Söğütözü Neighborhood, 2176th Street No:5 06520 Çankaya/ANKARA
Telephone No: (0 312) 218 30 00 Fax No: (0 312) 218 34 60
E-mail: halkla.iliskiler@titck.gov.tr Website:
https://www.titck.gov.tr
Kep Address: titck@hs01.kep.tr

GUIDELINE ON THE DEVELOPMENT SAFETY UPDATE REPORT IN CLINICAL TRIALS KAD-KLVZ-08

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1. PURPOSE This guideline concerns the presentation of a comprehensive review and evaluation of the relevant safety information collected during the reporting period for the investigational medicinal product (IMP) of clinical trials conducted in our country. 2. SCOPE In line with the Regulation on Clinical Trials on Human Medicinal Products published in the Official Gazette No. 32203 dated 27 May 2023, it covers matters relating to the Development Safety Update Report (DSUR) in clinical trials. 3. DEFINITIONS In addition to the following definitions, the definitions in the Guideline on Good Clinical Practice and in the relevant legislation shall apply. 3.1. Identified risk: An adverse event for which there is sufficient evidence of an association with the investigational medicinal product in question. Identified risks may include, but are not limited to, - An adverse reaction demonstrated in non-clinical studies and corroborated by clinical data, - An adverse reaction observed in well-designed clinical trials or epidemiological studies where the magnitude of the existing difference compared to the comparator product or placebo, in terms of the parameter in question, suggests a causal relationship, - An adverse reaction revealed in a well-documented series of spontaneous reports where causality is strongly supported by a temporal association or biological plausibility (e.g. anaphylactic reactions or administration site reactions). 3.2. Clinical development programme: It encompasses all clinical trials conducted with the same investigational medicinal product, regardless of indication or formulation. 3.3. Agency: Refers to the Turkish Medicines and Medical Devices Agency (TİTCK). 3.4. Important identified risk or important potential risk: An identified or potential risk that may affect the benefit-risk balance of the investigational medicinal product or may have various consequences for public health. 3.5. Expected efficacy or benefit: Efficacy or benefit that has not yet been demonstrated for the investigational medicinal product, but is anticipated based on information relating to the class to which it belongs or on data obtained from previous clinical trials or non-clinical studies. 3.6. Adverse event of special interest: A serious or non-serious adverse event of special interest is one of the scientific and medical concerns specific to the sponsor's product or programme, which requires continuous follow-up and for which expedited reporting by the investigator to the sponsor may be appropriate. Such an event may require further investigation in order to be characterised and understood. Depending on the nature of the event, expedited notification by the sponsor to the Agency and the relevant ethics committee may be required. 3.7. Potential risk: An adverse event for which there is a suspicion of a causal relationship with the investigational medicinal product but where this relationship has not been confirmed. Potential risks may include, but are not limited to, - Non-clinical safety concerns that have not been observed or have not been resolved in clinical trials,

- Adverse events where the magnitude of the existing difference compared to the control group (placebo, active substance, or unexposed group), in terms of the parameter in question, raises suspicion but is not large enough to suggest a causal relationship, - A signal arising from the spontaneous adverse reaction reporting system, - An event that is known to be associated with

