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GOOD CLINICAL PRACTICE GUIDE KAD-KLVZ-01

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1. INTRODUCTION Good clinical practice, which derives its underlying principles from the current Declaration of Helsinki, is an ethical and scientific quality standard pertaining to the design, conduct, recording and reporting of clinical trials to be performed on humans. Good clinical practice provides assurance to society that the rights, health and privacy of the volunteers participating in the trial are protected and that the data obtained from the trial are reliable. The purpose of the Good Clinical Practice Guide is to provide a single standard to facilitate the mutual international acceptance of clinical data. This guide provides guidance on the collection of clinical data to be submitted to the Turkish Medicines and Medical Devices Agency and to ethics committees, and sets out the principles and details of clinical trials that are being conducted or planned to be conducted in our country. 2. DEFINITIONS 2.1. Adverse Event: All untoward medical occurrences observed in a volunteer participating in a clinical trial, which arise whether or not there is a causal relationship with the treatment administered. 2.2. Adverse Reaction: Refers to all untoward and unintended responses to the investigational product that occur in a volunteer participating in a clinical trial. 2.3. Investigator: A physician or dentist who, under the supervision and oversight of the principal investigator, is assigned by the principal investigator to perform critical trial-related procedures or to take important trial-related decisions. 2.4. Investigator's Brochure: Documents containing the nonclinical and clinical data relating to the investigational product. 2.5. Trial Protocol: A document that describes in detail the objective(s) of the trial, its design, methodology, the statistical methods to be applied and the arrangements pertaining to the trial. 2.6. Trial Protocol Amendment: A document relating to the amendments made to the trial protocol. 2.7. Investigational Product: Refers to a medicinal product for human use that is tested or used as a reference in a clinical trial, including placebo. 2.8. Independent Data Monitoring Committee (Data Monitoring Board or Data and Safety Monitoring Committee): A committee composed of independent experts outside the trial that evaluates the progress of the clinical trial, the safety data and, where necessary, the critical efficacy endpoints, and makes recommendations to the sponsor, at certain intervals, as to whether the trial should be continued, modified or stopped. 2.9. Unexpected Serious Adverse Reaction: Refers to any serious adverse reaction whose nature, severity or outcome is not consistent with the reference safety information for the investigational product. 2.10. Informed Consent Form (ICF): A document that provides written evidence of the consent obtained for the volunteer's participation in the trial, after detailed and comprehensible information about the trial has been given to the volunteer or the volunteer's legal representative. 2.11. Validation of Computerised Systems: A process that demonstrates and

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documents that a computerised system consistently fulfils its specified requirements. The validation process should ensure the accuracy, reliability and consistent intended performance of the system from its design until its retirement from service or transition to a new system. 2.12. Bioequivalence: Refers to the situation where, after two medicinal products for human use containing the same active substance, which are pharmaceutically equivalent or pharmaceutical alternatives of each other, are administered at the same molar dose by the same route of administration, their bioavailabilities (rate and extent) are within predefined acceptable limits.

