**Information about this DSUR template**

This template is available for use by all investigators who are carrying out clinical trials sponsored by the University, if they so wish. However there is no requirement to do so.

All advisory text is highlighted in red and should be deleted before finalising the document. All example text is in **bold**. This text may be altered or deleted as required.

All sections should be completed. For each section, where information is available, the information should be presented concisely; when no information is available, or a DSUR section is not applicable, this should be stated.

Investigators/Study teams completing this report **must** contact CTRG to check for information about other trials/studies ongoing in the University that utilise the same IMP.

If you are using the same IMPs in 2 studies you might want to consider completing one DSUR per IMP.

For further guidance please refer to ICH E2F at this following link

<http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/development-safety-update-report.html>

**This page should be deleted once the DSUR is completed.**

|  |  |
| --- | --- |
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Developmental Safety Update Report

Report Number: [sequential number for report]

Trial Title: Applicable if DSUR is for one single trial. If DSUR covers more than one CTIMP please delete.

|  |  |
| --- | --- |
| Investigational drug(s) |  |
| EudraCT number(s) |  |
| DIBD (delete If not applicable) |  |
| Reporting period [time period covered by this report] |  |
| Date of the report |  |
| Sponsor | University of Oxford |
| Address of Sponsor | Joint Research Office  Boundary Brook House  Churchill Drive  Headington  Oxford, OX3 7LQ |
| Name of Chief Investigator: |  |
| Signature of Chief Investigator: |  |

The data contained in this report are confidential.

Please add the following statement, if applicable:

**This DSUR includes unblinded information.**

# EXECUTIVE SUMMARY

Concise summary of the important information contained in the report. Together with the title page, it should serve as a “stand-alone” document suitable for submission to ethics committees, if required.

Information on the following should be included in the Executive Summary:

* Introduction – report version and reporting period;
* Investigational drug – mode of action, class, indications, dose, route of administration;
* Estimated cumulative clinical trial exposure;
* Marketing authorisation(s) (yes/no) – If yes, number of countries;
* Summary of overall safety assessment;
* Summary of important risks (based on section 15 of the DSUR);
* Actions taken for safety reasons including significant changes to IB;
* Conclusion

All sections must be completed. When no information is available, this should be stated.

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# INTRODUCTION

This section should include:

1. DIBD (**D**evelopment **I**nternational **B**irth **D**ate) if known, or date used as DIBD with explanation of why:

The DIBD is the date of the **first authorisation** of a clinical trial in any country – **worldwide** ‐ for the investigational drug, or a designated date linked to the start of a CT in a country without a formal authorisation process.

Please check with CTRG if using date of first CTA to ensure yours is/was the first

The DIBD of an authorised drug is the IBD (International Birth Date), the date when the product was first authorised in any country worldwide. For EU/EEA harmonized IBD see the link within the Heads of Medicines Agencies (HMA) web page ([http://www.hma.eu/348.html](https://owa.nexus.ox.ac.uk/owa/redir.aspx?C=V-QWwhWTO0OtQPox2jZoUHcY2uFmHNEIF6EeiOfCuTQ0OtBivfsyYwxQfxekOT8ydDyFrhegQqI.&URL=http%3a%2f%2fwww.hma.eu%2f348.html)).

The **data lock point** (DLP) for a DSUR reporting period is the last day (or the last day of the month, see ICH E2F section 2.2.) before the anniversary of the DIBD.

The dates of a **DSUR and PSUR (Periodic Safety Report)** submission can be synchronised by preparing a DSUR based on the PSUR international birthday (IBD). Then the data lock point of the DSUR, the DIBD, is the same as the IBD for the PSUR – the IBD cannot be changed. The first DSUR period must not be longer than 1 year.