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other products of the same class or that is expected to occur based on the properties of the investigational medicinal product. 3.8. Signal: Reports of an event for which the causal relationship with treatment is unknown but which is considered worthy of further detailed examination and continued surveillance. 3.9. International development birth date: The date of the first authorisation or permission obtained to conduct a clinical trial in any country. 3.10. International approval date: Refers to the date on which the first approval for a medicinal product in any country was granted to the approval holder. 3.11. Data lock point: The date designated as the data cut-off date for the data to be included in the Development Safety Update Report (DSUR) (month and day), based on the international development birth date. 4. RESPONSIBILITIES 4.1. In addition to adverse event or adverse reaction reports, the sponsor shall submit to the relevant ethics committee and the Agency, once a year throughout the clinical trial or upon request, all safety information that has emerged during the reporting period, in the form of a DSUR. The notification of these reports shall be made in accordance with the format published on the official website of the Agency. 4.2. The DSUR shall be clear, understandable and in an appropriate format, and shall contain information that will provide assurance that sponsors adequately monitor and evaluate the evolving safety profile of the investigational medicinal product. All safety issues that have arisen during the reporting period shall be addressed within the DSUR text. 4.3. In order to support the presentation and a comprehensive analysis of the safety profile of the investigational medicinal product, a single DSUR shall be prepared with data relating to all doses, all indications and, where appropriate, all patient populations in which the investigational medicinal product is used. Where this is not possible, an explanation shall be provided in the introductory section of the DSUR. 4.4. The reporting period for the DSUR begins on the date of the first authorisation granted by the Agency for the clinical trial and ends with the completion of the trial in all countries. The completion of the trial in all countries may be defined as the closure of all sites included in the trial. 4.5. The sponsor shall submit the development safety update reports within 60 (sixty) days following the data lock point. 4.6. Where more than one sponsor is involved in a clinical trial or drug development programme, a single DSUR may be submitted. These include cases where the sponsor is in a formal co-development or licensing relationship with one or more partners, or where the clinical trial or drug development programme involves collaboration with public or private institutions, business partners or other parties. Where a single DSUR cannot be submitted, multiple sponsors may decide to prepare separate DSURs for the same investigational medicinal product. In this case, different indications,

route of administration or formulations, may occur when they are investigated by different parties. In this case, the justification for separate DSURs should be provided in each report. 4.7. A single DSUR may be prepared for clinical trials involving a fixed-combination product (a product consisting of at least two active substances in fixed doses in a single dosage form). If the sponsor is also conducting clinical trials with the separate components of the fixed-combination product, separate DSURs should be submitted for each component. 4.8. For trials involving multi-drug therapy, i.e., combinations of non-fixed drugs, the sponsor can prepare one of the following: - For investigational product (A) + authorised drugs (X, Y, Z), a single DSUR focused on (A+X+Y+Z) or a single DSUR focused on (A) that also includes multi-drug therapy data, - For two investigational products (A) + (B), a single DSUR focused on (A+B) or two separate DSURs focused on (A) and (B) that also include multi-drug therapy data, - For two or more authorised drugs as a combination of investigational products (X, Y, Z), a single DSUR focused on the multi-drug therapy (X+Y+Z). 4.9. The sponsor may delegate the preparation of the DSUR to a third party by written contract. 4.10. In cases where the sponsor does not have access to information such as manufacturing issues to be included in specific sections, non-clinical data and marketing status, this should be stated in the DSUR. 4.11. The investigator's brochure in effect at the start of the reporting period should serve as the reference safety information for determining whether information obtained during the reporting period remains consistent with previous information on the safety profile of the investigational product. 4.12. Even if the sponsor is conducting several clinical trials with the same

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investigational product, it should submit safety reports covering the necessary information relating to all such trials for each trial. 4.13. The DSUR should be prepared and presented in accordance with the format set out in the annex to this guideline. 4.14. All sections within the format described in the annex to the guideline should be completed; where no information is available, this should be indicated.

ANNEX-1: DEVELOPMENT SAFETY UPDATE REPORT (DSUR) FORMAT

TABLE OF CONTENTS

Title Page

The DSUR title page should include the following information:

- DSUR number (reports should be numbered sequentially)

- Investigational products,

- Reporting period,

- Date of the report,

- Names and addresses of sponsors,

- A statement of the confidentiality of the information contained in the DSUR,

- If applicable, a warning statement that the DSUR contains open information.

Executive Summary

A brief summary of the important information contained in the report should be provided in this section. The following information should be included in the executive summary: - Introduction: report number and reporting period, - Investigational products: modes of action, therapeutic classes, indications, doses, routes of administration, formulations, - Estimated cumulative exposure of clinical trial volunteers, - Marketing approvals (yes/no) (if yes, number of countries), - Summary of the overall safety evaluation, - Summary of important risks, - Actions taken for safety reasons, including significant changes to the investigator's brochure, - Conclusions

1. Introduction

This section should include the following:

