***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 Office (JRO)  4th Floor West  250 Euston Road  London NW1 2PG |
| **Contact** | Catherine Maidens  Pharmacovigilance Manager,  UCL Joint Research Office  Phone: 020 3108 9320  Email: c.maidens@ucl.ac.uk |
|  |  |

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

Catherine Maidens, Pharmacovigilance Manager, JRO, UCL

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

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

# Executive summary

*This section should be populated after all the information has been collated and reviewed. It is a concise summary of important information that can be used as a standalone document, covering the following areas:*

* *Report number and reporting period (from Section 1: Introduction)*
* *Scope of the DSUR - details of all trials included (from Section 1: Introduction)*
* *IMP(s) modes of action, indication, therapeutic areas, dose, route and formulation (from Section 1: Introduction)*
* *Marketing status (from Section 2: Worldwide Marketing Approval Status)*
* *Details of the current RSI for the trial and any updates during the reporting year (from Section 4: Changes to Reference Safety information)*
* *Cumulative exposure of IMP to trial subjects and overall safety assessment (from Section 18: Overall Safety Assessment)*
* *Evaluation of Risks (from Section 18.1:* *Evaluation of Risks)*
* *Conclusions (from Section 20: Conclusions)*

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# Acronyms

*Add/delete acronyms as applicable for the report*

|  |  |
| --- | --- |
| AE | Adverse Event |
| DIBD | Development International Birth Date |
| DLP | Data lock point |
| DSUR | Development Safety Update Report |
| FPFV | First Patient First Visit |
| IB | Investigator’s Brochure |
| IMP | Investigational Medicinal Product |
| JRO | Joint Research Office |
| MedDRA | Medical Dictionary for Regulatory Activities |
| RSI | Reference Safety Information |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SmPC | Summary of Product Characteristics |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| UCL | University College London |

# 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), trial acronym(s)/short title(s), EudraCT/IRAS number(s)]*.*

*Add a brief summary of the trial(s) including the indication and patient population being studied, any additional dosing information.*

*Provide the rationale here for submission of multiple DSURs for the investigational drug, if applicable.*

# Worldwide Marketing Approval Status

*Check Protocol/ eMC website for details. State:*

The drug [add IMP name] has a marketing authorisation in the UK/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, any 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 Participant Information Sheet (PIS) in relation to safety issues), any IMP safety information received from the drug supplier, 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:

*Example text:*

***Summary of Product Characteristics (SmPC) for Ketalar (ketamine hydrochloride) 10mg/ml Injection (Pfizer Ltd) PL 00057/0529 – Section 4.8: Undesirable Effects.***

***Investigator’s 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 of IB or Revision of Text (ROT) date from Section 10 of SmPC]. 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(s)]. The following has been updated:

*Add details here of updates (check eMC website), example text:*

Revision of text **20-Sep-2021**:

Change to section 4.4 – Special warnings and precautions for use

Change to section 4.6 – Fertility, pregnancy and lactation

Change to section 6.3 – Shelf life

Change to section 6.6 – Special precautions for disposal and other handling

Change to section 10 - Date of revision of the text

***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 any 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 document if there have been updates to the 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.

The following documents are provided in Appendix 1:

* *Include RSI document in place at the start of the reporting year, and any updated documents described in this section.*

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

This DSUR covers the following ongoing trial(s): [add trial name(s) here].

*Provide brief summary details of the trial(s), e.g. trial population and endpoints/outcomes, status of trial (e.g. recruiting, in follow-up).*

UCL is also sponsoring another trial / other trials which is / are trialling this IMP: [add details on ongoing and completed trials during the reporting period which are covered by other DSURs]. Separate DSUR(s) will be submitted for this/these trials. *(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.

*Or:*

Not Applicable. The IMP(s) are still in the developmental phase.

# Data in Line listings and Summary Tabulations

## Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA) v25.0. *(check version number, this can remain constant throughout the trial or if no version is specified for the trial use the latest version for each DSUR)* was used for the coding of Serious Adverse Events (SAEs) in this DSUR.

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

|  |  |
| --- | --- |
| **IMP** | **Reference Safety Information** |
| Add IMP name | *Examples:*  *SmPC for Ketalar (ketamine hydrochloride) 10mg/ml Injection (Pfizer Ltd),* ***ROT 03Jun2018*** *- Section 4.8: Undesirable Effects*  *or*  *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

There have been XX SARs reported to Sponsor during the DSUR Reporting period. Please see Appendix 5.

*Or:*

No SARs have been reported during the DSUR reporting period.

## Cumulative Summary Tabulations of Serious Adverse Events

A total of XX SAEs have been reported to Sponsor since the start of the trial. Please see Appendix 6.