1. Reporting period and sequential number of the report
2. Brief description of the drug, e.g., therapeutic class, mode of action, route of administration, formulation
3. Whether the report covers a development programme or a single clinical trial
4. This section should also note the scope of the trials covered by the report (e.g., all trials with the investigational drug, or indication-specific trials):

* A brief description of the indications and populations being studied
* A brief description and explanation of any information that has been excluded (e.g., when written agreements with a partner company do not provide for exchange of all safety data).

# WORLDWIDE MARKETING APPROVAL STATUS

Provide a brief narrative overview including: date of first approval, indication(s), approved dose(s), and where approved, if applicable. If you do not have this information, consider using the following example:

[Name of IMP] **has a marketing authorisation (MA), but we are not the MA holder and do not have access to the worldwide approval status**.

Or, if there is no MA for the product:

[Name of IMP] **does not currently have a marketing authorisation (MA).**

# ACTIONS TAKEN IN THE REPORTING PERIOD FOR SAFETY REASONS

Include a description of significant actions related to safety that have been taken by the Sponsor, regulators, Data and Safety Monitoring Boards or independent ethics committees that could have an impact on the conduct of a specific trial or the whole clinical development programme. Any relevant updates to previous actions should also be summarised in this section. Changes to the Investigator’s Brochure should be discussed separately in the “Changes to Reference Safety Information” section.

Examples of significant actions relating to safety issues include:

* Refusal of authorisation of a clinical trial for ethical or safety reasons;
* Partial or complete clinical trial suspension or early termination of a clinical trial due to lack of efficacy or safety issues;
* Resumption of a clinical trial after suspension;
* Failure to obtain marketing approval for a tested indication;
* Risk management activities, including:
  + Protocol modifications due to safety or efficacy concerns (e.g., dosage changes, changes in study inclusion criteria, intensification of monitoring);
  + Restrictions in study population or indications;
  + Changes to the informed consent document relating to safety issues;
  + Formulation changes for safety reasons;
  + Addition of a special reporting requirement;
  + Issuance of a communication to investigators or healthcare professionals;
  + Plans for new safety trials.
* Important specific advice for safety reasons from a regulatory authority that involves a constraint on development (e.g., requirement to conduct long-term animal studies before initiating a long-term clinical trial; need for thorough QT/QTc study prior to Phase III clinical trials).

In addition, a cumulative listing of advice from regulatory authorities should be provided as a table in an appendix.

* Risk management activities including:
  + Significant restrictions on distribution or introduction of risk minimisation measures;
  + Significant changes in labelling documents that could affect the development programme, e.g., restrictions to indication or population or a new warning;
  + Communications to health care professionals as a result of the above actions;
  + New post-marketing study requirement(s) imposed by regional authorities.

# CHANGES TO REFERENCE SAFETY INFORMATION

This section should list any significant safety-related changes to the IB or other reference safety information (e.g. SmPC) within the reporting period. Record the changes here, including changes to version numbers and date of issue of new IB/SmPC.

Examples include:

* information relating to exclusion criteria
* contraindications, warnings and/or precautions
* serious adverse drug reactions (SARs)
* adverse events of special interest
* interactions
* any important findings from non-clinical studies (e.g., carcinogenicity studies).

List any changes to the protocol and/or trial conduct that resulted from the updated information in the SmPC or IB.

Note a substantial amendment is always required to be submitted if there are changes to the RSI. The timing of this amendment should be considered with regards to the DSUR reporting window. For further details see the answers to Questions 11 and 12 in the MHRA recommended document below.

<http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf>

# INVENTORY OF CLINICAL TRIALS ONGOING AND COMPLETED DURING THE REPORTING PERIOD

This section should provide a brief overview/summary of the clinical trials using this IMP that are being sponsored by the University and are either ongoing or have been completed in the reporting period, including the trial(s) which this DSUR relates to. **Please note** this only applies where you have access to this information. If there are other trials being sponsored by the University with this IMP, which are being conducted in other departments and which will not be included in this DSUR then cross refer to the relevant wording at section 9 below.

Detailed information should be presented in a table (as an appendix if too long to fit easily into the text, see appendix 3). The table below can be used if required.

|  |  |
| --- | --- |
| Study ID / EudraCT number(s) | Insert the protocol number or other identifier. |
| Phase | I, II, II or IV |
| Status | Ongoing/on hold/completed (delete as appropriate) |
| Countries |  |
| Study title (abbreviated) |  |
| Study design | Uncontrolled/controlled, open-label/single blind/double blind, parallel/cross-over (delete as appropriate and include other relevant information, e.g. including treatment arms |
| Dosing regimen |  |
| Study population | age; sex; indication(s); specific patient groups, e.g., trial subjects with impaired renal function or trial subjects resistant to treatment |
| Date of clinical trial start (marked by date of activation of first site) | This might be the first visit of the first participant. |
| Planned enrolment |  |
| Planned date of completion |  |
| Estimates of cumulative numbers of exposed subjects (based upon total number of patients recruited) |  |

If there are other trials being sponsored by the University with this IMP, which are being conducted in other departments and which will not be included in this DSUR then the following wording can be used:

**This DSUR only relates to** [Study ID]**. The University of Oxford is also conducting (an)other trial(s) with this investigational product but a separate DSUR will be produced for this/these trial(s) as it is not possible to combine data from these trials.**

# ESTIMATED CUMULATIVE EXPOSURE

## CUMULATIVE SUBJECT EXPOSURE IN THE DEVELOPMENT PROGRAMME

This section should include the following information, in tabular format (see examples below).

* Cumulative number of subjects from ongoing and completed clinical trials listed above; the number exposed to the investigational drug, placebo, and/or active comparator(s) since the DIBD.
* Cumulative number of subjects exposed to the investigational drug from ongoing and completed clinical trials, sub-grouped by age range, sex, and racial group for the development programme when the data are available;
* Demographic characteristics for a single trial if the trial is of particular importance (e.g. a pivotal Phase II I trial).

The specific categorisation of age might be dependent on the subject population and indication.

This section should also include an explanation of the Sponsor’s rationale for selecting the method to estimate subject exposure, and the limitations of that method, based on the points above.

Table 1: Estimated cumulative subject exposure

|  |  |  |
| --- | --- | --- |
|  | | **Number of subjects** |
| **Treatment** | Drug |  |
| Comparator |  |
| Placebo |  |
| Total |  |

For blinded trials, the following statement can be used:

**The study remains blinded and the numbers of subjects have been estimated from the randomisation scheme, for subjects randomised up to** [insert date]

Table 2: Cumulative subject exposure to investigational product from completed clinical trials by age and sex

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | | **Number of subjects** | | |
|  | | **Male** | **Female** | **Total** |
| **Age range (years)** |  |  |  |  |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

Table 3: Cumulative subject exposure to investigational product from completed clinical trials by racial group

|  |  |
| --- | --- |
| **Racial group** | **Number of subjects** |
| Asian |  |
| Black |  |
| Caucasian |  |
| Other |  |
| Unknown |  |
| Total |  |

For blinded trials, the following statement can be used:

**Given that the trial remains blinded, we cannot provide demographic data by treatment group.**

## PATIENT EXPOSURE FROM MARKETING EXPERIENCE

**This is not applicable as this is an investigator-led study sponsored by a non-commercial Sponsor.**

# DATA IN LINE LISTINGS AND SUMMARY TABULATIONS

## REFERENCE INFORMATION

Briefly describe how events have been coded and assessed. If a coding dictionary was used, specify the version(s) used and, if applicable, the document and version used as Reference Safety Information for determining expectedness (e.g. IB, SmPC).

## LINE LISTINGS OF SERIOUS ADVERSE REACTIONS DURING THE REPORTING PERIOD

This section of the DSUR should summarise how case reports were selected for inclusion in the line listings. In addition please provide a summary of the SAEs, SARs and SUSARs that have occurred in this reporting period. This section should not serve to provide analyses or conclusions based on the SARs.