- The international development birth date or the international licence date,

- The reporting period and the sequential number of the report,

- Information on the investigational product (such as mechanism of action, therapeutic class, route of administration), - A brief description of the indication and the population studied, - A brief summary of the scope of the clinical trials included in the report, - A brief description and explanation of information not included in the DSUR, - If applicable, the justification for the submission of multiple DSURs for the investigational product. 2. Worldwide marketing approval status This section should provide a brief general statement including the date of first approval, the indication, the approved dose and, if applicable, where it was approved. 3. Actions taken for safety reasons during the reporting period This section should include safety-related actions taken during the reporting period by the sponsor, health authorities, data monitoring committees or ethics committees that have had an impact on the conduct of specific clinical trials or on the overall clinical development programme. The reasons for each action should be stated. Relevant updates on previous actions should also be summarised in this section. Changes made to the investigator's brochure should be discussed separately in the "Changes to Reference Safety Information" section. Examples of significant actions taken for safety reasons include the following: Actions related to investigational products: • Refusal to approve or permit a clinical trial for ethical or safety reasons,

• Suspension or complete halt of a clinical trial, or early termination of an ongoing clinical trial, due to safety findings or lack of efficacy, • Withdrawal of the investigational product or comparator product, • Failure to obtain a marketing authorisation for a tested indication, including voluntary withdrawal of the marketing authorisation application, • Protocol amendments made for reasons related to safety or efficacy, • Restrictions on the study population or indications, • Changes made to the informed consent form (ICF) in connection with safety issues, • Changes to

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the formulation, • Addition of safety-related specific reporting conditions imposed by licensing authorities, • Communication with investigators or other healthcare professionals, • Plans for new trials to address safety issues. Actions related to marketed drugs: • Failure to obtain renewal of a marketing authorisation, • Withdrawal or suspension of the marketing authorisation, • Introduction of significant restrictions on distribution or other risk minimisation measures, • Significant safety-related changes made to labelling documents that could affect the development programme, including restrictions on the use of the investigational product or the population treated, • Communications with healthcare professionals, • New post-marketing study requirements imposed by licensing authorities. This section should also summarise requests from health authorities imposing a specific limitation on current or future development (for example, requests to conduct long-term animal studies before initiating a long-term clinical trial, specification of the maximum dose to be evaluated, requests to submit specific safety data before initiating trials in children). If applicable, a cumulative list of such requests from health authorities, including updates, should also be presented. This list may be presented in tabular form, as an annex, or within this section. 4. Changes to reference safety information This section should list the significant safety-related changes made during the reporting period to the investigator's brochure or other reference safety information. Such changes may include information relating to exclusion criteria, contraindications, warnings, precautions, serious adverse reactions, adverse events of special interest, interactions and important findings obtained from non-clinical studies. Specific information on these changes should be provided in the appropriate section of the DSUR.

5. Inventory of clinical trials ongoing or completed during the reporting period This section should provide a brief overview of ongoing and completed clinical trials by the sponsor during the reporting period, with detailed information presented in tabular form as an appendix. Separate tables may be provided by indication, formulation and, if applicable, trial population. In addition, similar information should be provided for other therapeutic uses of the investigational product during the reporting period. The tables should include the following information for each clinical trial: - Trial identification (such as protocol number or other identifying information), - Phase of the trial, - Status of the trial (such as ongoing, completed), - Trial sites where the trial is being conducted, - If available, abbreviated trial title, - Design of the trial (such as controlled, randomized, open-label), - Dose and regimen of the investigational product and comparator product, - As appropriate, the trial population (age, sex, indication(s), specific patient subgroups, e.g., trial participants with impaired renal function or trial participants who are treatment-resistant), - Date of commencement of the clinical trial, - Total number of participants planned to be enrolled at all sites included in the trial, - For each treatment arm, where possible, estimated cumulative numbers of participants exposed to the investigational product (actual participant counts for ongoing or completed trials, or estimated counts obtained according to the randomization schedule for blinded trials, should be provided).

