issues. Or state:*

The safety profile of [add IMP] remains unchanged and no safety concerns have been highlighted in this reporting year. The risk-benefit balance remains unchanged.

# Appendices to the DSUR

***List of appendices:***

1. Investigator’s Brochure / SmPC: *(provided as a separate document(s))*
* [Add versions included]
1. Cumulative Table of Important Regulatory Advice: (*Not applicable)*
2. Status of Ongoing and Completed Clinical Trials: (*Table)*
3. Cumulative Summary Tabulations of Demographic Data:
* Estimated Cumulative Subject Exposure *(Table/Not applicable)*
* Subject Exposure of IMP by age and gender *(Table)*
* Subject Exposure to IMP by ethnic origin *(Table/Not applicable)*
1. Line Listing of Serious Adverse Reactions (SARs): *(Table)*
2. Cumulative Summary Tabulations of SAEs: *(Table)*
3. Scientific Abstracts: *(Included as separate document(s)/Not applicable)*
4. Regional Specific Information
* R1: Cumulative Summary Tabulation of Suspected Unexpected Serious Adverse Reactions *(Table/Not applicable)*
* R2: List of Subjects who Died during the Reporting Period *(Table/Not applicable)*
* R3: List of subjects who Dropped out of Clinical Trials in Association with an Adverse Event during the reporting period *(Table/Not applicable)*
* R4: Significant Phase 1 Protocol Modifications With Respect to a US Investigational New Drug Application (*include for US trials only*)
* R5: Significant Manufacturing Changes
* R6: Description of the General Investigation Plan for the Coming Year With Respect to a US Investigational New Drug Application (*include for US trials only*)
* R7: Log of Outstanding Business With Respect to a US Investigational New Drug Application (*include for US trials only*)

***Appendix 1:*** Provided as a separate document(s)

***Appendix 2:*** Not applicable

***Appendix 3:* Status of Ongoing and Completed Clinical Trials**

Overview of Ongoing Studies ([Add IMP])

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Phase** | **Country** | **Study Title** | **Study Design** | **Dosing regimen** | **Study population** | **First patient first visit** | **Planned enrolment** | **Subject exposure** |
| Protocol No: [add] EudraCT No: [Add ] |  |  |  |  |  | *Include disease group, age range* |  |  |  |

*\*Total number of patients recruited as of [add data lock date]*. *For an estimate of cumulative subject exposure to each treatment see Appendix 4, table 1. – For blinded studies include this sentence.*

Overview of Studies Completed during the DSUR period ([Add IMP]) *– delete table if not applicable*

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Study ID** | **Phase** | **Country** | **Study Title** | **Study Design** | **Dosing regimen** | **Study population** | **Subject exposure per treatment arm** |
| Protocol No: [add] EudraCT No: [Add ] |  |  |  |  |  | Include disease group, age range |  |

***Appendix 4:* Cumulative Summary Tabulations of Demographic Data**

Estimated cumulative subject exposure *– include this table for blinded studies only and estimate numbers based on randomisation schemes*

|  |  |
| --- | --- |
| **Treatment** | **Number of subjects** |
| Drug [add name] |  |
| Comparator [add name] |  |
| Placebo |  |

Subject Exposure to IMP by age and gender

|  |  |
| --- | --- |
|  | **Number of Subjects** |
| **Age range** | **Male** | **Female** | **Total** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

Subject Exposure to IMP by ethnic origin*Examples provided*

|  |  |
| --- | --- |
| **Ethnic Origin** | **Number of subjects** |
| Asian  |  |
| Black |  |
| Caucasian  |  |
| Others |  |
| Unknown |  |
|  |  |
| **Total** |  |

***Appendix 5:* Line Listing of Serious Adverse Reactions (SARs) for the reporting period [add dates]**

*If no SARs occurred within the reporting period state:* No SARs were reported to UCL for the reporting period [add dates].

*Where unblinded information is available (e.g. from SUSARs) provide in table below –* ***ensure a blinded DSUR is prepared for study team.***

EudraCT No: [Add]

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Subject No** | **Country****Gender****Age** | **Serious Adverse Reactions (SARs)** | **Outcome** | **Date of onset\*****Time to onset\*** | **Suspect Drug** | **Daily dose****Route****Formulation** | **Dates of treatment****Treatment duration** | **Comments** |
|  |  |  |  |  | *Provide unblinded information if known* |  |  | *State if unblinded or SAR remains blinded. Also highlight SUSARs. Provide any other relevant info* |
|  |  |  |  |  |  |  |  |  |

