**DEVELOPMENT SAFETY UPDATE REPORT**

**STUDY TITLE** *<insert study title here*

Investigational Medicinal Product:

Trial EudraCT Number(s):

Report Number:

Period covered:

Sponsor(s):

Address(es):

Manufacturer:

Date:

Signed ……………………………

[name, title]

Address:

Note: This Development Safety Update Report contains confidential

information. This report includes unblinded adverse event data.

**EXECUTIVE SUMMARY**

*Very briefly describe the nature of the Investigational Medicinal Product (IMP) and its use in the study(ies) concerned, safety concerns ongoing and justification of study(ies) continuation including management of risks.*

*Should serve as a stand-alone document – concise summary of information contained within the report.*

* *nth report over which period of time*
* *Brief description of IMP, mode of action, indication, dose, administration method*
* *Marketing approval – if available and where*
* *Summary of safety report (section 18)*
* *Summary of risks (section 19)*
* *Any urgent safety measures taken in response to IMP use*
* *Brief conclusion*

*Guidance Note – please do not remove headings. If information is not available or not applicable, this should be stated.*

*Purple text is there for guidance and should be removed prior to submission.*

*Blue text is used for examples and should be replaced prior to submission.*

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# 1. Introduction

* *No. of DSUR and reporting period*
* *Background to IMP – as bullet-point 2 in executive summary*
* *Objective of study (e.g. safety, efficacy etc.)*
* *Patient population, indication being studied*
* *Additional information (e.g. if certain data cannot be provided)*

# 2. Worldwide Marketing Authorisation Status

*As bullet-point 3 in executive summary.*

*Include approval date(s), indications, dose if applicable.*

# 3. Actions Taken in the Reporting Period for Safety Reasons

*List actions such as Urgent Safety Measures (USMs) and/or protocol revisions in relation to safety issues e.g. due to Data Monitoring Committee (DMC) conclusions, as a result of adverse events etc. Any such protocol revisions should be detailed.*

# 4. Changes to Reference Safety Information

*Detail any revisions to the Investigator’s Brochure (IB) or the Summary of Product Characteristics (SPC).*

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

Appendix 3 - Status of ongoing and completed clinical trials

*List known trials worldwide and include recruitment figures/targets if known. Guidance says ....‘CTs ongoing and completed by the Sponsor’ (and presumably the same IMP)*

*Use one table per clinical study.*

# 6. Estimated Cumulative Exposure

# 6.1 Cumulative Subject Exposure in the Development Program

Appendix 4 Table 1 - Estimated Cumulative Subject Exposure

Appendix 4 Table 2 - Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Age and Sex

Appendix 4 Table 3 - Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Age and Sex

*Exposure can only be estimated based on randomisation scheme, if study blinded and ongoing.*

*Include demographic data of subjects – if important to the study. Use tables 1-3 as appropriate.*

# 6.2 Patient Exposure from Marketing Experience

*This section should be completed if drug marketed by Sponsor, therefore ‘not applicable’ for ACCORD studies.*

# 7. Data in Line Listings and Summary Tabulations

# 7.1 Reference Information

*State data coding method and method of presentation of safety data eg.*

* *line listings in table format*
* *MedDRA version [number] used for coding serious adverse events*
* *SPC or IB [version] used as reference document for determination of ‘expectedness’ for all (serious) adverse events.*

# 7.2 Line Listings of Serious Adverse Reactions (SARs) during the Reporting

# Period

Appendix 5 - Interval Line Listings of Serious Adverse Reactions

*This information can be provided by ACCORD and any unblinded information will be incorporated into the report once it has been completed by the CI.*

# 7.3 Cumulative Summary Tabulations of Serious Adverse Events

Appendix 6 – Cumulative summary of Serious Adverse Events

*This information can be provided by ACCORD and any unblinded information will be incorporated into the report once it has been completed by the CI.*

# 8. Significant Findings from Clinical Trials during the Reporting Period

# 8.1 Completed Clinical Trials

*If applicable, summarise any safety concerns that have emerged.*

# 8.2 Ongoing Clinical Trials

*Summarise any clinically important information that has arisen (e.g. through interim safety analyses or through unblinding).*

# 8.3 Long-Term Follow-up

*If applicable, provide information on long-term follow-up.*

# 8.4 Other Therapeutic Use of Investigational Drug

*If applicable, summarise any clinically important information from other studies using the same IMP and conducted by the sponsor.*