6. Estimated cumulative exposure Cumulative exposure information should be provided in the DSUR. An estimated figure of cumulative participant exposure may be useful in preparing cumulative summary tabulations of serious adverse events and in the overall safety evaluation. Due to certain factors, such as rapid enrollment of participants and the number of ongoing trials in which the blinding has not been broken, the accuracy of the estimate of clinical trial exposure may be limited. The most appropriate method of data presentation should be based on certain factors. The following general considerations should be taken into account in preparing the estimated exposure for the DSUR: - Data should be presented in tabular format. - When there are important differences between trials with regard to factors such as dose, route of administration or patient population, these differences may be indicated in tables or separate tables may be prepared. - If summary tabulations of serious adverse events are presented by indication, exposure data should also, when available, be presented by indication. - When there are important differences in exposure durations among participants randomized to the investigational product or comparator product, or differences in exposure duration between clinical trials,

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it may be useful to express the exposure data as participant-time (participant-days, -months or -years). - Exposure of healthy volunteers to the investigational product, especially when participants are exposed to only a single dose, may be less relevant to the overall safety profile. Such data may, where appropriate, be presented separately with an explanation. - For marketed products under clinical trial (such as cases where the drug has been marketed for several years or has many indications), it may not be appropriate or useful to obtain precise cumulative clinical trial exposure data. Under these conditions, the sponsor should provide an explanation.

6.1. Cumulative participant exposure in the development programme This section should include the following information in tabular format: - Cumulative number of participants from ongoing and completed clinical trials (the number of participants exposed to the investigational product, placebo or active comparator since the international development birth date; when treatment assignment is blinded, the number of participants may be estimated based on the randomization schedule), - Where data are available, the cumulative number of participants exposed to the investigational product in ongoing and completed clinical trials, grouped by age range, sex and ethnic group for the development programme, - If the trial is of particular importance (e.g., if it is a pivotal Phase III trial), demographic characteristics for a single trial, - Specific age categorization may depend on the participant population or indication. This section should also include the sponsor's rationale for selecting the method used to estimate participant exposure and the limitations of that method based on the points above.

6.2. Patient exposure obtained from marketing experience If the investigational product is marketed by the sponsor, the DSUR should include an estimated figure of cumulative patient exposure in the marketed region and an explanation of the methods used to determine that estimated figure.

7. Data in line listings and summary tabulations Important clinical safety information should be presented in the DSUR: - Interval line listings of serious adverse reactions reported to the sponsor during the period covered by the DSUR, - Cumulative summary tabulations of serious adverse events reported to the sponsor since the international development birth date. Although causality assessment is generally useful for evaluating individual rare adverse reactions and making decisions regarding expedited reporting, group comparisons of rates are, where possible, of less value than individual case causality assessment in the analysis of pooled data. Therefore, the summaries in the DSUR

tables should include not only serious adverse reactions but all serious adverse events for the investigational product and comparator products. Line listings and tables should include data from blinded and unblinded clinical trials. Unblinded data can be obtained from completed trials and, if applicable, from individual cases unblinded for safety reasons (e.g., expedited reporting). Sponsors should not unblind data for the specific purpose of preparing the DSUR. Graphs and images may be used to display specific data, at the sponsor's discretion, if helpful to facilitate understanding. If the Medical Dictionary for Regulatory Activities (MedDRA) is used to code adverse event or reaction terms, the preferred term level should be presented in line listings and summary tables. In general, serious adverse event tables should include only the terms used to define the case as serious and should not include non-serious events. Certain adverse events may not be included in line listings and summary tables, but such excluded events should be described in the report. For example, adverse events defined in the protocol as exempt from collection and entry into the safety database, and adverse events that are part of efficacy endpoints, may not be included (e.g., deaths reported in a trial for congestive heart failure where all-cause mortality is the primary endpoint, or disease progression in cancer trials). 7.1. Reference information This section of the DSUR should specify the version of the dictionary used for coding. If applicable, where required by local regulations, the document and version used as reference safety information for the determination of expectedness in tables should also be specified. 7.2. Line listings of serious adverse reactions during the reporting period This section of the DSUR should summarize how the case reports included in the line listings were selected. This section should not

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serve to present analyses or conclusions based on serious adverse reactions. Line listings should be provided in an appendix. Line listings should provide key information on all serious adverse reactions (blinded and unblinded) reported by the sponsor in clinical trials during the reporting period. Data should be organised by trial and then by system organ class. Where possible, line listings should include each participant only once, regardless of how many serious adverse reactions were reported for the case. If there is more than one reaction, all should be mentioned, but the case should be listed under the heading of the most serious adverse reaction (sign, symptom or diagnosis) as assessed by the sponsor. It is possible for the same participant to experience different serious adverse reactions at different times. In such cases, the serious adverse reactions may be listed separately, and a single participant may be included more than once in a line listing. The following information should be included in the line listing: - Trial code, - Participant code, - Sponsor's adverse reaction case reference number (Mfr Control No.),