2.13. Bioavailability: The rate and extent to which the active substance or the moiety responsible for the therapeutic effect is absorbed from the pharmaceutical form, enters the systemic circulation, and thus becomes present at the site of action in the body or in biological fluids that reflect it (usually serum or plasma). 2.14. Serious Adverse Event or Reaction: Refers to an adverse event or reaction that results in death, is life-threatening, requires hospitalisation or prolongation of the duration of hospital stay, results in persistent or significant disability or incapacity, or in a congenital anomaly or defect, or that, given the possibility that it may otherwise jeopardise the volunteer, requires medical or surgical intervention to prevent one of the outcomes listed, or that leads to the development of dependence or drug abuse. 2.15. Double-Blind Masking (Double Dummy): A blinding method used in trials in which two different pharmaceutical forms of an investigational product are to be compared, in order to mask which products are administered to the trial groups. Accordingly, for example, administration to the trial groups is carried out by giving one group a placebo tablet and an ampoule containing the active substance, and the other group a tablet containing the active substance and a placebo ampoule. 2.16. Multicentre Clinical Trial: A clinical trial conducted according to a single protocol at more than one trial site, and therefore involving more than one principal investigator. 2.17. Inspection: Activities whereby the Agency examines, with respect to compliance with this Regulation and other relevant legislation, the activities and records relating to the clinical trial carried out by the natural or legal persons involved in the clinical trial, the sites where the clinical trial is conducted, the service providers or trial sites — including the sponsor, its legal representative where applicable, and other parties to whom tasks have been delegated — the quality assurance arrangements, and the other institutions, boards and organisations involved in the trial, including ethics committees. 2.18. Inspection Report: A report prepared by the relevant health authority as a result of an inspection. 2.19. Sponsor: A person, institution or organisation that is responsible for the initiation, conduct and financing of a clinical trial. 2.20. Direct Access: Permission to examine, analyse, verify and copy the records and reports pertaining to the trial for the purpose of evaluating the clinical trial. All parties that have direct access, such as the Ministry of Health and its affiliated organisations, the Turkish Medicines and Medical Devices Agency, the relevant health authorities and monitors, shall take the necessary measures, within the framework of the restrictions introduced by the relevant legislation, in order to protect the confidentiality of the identities of the volunteers or of the information owned by the sponsor. 2.21. Documentation: Any kind of document, such as written, electronic and magnetic records, scan records, X-ray and electrocardiogram records, that describes or records the methods, conduct or results of the clinical trial, the factors affecting the trial and the actions taken. 2.22. Ethics Committee: Refers to the independent clinical trial ethics committees or bioavailability and bioequivalence ethics committees that are established in order to provide opinions from a scientific and ethical standpoint on the natural or legal persons involved in the clinical trial, the sites where the clinical trial is conducted, the information and documents required to be submitted in the clinical trial application dossier, as well as on the suitability of the methods and materials to be used for obtaining and documenting informed consent from volunteers, for the purpose of protecting the rights, safety and well-being of volunteers, and that are approved by the Agency. 2.23. Vulnerable Population: Groups of volunteers composed of persons with limited or diminished autonomy who are located within a certain hierarchical structure or in whom the capacity for self-protection has not yet developed, has diminished or has completely disappeared due to economic, social and medical reasons.

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2.24. Essential Documents: Documents that individually and collectively permit the evaluation of the manner in which the trial is conducted and the quality of the data produced. 2.25. Confidentiality: The prevention of disclosure, to parties other than authorized persons, of information owned by the sponsor or information relating to the identity of the volunteer. 2.26. Volunteer: A patient or healthy person who participates in a clinical trial, with the written consent of himself/herself or his/her legal representative, in accordance with the provisions of this Regulation and the relevant legislation. 2.27. Volunteer Code: A code assigned to each volunteer by the principal investigator or investigators in order to keep the identity of the volunteers participating in the trial confidential, and used in place of the volunteer's name when reporting any adverse event or data related to the trial. 2.28. Administrative Responsible: In a multicentre trial, preferably a person who has completed specialty or doctoral training, who is responsible, when necessary during the conduct of the trial, for the coordination on administrative matters related to the trial between the principal investigators of these trial sites and the ethics committee or the sponsor, and, where necessary, between them and the Agency. 2.29. Good Clinical Practice (GCP): The rules covering provisions on the design, conduct, monitoring, budgeting, evaluation and reporting of trials in order to ensure that trials are performed in accordance with international scientific and ethical standards, the protection of all rights of the volunteer and his/her physical integrity, the assurance of the reliability of trial data, and the maintenance of confidentiality, and which must be complied with by the parties participating in the trial. 2.30. Authorization (Turkish Medicines and Medical Devices Agency Authorization): The favorable decision of the Turkish Medicines and Medical Devices Agency that the trial may be conducted at the relevant trial sites within the limits determined in accordance with good clinical practice and the relevant legislation. 2.31. Monitoring: Refers to the oversight of the conduct of a clinical trial and to the activity of ensuring that the clinical trial is conducted, recorded and reported in compliance with the protocol, standard operating procedures, good clinical practice and the relevant legislation. 2.32. Monitoring Report: A written report, prepared on the basis of the sponsor's standard operating procedures following each trial site visit made or following communication with the parties related to the trial, and submitted by the monitor to the sponsor. 2.33. Quality Assurance: The entirety of planned systematic actions established to ensure that the trial is performed and that data are generated, documented, recorded and reported in compliance with good clinical practice and the relevant legislation. 2.34. Quality Control: The operational techniques and activities undertaken within the quality assurance system to verify that the quality requirements of the trial-related activities have been fulfilled. 2.35. Legal Representative: A person who, in accordance with the legislation in force, is authorized to give consent, on behalf of a potential volunteer, to the volunteer's participation in a clinical trial. 2.36. