**DEVELOPMENT SAFETY UPDATE REPORT**

**STUDY TITLE**

 **Investigational drug(s): Report Number: XX**

**Period covered: XXXX – XXXX**

|  |  |
| --- | --- |
| **EudraCT number:** |  |
| **Sponsor reference:** |  |
| **REC reference:** |  |
| **Details of Sponsor:** | **University Hospitals Bristol and Weston NHS Foundation Trust****Research & Development****East wing, Ground Floor,** **St James Court,** **Cannon Street,** **Bristol,** **BS1 3LH****Email address:** **R&DSponsorship@UHBW.nhs.uk****Telephone number: 0117 342 0233** |
| **Chief Investigator:** |  |
| **Details of person completing the report:** | **Name****Job title/role in study****Email address****Telephone number** |

**This Development Safety Update Report (DSUR) contains confidential information and should not be distributed without permission from the Sponsor**

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**Chief Investigator Signature Date**

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**Sponsor representative Signature Date**

**If applicable, please insert a cautionary statement that the DSUR includes unblinded information.**

All sections must be completed; where no information is available or the section is not applicable, this must be stated. All sections in green highlighted text are guidance taken from the ICH E2F Guidelines and should be deleted when completing the template.

Full comprehensive guidance on information to insert into each section can be found: <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf>

**EXECUTIVE SUMMARY**

Provide a concise summary of the important information contained in the report

To include the following:

 • Introduction – report number and reporting period;

 • Investigational drug(s) – mode(s) of action, therapeutic class(es), indication(s), dose(s), route(s) of administration, formulation(s);

• Estimated cumulative exposure of clinical trial subjects;

• Marketing approval(s)? (yes/no) – If yes, number of countries; ICH guideline E2F on development safety update report EMA/CHMP/ICH/309348/2008 Page 10/35

 • Summary of overall safety assessment (based on section 18 of the DSUR);

• Summary of important risks (based on section 19 of the DSUR);

• Actions taken for safety reasons including significant changes to Investigator’s Brochure (IB) as applicable;

• Conclusions.

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1. **Introduction**

This section should include:

• Development International Birth Date (DIBD) or IBD (as applicable) –e.g. date of Clinical Trials Authorisation (CTA) approval (date DSUR starts).

• Reporting period and sequential number of the report;

• Investigational drug(s) – mode(s) of action, therapeutic class(es), dose(s), route(s) of administration, formulation(s);

• A brief description of the indication(s) and population(s) being studied;

• A short summary of the scope of the clinical trials covered by the report (e.g., all trials with the investigational drug, indication-specific trials, trials with combination products);

• A brief description and explanation of any information that has not been included in the DSUR

• The rationale for submission of multiple DSURs for the investigational drug, if applicable.

1. **Worldwide Marketing Approval Status**

This section is only applicable where Sponsor is Marketing Authorisation Holder for the Investigational Medicinal Product (IMP).

1. **Actions Taken in the Reporting Period for Safety Reasons**

Include a description of **significant actions** related to safety that have been taken during the reporting period by the sponsor, regulators, data monitoring committees (DMC) or ethics committees that had an impact on the conduct of a specific clinical trial(s). The reason(s) for each action should be provided if known

NB. Examples of significant actions can be found on page 12 of the ICH E2F guideline <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf>

Relevant updates to previous actions should also be summarised in this section (e.g., resumption of a clinical trial after suspension) if applicable.

This section should also summarise requests from regulatory authority(ies) that place a specific limitation on current or future development,

Please note if no action has been taken please note when the DMC (or applicable) met and that no significant safety concerns were identified.

1. **Changes to Reference Safety Information**

Note current Reference Safety Information (e.g. Summary of Product Characteristics version number and date)

List any significant safety-related changes to the IB or other reference safety information within the reporting period e.g. information relating to exclusion criteria, contraindications, warnings, precautions, serious adverse drug reactions, adverse events of special interest interactions, and any important findings from non-clinical studies (e.g., carcinogenicity studies).

1. **Inventory of Clinical Trials Ongoing and Completed during the Reporting Period**

Provide a brief overview of the clinical trial(s) ongoing and completed in the reporting period.

Where multiple trials are being reported on a single DSUR detailed information to be presented in a table as an appendix to this report.