\*Primary SAR only if multiple events reported

***Appendix 6:* Cumulative Summary Tabulations of Serious Adverse Events (SAEs)**

|  |  |
| --- | --- |
| **System Organ Class (SOC)**Preferred Term*Delete rows if SOC non required* | **Total up to [add data lock date]** |
| **[drug]** *or* **[drug/ placebo/comparator]** *if blinded* | **[add comparator]** *or remove column*  |
| **Blood and lymphatic system disorders**[insert SAE term] | **[total for SOC]**[total for SAE term] | **[total for SOC]**[total for SAE term] |
| **Cardiac disorders** | *Delete rows if SOC non applicable* |  |
| **Congenital, familial and genetic disorders** |  |  |
| **Ear and labyrinth disorders** |  |  |
| **Endocrine disorders** |  |  |
| **Eye disorders** |  |  |
| **Gastrointestinal disorders** |  |  |
| **General disorders and administration site conditions** |  |  |
| **Hepatobiliary disorders** |  |  |
| **Immune system disorders** |  |  |
| **Infections and infestations** |  |  |
| **Injury, poisoning and procedural complications** |  |  |
| **Investigations** |  |  |
| **Metabolism and nutrition disorders** |  |  |
| **Musculoskeletal and connective tissue disorders** |  |  |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** |  |  |
| **Nervous system disorders** |  |  |
| **Pregnancy, puerperium and perinatal conditions** |  |  |
| **Product issues** |  |  |
| **Psychiatric disorders** |  |  |
| **Renal and urinary disorders** |  |  |
| **Reproductive system and breast disorders** |  |  |
| **Respiratory, thoracic and mediastinal disorders** |  |  |
| **Skin and subcutaneous tissue disorders** |  |  |
| **Social circumstances** |  |  |
| **Surgical and medical procedures** |  |  |
| **Vascular disorders** |  |  |
| **Total**  |  |  |

***Appendix 7:*** **Scientific Abstracts** - Provided as a separate document(s)

***Appendix 8:* Regional Specific Information**

**R1: Cumulative Summary Tabulation of Suspected Unexpected Serious Adverse Reactions (SUSARs)**

|  |  |
| --- | --- |
| **System Organ Class (SOC)**Preferred Term*Delete rows if SOC non required* | **Total up to [add data lock date]** |
| **[drug]** *or* **[drug/ placebo/comparator]** *if blinded* | **[comparator]** *or remove column*  |
| **Total up to [add data lock date]** | **Total up to [add data lock date]** |
| **Blood and lymphatic system disorders**[insert SAE term] | **[total for SOC]**[total for SAE term] | **[total for SOC]**[total for SAE term] |
| **Cardiac disorders** |  |  |
| **Congenital, familial and genetic disorders** |  |  |
| **Ear and labyrinth disorders** |  |  |
| **Endocrine disorders** |  |  |
| **Eye disorders** |  |  |
| **Gastrointestinal disorders** |  |  |
| **General disorders and administration site conditions** |  |  |
| **Hepatobiliary disorders** |  |  |
| **Immune system disorders** |  |  |
| **Infections and infestations** |  |  |
| **Injury, poisoning and procedural complications** |  |  |
| **Investigations** |  |  |
| **Metabolism and nutrition disorders** |  |  |
| **Musculoskeletal and connective tissue disorders** |  |  |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** |  |  |
| **Nervous system disorders** |  |  |
| **Pregnancy, puerperium and perinatal conditions** |  |  |
| **Product issues** |  |  |
| **Psychiatric disorders** |  |  |
| **Renal and urinary disorders** |  |  |
| **Reproductive system and breast disorders** |  |  |
| **Respiratory, thoracic and mediastinal disorders** |  |  |
| **Skin and subcutaneous tissue disorders** |  |  |
| **Social circumstances** |  |  |
| **Surgical and medical procedures** |  |  |
| **Vascular disorders** |  |  |
| **Total**  |  |  |

**R2: List of Subjects who Died within the Reporting Period [add dates]**

|  |  |  |  |
| --- | --- | --- | --- |
| **Subject No** | **Cause of Death** | **Treatment arm *(include if known)*** | **Comments** *(****Including causality)*** |
|  |  |  |  |
|  |  |  |  |

**R3: List of subjects who dropped out of the clinical trial(s) in Association with an Adverse Event during the reporting period [add dates]**

|  |  |  |
| --- | --- | --- |
| **Subject No** |  **Treatment arm *(include if known)*** | **Reason for withdrawal *(include adverse event details)*** |
|  |  |  |
|  |  |  |

**R4: Significant Phase 1 Protocol Modifications With Respect to a US Investigational New Drug Application (*include for US trials only*)**

**R5: Significant Manufacturing Changes**

**R6: Description of the General Investigation Plan for the Coming Year With Respect to a US Investigational New Drug Application (*include for US trials only*)**

**R7: Log of Outstanding Business With Respect to a US Investigational New Drug Application (*include for US trials only*)**

*Note: Please refer to the following link for the ICH E2F guidance document which contains detailed information on description of contents:*

https://database.ich.org/sites/default/files/E2F\_Guideline.pdf