The line listings should be provided in an appendix.

Where possible, the line listing(s) should include each subject only once, regardless of how many SAR terms are reported for the case. If there is more than one reaction, they should all be mentioned but the case should be listed under the most serious adverse reaction (sign, symptom or diagnosis). It is possible that the same subject could experience different SARs on different occasions (e.g. weeks apart during a clinical trial). Under such circumstances, the SARs can be listed separately, and a single subject can be included in a line listing more than once. See Appendix 4 for the information to be included in the line listings.

## CUMULATIVE SUMMARY TABULATIONS OF SERIOUS ADVERSE EVENTS

**Please refer to the Serious Adverse Events cumulative summary table at the end of this document (see Appendix 5).**

Please provide an explanation for any omitted data.

This section should not serve to provide analyses or conclusions based on the SAEs.

# SIGNIFICANT FINDINGS FROM CLINICAL TRIALS DURING THE REPORTING PERIOD

If this section is not applicable the following wording may be used;

**This section is not applicable**

If there are other trials being sponsored by the University with this IMP, which are being conducted in other departments and which will not be included in this DSUR then the following wording can be used:

**The University of Oxford is also conducting (an)other trial(s) with this investigational product but a separate DSUR will be produced for this/these trial(s) as it is not possible to combine data from these trials.**

## COMPLETED CLINICAL TRIALS

Please provide a brief summary of clinically important emerging efficacy and safety findings obtained from final study reports of clinical trials **completed** during the reporting period. This information can be presented in narrative format or as a synopsis.It could include information that supports or refutes previously identified safety issues, as well as evidence of new safety signals.

## ONGOING CLINICAL TRIALS

Please provide a concise summary of any clinically important information that has arisen from **ongoing** clinical trials including safety issues that are the same or similar to those previously identified (e.g. learned through interim safety analyses or as a result of unblinding of subjects with adverse events). It could include information that supports or refutes previously identified safety issues, as well as evidence of new safety signals.

## LONG-TERM FOLLOW-UP

Where applicable, this section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs, particularly advanced therapy products (e.g. gene therapy, cell therapy products and tissue engineered products). When the development programme is completed and long-term follow-up is the only ongoing activity generating data for the DSUR, this could be the only section where new information is presented.

If no long term follow-up required the following statement should be used;

**This section is not applicable**

## OTHER THERAPEUTIC USE OF INVESTIGATIONAL DRUG

This section is not likely to be applicable for studies sponsored by the University of Oxford, but check the guidance below.

**If applicable;**

This section of the DSUR should include clinically important safety information from other University-sponsored programmes that follow a specific protocol (e.g. compassionate use programmes, expanded access programmes, a particular patient use), with solicited reporting as per ICH E2D (see <http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf>).

If not applicable the following statement could be used;

**This section is not applicable as we do not have access or compassionate use programmes**

## NEW SAFETY DATA RELATED TO COMBINATION THERAPIES

If there is a separate DSUR for a multidrug regimen or fixed combination product containing the single investigational drug that is the subject of this DSUR, relevant findings from that DSUR should be summarised in this section.

If this DSUR is for a multidrug regimen or fixed combination product, important safety information arising from trials on the individual components should be briefly summarised here.

Alternatively, the information specific to the combination can be incorporated into a separate section(s) of the DSUR for one or all of the individual components of the combination

For further information, see ICH E2F/section 2.5.

# SAFETY FINDINGS FROM NON-INTERVENTIONAL STUDIES

If not applicable the following statement could be used

**This is not applicable as we are not conducting any non-interventional studies.**

# OTHER CLINICAL TRIAL/STUDY SAFETY INFORMATION

Please provide a brief summary of **relevant safety information** from any other trial, such as pooled analyses or meta-analyses that becomes available during the reporting period. If not applicable the following statement could be used:

**This is not applicable as we have not received any relevant information from other trials.**

# SAFETY FINDINGS FROM MARKETING EXPERIENCE

If it is possible to contact the holder of the marketing authorisation for this information then every effort must be made to do so.

Insert the applicable statement:

[Name of IMP] **is not a marketed product and hence this section is not applicable.**

or

**We are not aware of any findings from the marketing experience.**

# NON-CLINICAL DATA

In this section include all relevant major safety findings (**not** implications of these findings) from any non-clinical *in vivo* and *in vitro* studies ongoing or completed during the reporting period. If you do not have access to this information you could use the following statement:

**This section is not applicable as we have not conducted non-clinical studies and do not have access to information from such studies.**

# LITERATURE

Please provide a summary of new and significant safety findings relevant to the investigational drug that were either published in the scientific literature or available as unpublished manuscripts **during the reporting period**. This section should include information from non-clinical and clinical studies and, if relevant and applicable, information on drugs of the same class. It should also summarise significant new safety information presented at a scientific meeting and published as an abstract. The information can be presented in the table below. Attach copies of abstracts in an appendix.

If no new information is available you could use the following statement;

**No significant new safety findings have emerged in the literature for** [Name of IMP(s)] or their use in combination *(delete if not applicable)* **during the reporting period**

# OTHER DSURS

If there are multiple DSURs for this IMP (e.g. covering different indications, development programmes or formulations), summarise significant findings from other DSURs in this section. *The Investigator should contact CTRG for information on any other DSUR submitted in the period for the same IMP. It is possible though unlikely that related information may need to be included*

The information can be presented in the table below.

|  |  |  |
| --- | --- | --- |
| Trial | DSUR reference No. | Summary of significant findings |
|  |  |  |
|  |  |  |
|  |  |  |

If there are no other DSURs for this IMP, the following statement can be used.

**This section is not applicable, as there are no other DSURs submitted by the University of Oxford for [name of IMP] in this reporting period.**

# LACK OF EFFICACY

If applicable, provide a summary of any data indicating a lack of efficacy, or lack of efficacy relative to established therapies, for the IMP. If not applicable, the following statement could be used.

**Not applicable for this reporting period.**

# REGION-SPECIFIC INFORMATION

This section is applicable only for multi-centre studies that have sites located in different regions or countries. If applicable, the information for specific regions can be provided in an appendix. Examples include:

* Cumulative summary tabulation of SARS (refer to Appendix 4). This should include all SARs from the start of the trial, not just for the reporting period.
* List of subjects who died during the reporting period.

The list of subjects who died during participation in the clinical trials should include the following information at a minimum: case number, assigned treatment (could still be blinded), and cause of death of each subject. Any safety issues identified from a review of these deaths should be addressed in Section 18 of the DSUR as appropriate.

* List of subjects who dropped out of clinical trials in association with an adverse event during the reporting period

This list should include all subjects who dropped out of clinical trials in association with adverse events during the reporting period, whether or not thought to be drug-related. Any safety issues identified from a review of these withdrawals should be addressed in Section 18 of the DSUR as appropriate.

* Significant manufacturing changes

This section should include a summary of significant manufacturing or microbiological changes during the reporting period and discuss potential safety issues arising from these changes in Section 18 of the DSUR, if applicable.

* If applicable (where IMPs are being developed by University researchers) a description of the general investigation plan for the next year

For single-centre studies use the following text:

**This section is not applicable for this study.**

# LATE-BREAKING INFORMATION

This section should summarise information on potentially important safety findings that arise after the data lock point but while the DSUR is in preparation. Examples include clinically significant new case reports, important follow-up data, clinically relevant toxicological findings and any action that the sponsor or co-sponsors, data monitoring committee, or a regulatory authority has taken for safety reasons. Section 18 should also take account of this new data as appropriate. If not applicable, the following statement can be used.