- Country where the case occurred, - Age and sex of the participant, - Treatment group (described as "blind" if unblinding has not occurred), - Dose and dosing interval of the investigational product (and, if necessary, dosage form and route of administration), - Date of the most serious adverse reaction or time to the most serious adverse reaction, - Treatment dates or estimated best treatment duration, - Serious adverse reactions (when MedDRA is used, the preferred term should be presented), - Outcome [(should indicate the outcomes of the reactions for the participant (such as recovered, resolving, sequela, fatal, unknown)) (using the worst of the different outcomes if there is more than one reaction)], - Sponsor's comments (causality if the sponsor is of a different opinion than the reporter, concomitant medications suspected of playing a direct or interactive role in the reaction, indications treated with the suspect medicines, etc.). 7.3. Cumulative summary tables of serious adverse events This section should refer to an appendix presenting a cumulative summary table of serious adverse effects reported in the sponsor's clinical trials from the international development birth date to the data lock point of the current DSUR. The sponsor should explain any lack of data. Tables should be prepared by system/organ class for both the investigational product and the comparator groups used in the programme. Data can be integrated across the programme. Alternatively, where appropriate and feasible, tables of serious adverse effects can be presented by protocol, indication, route of administration and other variables. This section should not include analyses and conclusions based on serious adverse effects. 8. Important findings from clinical trials during the reporting period Information in this section may be presented by indication, where appropriate, and should address the following topics, as applicable. 8.1. Completed clinical trials This section of the DSUR should contain a brief summary of clinically significant efficacy and safety findings that have emerged from clinical trials completed during the reporting period. This information may also be presented in summary form. It may include information supporting or contradicting previously identified safety issues, and findings of new safety signals. 8.2. Ongoing clinical trials This section should briefly summarise issues if the sponsor is aware of clinically significant information emerging from ongoing trials (learned through interim safety analyses or through unblinding of participants who experienced adverse events). It may include information supporting or contradicting previously identified safety issues, and findings of new safety signals. 8.3. Long-term follow-up Where applicable, this section should present information obtained from long-term follow-up of participants enrolled in clinical trials of investigational products, in particular advanced therapy medicinal products. When the development programme is completed and long-term follow-up provides data for the DSUR

constitutes the single ongoing activity, this section may be the only section in which new information is presented. 8.4. Other therapeutic uses of the investigational product This section of the DSUR should contain clinically important safety information obtained from other programmes that follow a specific protocol and are conducted by the sponsor, together with notifications requested under the relevant legislation (e.g. expanded access programmes, compassionate use programmes for early access to a medicinal product, named patient use). 8.5. New safety data related to combination therapies If the DSUR is for an investigational medicinal product that is also

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being developed as an element of a fixed combination product or a multi-drug regimen, this section should summarise the important safety findings of the DSUR for the combination therapy. Conversely, if the DSUR is for a multi-drug therapy or a fixed combination product, this section should summarise the important safety data arising from trials of the individual elements. Alternatively, combination-specific information may be included in a separate section or sections of the DSUR for one or all of the elements of the combination. 9. Safety findings from non-interventional clinical trials This section should summarise safety-related information from non-interventional studies that became available to the sponsor during the reporting period. 10. Safety information from other clinical trials This section should summarise safety-related information from other clinical trial sources that became available to the sponsor during the reporting period (e.g. results of pooled analyses or meta-analyses of randomised clinical trials, safety information provided by investigator-initiated studies). 11. Safety findings from marketing experience If the investigational medicinal product has been approved for marketing in any country (in particular, if the findings have resulted in changes to the product information, the investigator's brochure, the informed consent form (ICF), or modifications to the product risk management plan), this section should include a brief summary of key safety findings that emerged from marketing experience and became available to the sponsor during the reporting period. This section should include safety findings not only related to approved uses, but also those related to off-label use, administration to special populations, medication errors, overdose and abuse. 12. Non-clinical data This section should summarise major safety findings from ongoing or completed non-clinical in vivo and in vitro studies during the reporting period. The potential implications of these findings should be discussed in the overall safety assessment section. 13. Literature This section should summarise new and significant safety findings regarding the investigational medicinal product that became available to the sponsor during the reporting period, published in the scientific literature or available in unpublished drafts. This section should include information from non-clinical studies and clinical trials and, where relevant and applicable, from medicinal products of the same class.