*Add details describing any SAEs 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

## Completed Clinical Trials

*Include a summary of any clinically important efficacy or safety findings from clinical trials covered by this DSUR that were completed during the reporting period. Or state:*

The following clinical trial(s) using the IMP [add IMP name] was/were completed during the reporting year. There are no significant safety of efficacy findings to report.

*Or:*

No UCL clinical trials using the IMP [add IMP name] were completed during the DSUR reporting period.

## Ongoing Clinical Trials

*Include a summary of any clinically important information that has arisen from ongoing clinical trials covered by this DSUR during the reporting period (e.g., any interim safety analysis, unblinding due to adverse events, etc.). Or state:*

No clinically significant safety or efficacy findings were obtained from the ongoing trial(s) using the IMP [add IMP name] in the reporting period.

## Long-term Follow-up

*Include a summary of any clinically important information that has arisen from any clinical trials in long-term follow-up covered by this DSUR during the reporting period. Or state:*

The following clinical trial(s) using the IMP [add IMP name] is/are in long term follow-up. There are no significant safety findings to report.

*Or:*

There are currently no UCL clinical trials using the IMP [add IMP name] in long-term follow-up.

## Other Therapeutic Use of Investigational Drug

Not applicable. UCL is a non-commercial sponsor and does not conduct other therapeutic use programmes such as expanded access or compassionate use.

## New Safety Data Related to Combination Therapies

*If the DSUR is for an IMP that is also covered in another DSUR for a combination therapy or multi-drug regimen this section should include a summary of important safety findings from the combination therapy DSUR. Or state:*

There are currently no UCL clinical trials using the IMP [add IMP name] as part of a combination therapy or multi-drug regimen.

# Safety Findings from Non-interventional Studies

Include any important safety information regarding the IMP that became available to Sponsor within the reporting period from any non-interventional studies. *Or state:*

There were no safety findings made available to UCL from non-interventional studies.

# Other Clinical Trial/Study Safety Information

Include any important safety information regarding the IMP that became available to Sponsor within the reporting year from any other clinical trial/study sources. *Or state:*

There were no safety findings made available to UCL from other clinical trial/study sources.

# Safety Findings from Marketing Experience

Not Applicable. UCL is a non-commercial sponsor and does not have access to safety information from marketing experience.

*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

Add a summary of any safety findings from non-clinical studies that became available to Sponsor within the reporting year. *Or state:*

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.

# Other DSURs

*If the JRO prepares additional DSURs for the IMP then this section should summarise any significant findings from the other DSURs if the information is not present in other sections of the report. Or state:*

The UCL Joint Research Office have not submitted any additional DSURs detailing the IMP [add IMP name].

# Lack of Efficacy

*This section should contain any available data indicating lack of efficacy, or lack of efficacy relative to established therapies. 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 Serious Adverse Reactions

A total of XX SARs have been reported for the IMP [add IMP name] since the DIBD, *(include details of which treatment arm these are in if applicable/available),* of these XX have been identified as SUSARs. Please See Appendix 8 (R1) for details.

*Or:*

No SARs 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

*For non-US trials state:*

Not Applicable for UK/EEA regional requirements.

*For US trials this section should describe any significant Phase 1 protocol modifications made during the reporting year not previously submitted to the FDA. State:*

There were no significant Phase 1 protocol amendments made during the reporting year that have not been submitted to the Food and Drug Administration as updates to the Investigational New Drug application.

*Or:*

Please see Appendix 8 (R4) for details of Phase 1 protocol modifications that have not been submitted as protocol amendments to the Food and Drug Administration.

*Or:*

The DSUR does not include any Phase 1 trials.

## Significant Manufacturing Changes

*Add any details here of significant manufacturing changes, and discuss any potential safety issues arising, (e.g. new source of IMP), this information should be included in Appendix 8(R5). State:*

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 name].

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

*For non-US trials state:*

Not Applicable for UK/EEA regional requirements.

*For US trials this section should describe the investigational plan for the next year, e.g. list all ongoing trials and any new proposed trials in the pipeline with the same IMP, this information should be included in Appendix 8(R6). State:*

See Appendix 8 (R6) for details.

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

*For non-US trials state:*

Not Applicable for UK/EEA regional requirements.

*For US trials this section should provide a log of any outstanding Sponsor actions/questions from the FDA, this information should be included in Appendix 8(R7). State:*

See Appendix 8 (R7) for details. *(US trials only)*

*Or:*

There is no outstanding business with respect to a US Investigational New Drug application.