# 8.5 New Safety Data Related to Combination Therapies

*The following table shows examples of how to compose the DSUR if IMP is used in combination or as part of a multi-drug regimen:*

|  |  |
| --- | --- |
| ***Multi-drug therapy used in clinical trial(s)*** | ***DSUR*** |
| *Investigational drug (A) + marketed drug(s) (X, Y, Z)* | *Either a single DSUR focusing on (A+X+Y+Z)*  *or*  *A single DSUR focusing on (A)*  *including data on the multi-drug therapy* |
| *Two investigational drugs (A) + (B)* | *Either a single DSUR focusing on (A + B)*  *or*  *Two separate DSURs (A) and (B), each including data on the multi-drug therapy* |
| *Two (or more) marketed drugs as an investigational drug combination (X, Y, Z)* | *A single DSUR focusing on the multi-drug therapy (X + Y + Z)* |

*Summarise any important safety findings from the IMP in combination.*

*This section should only be completed if IMP is not used as a monotherapy.*

# 9. Safety Findings from Non-interventional Studies

*If applicable, summarise any relevant safety information from any observational or epidemiological studies during the reporting period.*

# 10. Other Clinical Trial/Study Safety Information

*If applicable, summarise any relevant safety information from other clinical trial sources that become available to the sponsor during the reporting period.*

# 11. Safety Findings from Marketing Experience

*If applicable, summarise any key safety findings that have become available to the sponsor during the reporting period. Eg changes to IB, labels etc. This applies to approved use, off-label use, special populations, medication errors, overdose and abuse.*

# 12. Non-clinical Data

*If applicable, summarise any major safety findings from any non-clinical in vivo or in vitro studies which are ongoing or completed during the reporting period.*

# 13. Literature

*Summarise any new clinical or non-clinical safety information that has become available during the reporting period. This includes scientific literature and presentations at scientific meetings. A copy of the abstract should be provided if available.*

# 14. Other DSURs

*Summarise any significant findings from other DSURs prepared by the sponsor using the same IMP. If possible, any significant findings from DSURs prepared by other sponsors using the same IMP should be reported.*

# 15. Lack of efficacy

*If applicable, provide any data relating to lack of efficacy of IMP.*

# 16. Region-Specific Information

# 16.1 Cumulative Summary Tabulation of Serious Adverse Reactions

*Refer to 7.2 if the data is the same.*

# 16.2 List of Subjects Who Died during the Reporting Period

*List all subjects who died during participation in the trial, include subject ID, assigned treatment (if known), cause of death.*

# 16.3 Subjects who Dropped Out in Association with any Adverse Event in the

# Reporting Period

*List all subjects who dropped out of trial in association with an Adverse event, whether IMP-related or not.*

# 16.4 Significant Phase I Protocol Modifications

*If applicable, describe any significant Phase I protocol modifications made if not submitted as a protocol amendment.*

# 16.5 Significant Manufacturing Changes

*If applicable, summarise any significant changes during the reporting period and any potential safety issues arising. Refer to section 4 if necessary.*

# 16.6 Description of the General Investigation Plan for the Coming Year

*Discuss recruitment plans for the next period.*

# 17. Late-Breaking Information

*If applicable, summarise any potentially important safety findings arising after the DSUR data lock point but while DSUR is still being prepared. Eg. new case reports, follow-up data, any actions taken by sponsor, DMC or regulatory authorities for safety reasons. Section 18 should reflect any findings.*

# 18. Overall Safety Assessment

*Provide a concise evaluation of all new, relevant safety information obtained during the reporting period relative to precious knowledge of IMP. This is not a repetition of previously detailed information but an interpretation of it and its implication for trial subjects.*

# 18.1 Evaluation of the Risks

*Summarise risks with particular emphasis on data related to newly identified safety concerns or information. Points to consider:*

* *newly identified safety issues (detailed description of adverse events or reactions; 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);*
* *symptoms, signs, and laboratory evidence of newly and previously identified clinically significant toxicities, for example:*
* *meaningful changes in previously identified adverse reactions (e.g., increased frequency or severity, outcome, specific at-risk populations);*
* *deaths that are an outcome of an adverse event;*
* *study drug discontinuations because of adverse events, including abnormal laboratory values or investigations;*
* *drug–drug and other interactions;*
* *important non-clinical safety findings;*
* *manufacturing issues that could affect risk;*
* *lack of efficacy where this would place trial participants at risk;*
* *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);*
* *pregnancy and lactation exposure and outcomes;*
* *safety findings arising from experience with long-term treatment;*
* *evidence of clinically significant medication errors;*
* *evidence of lack of patient compliance;*
* *experience with overdose and its treatment;*
* *occurrences of drug misuse and abuse;*
* *any safety issues resulting from procedures required by the protocol (e.g., bronchoscopy, biopsy, central line insertion) or associated with the conduct or design of a particular study (e.g., inadequate subject monitoring schedule, excessive period without active treatment); and*
* *potential impact of significant new safety issues identified with another drug on the same class.*