It should also summarise important new safety information presented at a scientific meeting and published as an abstract. Where possible, the sponsor should provide a copy of the abstract. 14. Other DSURs In this section, the sponsor should prepare a single DSUR for a single investigational medicinal product. However, if the sponsor prepares more than one DSUR for a single investigational medicinal product (e.g. covering different indications, development programmes or formulations) and it has not been presented elsewhere in this report, the sponsor should summarise the important findings of the other DSURs. When available, the sponsor should summarise important findings from DSURs provided by other sponsors conducting clinical trials with the same investigational medicinal product during the reporting period. 15. Lack of efficacy Data suggesting a lack of efficacy, or inferiority relative to established treatments, for investigational medicinal products (e.g. serious cardiovascular adverse events in the investigation of a new antiplatelet agent for acute coronary syndrome) may represent a significant risk to participants (volunteers). This should be summarised in this section. 16. Region-specific information The information in this section may be used to comply with local legislation and may be presented in DSUR appendices. Sponsors should consult local legislation to determine which of the following sections should be included and the clinical trial topics these sections should cover. Examples are as follows: - Cumulative summary tabulations of serious adverse reactions: These cumulative summary tabulations of all serious adverse reactions should provide the number of serious adverse reactions by system organ class, adverse reaction term and treatment group, as appropriate. Unexpected adverse reaction terms should be identified. - List of participants (volunteers) who died during the reporting period: The list of participants (volunteers) who died during the clinical trials should include, at a minimum, the case number, the assigned treatment (which may still be blinded) and the cause of death for each participant. Any safety issues identified through review of these deaths should be addressed appropriately in the DSUR. - List of

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participants (volunteers) who withdrew from clinical trials in association with an adverse event during the reporting period: This list should include all participants (volunteers) who withdrew from clinical trials in association with an adverse event during the reporting period, whether or not the adverse event was considered related to the investigational medicinal product. Any safety issues identified through review of these withdrawals should be addressed appropriately in the DSUR. - Significant Phase I protocol amendments: This section should include significant Phase I protocol amendments made during the reporting period, if they have not been presented previously as a protocol amendment. - Significant manufacturing changes: This section should include a summary of significant manufacturing or microbiological changes that occurred during the reporting period, and any potential safety issues arising from these changes should be discussed in the DSUR, as appropriate. - Indication of the general trial plan for the coming year: This section should outline a trial plan to take the place of the one presented the previous year.

17. Updated Information This section summarizes information on potentially significant safety findings that emerged after the data lock point, during the preparation of the DSUR. For example, clinically important new case reports, significant follow-up data, clinically significant toxicological findings, and any action taken by the sponsor, the data monitoring committee, or the regulatory authority for safety reasons may be provided. The overall safety assessment should take these new data into account. 18. Overall Safety Assessment The overall safety assessment should be a concise, integrated evaluation of all important clinical, non-clinical, and epidemiological information obtained during the reporting period that is new in relation to previous information on the investigational product. This evaluation should take into account cumulative experience, new information gathered within the period covered by the DSUR, and, for investigational products that have received marketing authorization, clinically important post-marketing data. It should not summarize or repeat information presented in previous sections of the DSUR. However, it should present an interpretation of that information and conclusions regarding the clinical trial population and the development program. Where appropriate, separate assessments may be provided by therapeutic area, route of administration, formulation, or indication.