## Identification of New Safety Issues with the Investigational Drug (United Kingdom and Canada trials)

*This section should provide details of how the Sponsor reviews all safety data for the IMP, any new safety signals identified (an event with an unknown causal link to the IMP) and if any mitigations have been put in place. Example wording:*

The new events with possible causal links to the IMP are included in ***Appendix 5:* Line Listing of Serious Adverse Reactions (SARs)**. XX of these events have been assessed as SUSARs, [include details of the SUSARs]. These events have been reviewed by the Trial Management Group and Trial Steering Committee/ Independent Data Monitoring Committee.

The following actions/mitigations have been proposed: [include any updates to trial procedures/safety surveillance, IB, Protocol, PIS, etc.] / No actions or mitigations were deemed necessary *(delete as applicable)* following the review of this safety data.

*Or:*

No new events with possible causal links to the IMP have been identified in this reporting year. The Trial Management Group and Trial Steering Committee/ Independent Data Monitoring Committee meet regularly to review safety data.

*Where the IMP is a marketed drug also state:*

As UCL are a non-commercial sponsor, and not the Marketing Authorisation Holder, it does not have access to all worldwide safety information regarding this IMP.

# Late Breaking Information

*This section should summarise any new safety information that arises after the DLP (e.g. clinically significant new SAE reports, action from DMC or sponsor). Or state:*

There is no late breaking information applicable for this DSUR.

# Overall Safety Assessment

*The overall safety assessment should be a concise evaluation of all new safety information presented in the DSUR, and its implication for the ongoing clinical trial(s) and trial population(s). Example wording (amend as appropriate).*

As of [insert data lock point], XX participants have been treated with [add IMP name] on the [add short trial name]. There have been XX SAEs reported of which XX were SARs, and XX of the SARs have been assessed as SUSARs in this DSUR. The trial safety profile remains unchanged and is in line with the current information available in the IB/SmPC *(delete as appropriate)*. The have been no safety issues highlighted in literature articles. Safety data has been reviewed by the Trial Management Group (last meeting [add date]) and Trial Steering Committee/ Independent Data Monitoring Committee (last meeting [add date]) *(delete as appropriate)*, and no new safety concerns have been raised regarding the use of [add IMP name] in the [add trial name].

## Evaluation of Risks

*This section should take into account data related to newly identified safety concerns or providing significant new information relative to previously identified safety concerns. Include detailed description of SARs, any clinically significant toxicities, pregnancy and lactation exposure and outcomes, instances of clinically significant medication errors, overdose, misuse and abuse, any safety issues resulting from other trial procedures.*

*Or state:*

Overall [add IMP name] has been well tolerated. There have been no SARs reported during the reporting period. No new risks to trial subjects have been identified.

## Benefit-Risk Considerations

*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 name] on the [add trial short name] remains unchanged.

# Summary of Important risks

*Detail the most important identified and potential risks to trial participants and how they are mitigated, can be narrative or tabular format. Include risks associated with IMP detailed in protocol, IB/SmPC 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 – this should include the current approved versions and any updated versions described in Section 4]

*Add ‘Not Applicable’ next to all appendices not included in the DSUR:*

1. Cumulative Table of Important Regulatory Advice - *Not applicable*
2. Status of Ongoing and Completed Clinical Trials
3. Cumulative Summary Tabulations of Demographic Data:

* Estimated Cumulative Subject Exposure
* Subject Exposure of IMP by age and gender
* Subject Exposure to IMP by ethnic origin

1. Line Listing of Serious Adverse Reactions
2. Cumulative Summary Tabulations of Serious Adverse Events
3. Scientific Abstracts: *(Included as separate document(s))*
4. Regional Specific Information

* R1: Cumulative Summary Tabulation of Serious Adverse Reactions
* R2: List of Subjects who Died during the Reporting Period
* R3: List of subjects who Dropped out of Clinical Trials in Association with an Adverse Event during the reporting period
* R4: Significant Phase 1 Protocol Modifications With Respect to a US Investigational New Drug Application
* R5: Significant Manufacturing Changes
* R6: Description of the General Investigation Plan for the Coming Year With Respect to a US Investigational New Drug Application
* R7: Log of Outstanding Business With Respect to a US Investigational New Drug Application

***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/ IRAS No: [Add ] |  |  |  |  |  | *Include disease group, age range* |  |  |  |

*For blinded trials add an \* to the number in the ‘subject exposure’ column and include this footnote \*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.*

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 trials 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.

*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 8:* Regional Specific Information**

**R1: Cumulative Summary Tabulation of Serious Adverse Reactions (SARs)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **System Organ Class (SOC)**  Preferred Term  *Delete rows if SOC non required* | **[drug]** *or* **[drug/ placebo/comparator]** *if blinded* | | **[comparator]** *or remove column* | |
| **Total up to [add data lock date]** | **Unexpected?**  **Y/N** | **Total up to [add data lock date]** | **Unexpected?**  **Y/N** |
| **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*)**