# 18.2 Benefit-risk Considerations

*Provide a concise summary of identified risks in relation to anticipated benefits and briefly discuss justification for continuation of the study.*

# 19. Summary of Important Risks

*Concise, cumulative list of important known or identified risks and all actions taken to mitigate risks. Each risk is re-evaluated annually (so any resolved risks should remain in the summary). Can be provided in the form of a narrative or a table.*

*See Appendix 8 for example table.*

# 20. Conclusions

*The conclusion should 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 in the clinical development programme.*

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1. Investigator’s Brochure
2. Cumulative Table of Important Regulatory Requests
3. Status of Ongoing and Completed Clinical Trials
4. Cumulative Summary Tabulations of Demographic Data
5. Line Listings of Serious Adverse Reactions
6. Cumulative Summary Tabulation of Serious Adverse Events
7. Scientific Abstracts (if relevant)
8. Summary of important risks

**Appendix 3 Status of ongoing and completed clinical trials**

|  |  |
| --- | --- |
| **Study Title** |  |
| **CTA No** |  |
| **Phase** | *I, II, III, IV* |
| **Single or multicentre** | *Provide details* |
| **Stage** | *Ongoing, completed* |
| **Design** | *Uncontrolled, controlled, open, single blind, double blind, parallel, cross-over, etc., including treatment arms* |
| **Dose of IMP and comparator** |  |
| **Study Population** | *Age; sex; indication(s); specific patient groups* |
| **Start date and FPFV** |  |
| **Recruitment target and recruitment to date** | *Current recruitment figures, whether ongoing or completed* |

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

Table 1 - Estimated Cumulative Subject Exposure

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

Table 2 - Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Age and Sex

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

Table 3 – Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Racial Group\*

|  |  |
| --- | --- |
| **Racial Group** | **Number of Subjects** |
| **Asian** |  |
| **Black** |  |
| **Caucasian** |  |
| **Other** |  |
| **Unknown** |  |
| **Total** |  |

\*Data from completed studies to date

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial reference**  **(EudraCT**  **number)** | **Trial**  **subject**  **number** | **Country**  **in which**  **case**  **occurred** | **Subject**  **age** | **Subject sex** | **IMP dose** | **IMP route of admin** | **Dates of treatment**  *(if not known, best estimate of duration of treatment)* | **Date of onset of SAR**  *(If not known, best estimate of time to onset from therapy*  *initiation* | **Body**  **System** | **SAR details**  ***(medDRA should be used)*** | **Outcome of SAR** | **Comments** | **Unblinding** |
| *Example* | *001* | *UK* | *46* | *F* | *0.5mg* | *Oral* | *15/06/10 to*  *28/11/10* | *14/07/2010* | *CNS* | *Dizziness and numbness right arm* | *Resolved* | *None* | *NA* |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
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|  |  |  |  |  |  |  |  |  |  |  |  |  |  |

**Appendix 5 Line Listings of Serious Adverse Reactions**

TO BE COMPLETED BY ACCORD IF RELEVENT

**Total number of SARs reported during this DSUR reporting period:**

**Cumulative Total number of SARs reported:**

**Appendix 6 Cumulative Summary Tabulation of Serious Adverse Events**

TO BE COMPLETED BY ACCORD IF RELEVENT

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **System organ class** | **Total up to dd-mmm-yy** | | | |
| Preferred term | Study drug | Blinded | Active comparator | Placebo |
| **Investigations** | **18** | **4** | **7** | **2** |
| Alanine aminotransferase increased | 9 | 2 | 4 | 1 |
| Aspartate aminotransferase increased | 9 | 2 | 3 | 1 |
| **Nervous system disorders** | **2** | **2** | **4** | **7** |
| Syncope | 2 | 2 | 4 | 7 |

**Total number of SAEs reporting during this DSUR reporting period:**

**Cumulative Total number of SAEs reported:**

**Appendix 7 Scientific abstracts**

**Appendix 8 Summary of Important Risks**

|  |  |  |  |
| --- | --- | --- | --- |
| New or updated risks are denoted with an asterisk. Risk | Non-clinical data | Clinical data | Actions |
| 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, and 48. |