**There was no significant safety information between the data lock point for this report and the time of submission.**

# OVERALL SAFETY ASSESSMENT

## EVALUATION OF THE RISKS

Provide an evaluation of risks to trial subjects, with particular emphasis on interpretation of data relating to newly identified safety concerns or new information relating to previously identified safety concerns and any other safety information.

When relevant, the following points should be considered:

* meaningful changes in previously identified reactions (e.g., increased frequency or severity, outcome, specific at-risk populations)
* newly identified safety issues (detailed description of adverse reaction; associated laboratory values; risk factors; relationship to dose, duration, time course of the treatment; reversibility; factors that could be useful in predicting or preventing reactions);
* particular emphasis should be placed on symptoms, signs, and laboratory evidence of newly and previously identified, clinically significant:
  + Hepatotoxicity
  + Cardiovascular effects including QT interval prolongation and results from thorough QT/QTc studies
  + Bone marrow toxicity
  + Renal toxicity
  + Central nervous system toxicity
  + Immunogenicity and hypersensitivity
  + Reactive metabolites
* deaths that are an outcome of an adverse reaction;
* withdrawals due to safety reasons;
* any specific safety issues related to special populations, such as the elderly, children, patients with hepatic or renal impairment, or any other at risk groups (e.g. slow or fast metabolisers);
* positive and negative experiences during pregnancy or lactation;
* overdose and its treatment;
* drug misuse and abuse;
* experience with long-term treatment;
* risks associated with protocol procedures, including administration of the investigational drug and diagnostic procedures;
* evidence of clinically significant medication errors;
* potential impact of significant new safety issues identified with another drug in the same class; and
* drug–drug and other interactions

Also consider/discuss other relevant findings such as non-clinical research, manufacturing issues, lack of efficacy and lack of patient compliance, when available.

## BENEFIT-RISK CONSIDERATIONS

Provide a concise statement on the perceived balance between risks identified from cumulative safety data and anticipated efficacy or benefits. Also note whether there have been any changes in this balance since the last DSUR. This section is not intended to be a full benefit-risk assessment of the IMP.

# SUMMARY OF IMPORTANT RISKS

This section should provide a concise, cumulative, issue-by-issue list of important identified and potential risks (e.g. those that might lead to warnings, precautions, or contraindications on labelling). Examples of risks include toxicities known to be associated with a particular molecular structure or drug class, or concerns based on accumulating non-clinical or clinical data. Evaluate and summarise each risk annually, with consideration to current knowledge and highlighting new information. The appropriate level of detail is likely to be dependent on the stage of the drug development. For example, summaries covering drugs in early development might include information on individual cases, whereas in later development, as more knowledge and perspective are gained the information on each risk might be less detailed.

Risks that have been fully addressed or resolved should remain in the summary and be briefly described (e.g. findings from toxicology studies or early clinical trials that were not borne out by later clinical data).

The information in this section can be presented as a narrative or in tabular form (see Appendix 6 for example of each format).

# CONCLUSIONS

Provide a brief conclusion describing 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 in the clinical development programme.

# APPENDICES TO THE DSUR

|  |  |
| --- | --- |
| **Documents** | 🗸/Not applicable |
| 1. Investigator Brochure or SmPC (include version and date) |  |
| 1. Cumulative Table of important regulatory advice |  |
| 1. Status of ongoing and completed clinical trials |  |
| 1. Line listing of serious adverse reactions (SARs) |  |
| 1. Cumulative summary tabulations of serious adverse events (SAEs) |  |
| 1. Scientific abstracts |  |

### APPENDIX 1

(this should be renumbered as appropriate)

**INVESTIGATOR BROCHURE VERSION NUMBER AND DATE**

**OR**

**SMPC, DATE LAST UPDATED**

### APPENDIX 2 - CUMULATIVE TABLE OF IMPORTANT REGULATORY ADVICE

(this should be renumbered as appropriate)