1. **Estimated Cumulative Exposure**
* Describe dosage regime in trial(s).
* Where several trials are being reported and there are important differences among trials in dose, route of administration, or patient population, these differences can be noted in the tables, or separate tables can be considered;
* When there are substantial differences in time of exposure between subjects randomised to the investigational drug and comparator(s), or disparities in length of exposure between clinical trials, it can be useful to express exposure data in subject-time (subject-days, -months, or - years);
* If the summary tabulations of SAEs are presented by indication, the exposure data should also be presented by indication, when available;
* For marketed drugs that are under clinical investigation, it might not be feasible or useful to obtain precise cumulative clinical trial exposure data, e.g., when the drug has been marketed for a number of years and/or has many indications. In these circumstances an explanation should be provided.
* Investigational drug exposure in healthy volunteers might be less relevant to the overall safety profile, particularly when volunteers are exposed to only a single dose. Such data can be presented separately with explanation, when appropriate;
	1. **Cumulative Subject Exposure in the Development Programme**

*Where applicable this section should include in tabular format:*

The cumulative number of subjects from ongoing and completed clinical trials;

the number exposed to the investigational drug, placebo, and/or active comparator(s) since the DIBD (Note: When treatment assignment is blinded, numbers of subjects can be estimated based on the randomisation scheme.);

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 III trial).

*Example tables below - please delete if not applicable*

Estimates of cumulative subject exposure, based upon actual exposure data from completed clinical trials and the enrolment/randomisation schemes for ongoing trials.

|  |  |
| --- | --- |
| Treatment | Number of subjects |
| drug |  |
| comparator |  |
| placebo |  |

Cumulative Subject Exposure to Investigational Drug from Completed Clinical Trials by Age and Sex\*

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

\* Data from completed trials as of [date]

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 as of [date]

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

* 1. **Patient Exposure from Marketing Experience**

Not applicable – this section to be used only where investigational drug is marketed by sponsor.

1. **Data in Line Listings and Summary Tabulations**

Provide:

* Cumulative summary tabulations of serious adverse events that have been reported to the sponsor since the DIBD.

NB. the summary tabulations in a DSUR should include all SAEs and not just Serious Adverse Reactions for the investigational drug and comparators

Certain adverse events can be excluded from the line listings and summary tabulations, but such exclusions should be explained in the report. E.g, adverse events that have been defined in the protocol as “exempt” from special collection and entry into the safety database, and those that are integral to efficacy endpoints, can be excluded (e.g., deaths reported in a trial of a drug for congestive heart failure where all-cause mortality is the primary efficacy endpoint, disease progression in cancer trials).

* 1. **Reference Information**

Provide details of Reference Safety Information (RSI) used including version number and date – e.g. SmPC/IB etc. This must be the version approved by the MHRA for use as RSI in the trial.

This section of the DSUR should specify the version(s) of the coding dictionary used

* 1. **Line Listings of Serious Adverse Reactions during the Reporting Period**

Provide line listings in an appendix and refer to that in this section.

Ensure to provide key information on all SARs (blinded and unblinded) reported from the sponsor’s clinical trials during the reporting period. The data should be organised by trial and then by System Organ Class (SOC).

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), as judged by the sponsor. 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.

* 1. **Cumulative Summary Tabulations of Serious Adverse Events**

Provide cumulative summary tabulations, as an appendix, of all reported SAEs for trials covered by this DSUR.

The tabulation(s) should be organised by SOC and where applicable by the investigational drug (active, comparator, placebo). Where blinded, put treatment unknown.

1. **Significant Findings from Clinical Trials during the Reporting Period**
	1. **Completed Clinical Trials**

Provide a brief summary of clinically important emerging efficacy and safety findings obtained from clinical trials completed during the reporting period.

It could include information that supports or refutes previously identified safety issues, as well as evidence of new safety signals

* 1. **Ongoing Clinical Trials**

Summarise the issue(s) of clinically important information that has arisen from ongoing clinical trials (e.g., learned through interim safety analyses or as a result of unblinding of subjects with adverse events),

* 1. **Long-term Follow-up**

Where applicable, this section should provide information from long-term follow-up of subjects from clinical trials of investigational drugs.

* 1. **Other Therapeutic Use of Investigational Drug**

This section of the DSUR should include clinically important safety information from other programmes conducted by the sponsor that follow a specific protocol, with solicited reporting as per ICH E2D (e.g., expanded access programmes, compassionate use programmes, particular patient use, single patient Investigational New Drugs (INDs) and treatment INDs).