- Evidence of lack of participant compliance, - Overdose and overdose treatment, - Misuse and/or abuse of the drug, - Safety issues arising from procedures anticipated in the protocol or from procedures related to the manner in which or design of a particular study, - The potential impact of significant new safety issues identified during the use of another medicinal product of the same class. 18.2. Benefit-Risk Evaluations This section should provide a brief explanation of the balance between the risks identified in the cumulative safety data and the anticipated efficacy or benefits, and should indicate whether there has been any change in this balance since the previous DSUR. This section is not intended to be a comprehensive benefit-risk evaluation of the investigational product.

19. Summary of Important Risks This section should present a short, cumulative, issue-by-issue listing of important identified and potential risks (such as risks that might warrant a warning, precaution, or contraindication in the labeling). These risks include toxicities known to be associated with a particular molecular structure or class, or concerns relating to the collection of non-clinical or clinical data. Each risk should be re-evaluated once a year based on the current information and, where appropriate, re-summarized. New information should be highlighted. The appropriate level of detail will likely depend on the stage of drug development. For example, summaries covering drugs in early stages of development will include information on individual cases, whereas in later stages of development, as more information and perspective are gained, the level of detail for each risk decreases. The information in this section may provide the rationale for the safety specification of a risk management plan. Risks that have been fully evaluated or resolved should remain in the summary and be briefly explained (for example, findings from toxicology studies or early clinical trials that were not substantiated by subsequent clinical data).

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20. Conclusions The conclusions section should briefly describe the changes made to the previous efficacy and safety data along with the information obtained since the last DSUR. This section should outline the activities that have been carried out or are planned to be carried out in order to address safety issues that have arisen in the clinical development program.

- List of participants who died during the reporting period, - List of participants who withdrew from the trial during the reporting period, - Significant Phase I protocol amendments, - Significant manufacturing changes, - Description of the general trial plan for the coming year, - Record of activities to be carried out, - Scientific abstracts.

ANNEX 2 - TABLE AND TABLE CAPTION EXAMPLES FOR CLINICAL TRIAL LISTINGS

TABLE 1: Status of Ongoing and Completed Clinical Trials

Summary of Ongoing Trials [Investigational Product]

Trial Code Phase Country Title of the Trial Design of the Trial Dose Regimen Trial Population FPFV (first participant first visit)

Planned Number of Cases to Be Enrolled Participant Exposure*

*Based on the total number of participants enrolled and randomized in the trial as of [date]

Status of Clinical Trials Completed During the DSUR Period [Investigational Product]

Trial Code Phase Country Title of the Trial Design of the Trial Dose Regimen Trial Population Participant/patient exposure in each treatment arm (M/F)

TABLE 2: Estimated Cumulative Participant Exposure

Estimates of cumulative participant exposure based on current exposure data from completed clinical trials and on enrollment or randomization schemes from ongoing trials

Treatment Number of participants Drug Comparator drug Placebo

TABLE 3: Cumulative Participant Exposure to the Investigational Medicinal Product by Age and Sex, from Completed Clinical Trials *

Number of participants Age range Male Female Total

* Data obtained from trials completed as of [date]

TABLE 4: Cumulative Participant Exposure to the Investigational Medicinal Product by Race Group, from Completed Clinical Trials *

Race group Number of participants Asian Black White (Caucasian) Other Unknown Total * Data obtained from trials completed as of [date]

TABLE 5: Example Headings to Be Used for Periodic Listing Line Listings of Serious Adverse Reactions

Periodic Line Listings of Serious Adverse Effects

Study Code

Participant Initials Participant No.* Country Sex Age Serious Adverse Drug Reactions Outcome Onset Date Time to Onset** Suspected Drug Daily Dose/Dose Regimen Route of Administration Formulation Treatment Dates/Duration of Treatment Comments

*Study/site/participant **Primary serious adverse reaction only

TABLE 6: Example Cumulative Tables for Serious Adverse Events

Example of a Cumulative Summary Table for Serious Adverse Events

System organ class Total up to 21/10/2015 Preferred term Investigational drug Blinded Active Comparator Drug Placebo Investigations 18 4 7 2 Alanine aminotransferase increased 9 2 4 1 Aspartate aminotransferase increased 9 2 3 1 Syncope 2 2 4 7

REVISION HISTORY Revision No. Revision Date Rationale and Explanations

00 03.11.2015 Updated prior to the establishment of the quality management system. 01 01.02.2024 Updated due to a change in the regulation.

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