*To be completed by the CI/PI. This could include any serious breaches that may have been reported and any guidance received on implementation of resulting CA(corrective action)/PA(preventive action), any direct queries to the MHRA and their response, requests for alterations to amendment requests in order to gain further approval.*

|  |  |  |  |
| --- | --- | --- | --- |
| **Date** | **Query** | **Regulatory Response** | **Application to the trial** |
|  |  |  |  |
|  |  |  |  |
|  |  |  |  |

### APPENDIX 3 - STATUS OF ONGOING AND COMPLETED CLINICAL TRIALS

(this should be renumbered as appropriate)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Clinical Trial Short Term** | **Clinical Trial Full Title** | **EudraCT No.** | **Phase** | **IMP regimen & Comparators (inc. dose)** | **Study Population** | **Study design** | **Start Date** | **Ongoing/ Completed** | **Stop Date** |
|  |  |  |  |  |  |  |  |  |  |
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### APPENDIX 4 - LINE LISTINGS OF SERIOUS ADVERSE REACTIONS (SARS)

(this should be renumbered as appropriate)

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **EudraCT number** | **Case ID/**  **Subject number†** | **Country**  **Gender**  **Age** | **SARs** | **Outcome** | **Date of onset‡**  **Time to onset‡** | **Suspect Drug** | **Daily dose**  **Route**  **Formulation** | **Dates of treatment**  **Treatment duration** |
|  |  |  |  |  |  |  |  |  |
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†Study/centre/patient

‡ ‘Primary’ SAR only

### APPENDIX 5 - SERIOUS ADVERSE EVENTS CUMULATIVE SUMMARY

(this should be renumbered as appropriate)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **System/organ/class**  **Preferred term** | **Total up to [insert date]** | | | |
|  | **Study drug** | **Blinded** | **Active comparator** | **Placebo** |
|  |  |  |  |  |
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### APPENDIX 6 - SUMMARY OF IMPORTANT RISKS

(this should be renumbered as appropriate)

**Tabular format:** *(see example of required information below)*

|  |  |  |  |
| --- | --- | --- | --- |
| Risk | Non-clinical data | Clinical data | Actions |
| *Nephrotoxicity* | *Nephrotoxicity in rats and rabbits at doses of 20 and 60 mg/kg/d, respectively* | *Drug Z is a para-aminoglycolate, in drug class structurally similar to aminoglycosides. Nephrotoxicity well known.*  *Phase I: A 100 mg dose was dropped from further development because of increases in creatinine and proteinuria in normal volunteers.*  *Phase II: Increases in creatinine >1.25 but <1.5 times baseline were observed in 7.8%, 6.8%, and 5.8% of subjects in the 50, 25, and 10 mg treatment groups, respectively, versus 6.3% in the placebo group.*  *Increases in creatinine >1.5 times baseline were observed in 1.5%, 0.5%, and 1.9% of subjects in the 50, 25, and 10 mg treatment groups, respectively, versus 2.7% in the placebo group.* | *In Phase III trial (301), serum creatinine, eGFR, blood urea nitrogen, and urinalysis monitored at baseline, Weeks 1, 4, 12, and 48.*  *24-hour urinary protein excretion is determined in subjects who develop >2+ or proteinuria by dipstick.* |
| *Hepatotoxicity* | *Rat study KR-102: 2 of 8 rats in the highest dose group (60 mg/kg/d) developed centrilobular necrosis. At lower doses, no rats had evidence of hepatotoxicity.*  *No hepatotoxicity seen in rabbits at doses < 60 mg/kg/d.* | *With frequent monitoring of ALT, AST, alkaline phosphatase, and bilirubin in the Phase I and II trials, no consistent pattern of laboratory abnormalities emerged suggestive of liver injury.* | *Routine monitoring in ongoing Phase III study (301): ALT, AST, alkaline phosphatase, and bilirubin monitored at baseline, Weeks 1, 4, 12* |