* 1. **New Safety Data Related to Combination Therapies**

This section is only applicable to an investigational drug that is also under development as a component of a fixed combination product or a multi-drug regimen or is a multi-drug therapy or fixed combination product. Further information on what should be included in this section can be found in the ICH EF2 guideline.

1. **Safety Findings from Non-interventional Studies**

This section should summarise relevant safety information from non-interventional studies that became available to the sponsor during the reporting period (e.g., observational studies, epidemiological studies, registries and active surveillance programmes).

1. **Other Clinical Trial/Study Safety Information**

This section should summarise relevant safety information from any other clinical trial/study sources that became available during the reporting period.

1. **Safety Findings from Marketing Experience**

This section is only applicable if sponsor is responsible for marketing of IMP and investigational drug has been approved for marketing in any country.

1. **Non-clinical Data**

This section should summarise major safety findings from non-clinical in vivo and in vitro studies (e.g., carcinogenicity, reproduction, or immunotoxicity studies) ongoing or completed during the reporting period.

Implications of these findings should be discussed in the Overall Safety Assessment.

1. **Literature**

This section should summarise new and significant safety findings, either published in the scientific literature or available as unpublished manuscripts, relevant to the investigational drug that the sponsor became aware of 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 sponsor should provide a copy of the abstract, if possible.

1. **Other DSURs**

If multiple DSURs are prepared for a single investigational drug (e.g., covering different indications, development programmes, or formulations), this section should summarise significant findings from the other DSURs if they are not presented elsewhere within this report.

When available, significant findings should be summarised from DSURs provided by other sponsors conducting clinical trials with the same investigational drug during the reporting period.

1. **Lack of Efficacy**

Data indicating lack of efficacy, or lack of efficacy relative to established therapy(ies), for investigational drugs intended to treat serious or life-threatening illnesses (e.g., excess cardiovascular adverse events in a trial of a new anti-platelet drug for acute coronary syndromes), could reflect a significant risk to clinical trial subjects and should be summarised in this section.

1. **Region-Specific Information**

Only applicable where conducting a trial across more than one region – if required guidance can be found on: <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/09/WC500097061.pdf>

1. **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, a DMC, or a regulatory authority has taken for safety reasons. The Overall Safety Assessment (section 18) should also take these new data into account.

1. **Overall Safety Assessment**

The overall safety assessment should be a concise, integrated evaluation of all new relevant clinical, non-clinical, and epidemiologic information obtained during the reporting period relative to previous knowledge of the investigational drug. This assessment should consider cumulative experience, new information collected in the period covered by the DSUR and, for investigational drugs with a marketing approval, clinically significant post-marketing data. It should not summarise or repeat information presented in previous sections of the DSUR, but should provide an interpretation of the information and its implications for the clinical trial population and the development programme. If appropriate, separate assessments can be provided by therapeutic area, route of administration, formulation and/or indication.

* 1. **Evaluation of the Risks**

Particular emphasis should be placed on interpretation of data related to newly identified safety concerns or providing significant new information relative to previously identified safety concerns. Relevant points to consider include (where applicable):

• 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);

• meaningful changes in previously identified adverse reactions (e.g., increased frequency or severity, outcome, specific at-risk populations);

• symptoms, signs, and laboratory evidence of newly and previously identified clinically significant toxicities, deaths that are an outcome of an adverse event; ICH guideline E2F on development safety update report EMA/CHMP/ICH/309348/2008 Page 20/35

• 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 in the same class.

* 1. **Benefit-risk Considerations**

This section should provide a succinct statement on the perceived balance between risks that have been identified from cumulative safety data and anticipated efficacy/benefits and should note whether there have been any changes in this balance since the previous DSUR.

1. **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 in labelling.

Such risks might include, for example, toxicities known to be associated with a particular molecular structure or drug class, or concerns based on accumulating non-clinical or clinical data. Each risk should be re-evaluated annually and re-summarised as appropriate, based on the current state of knowledge. New information should be highlighted.

Risks that have been fully addressed or resolved should remain in the summary and be briefly described

Information can be provided in either narrative or tabular format

1. **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.

**Appendices to the DSUR**

The DSUR should be accompanied by the following appendices, as appropriate, numbered as follows:

1. Investigator’s Brochure (if required by national or regional laws or requirements);

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).

The DSUR should also be accompanied by the following Regional Appendices, as appropriate:

o Cumulative summary tabulation of serious adverse reactions;

o List of subjects who died during the reporting period;

o List of subjects who dropped out of studies during the reporting period;

o Significant manufacturing changes;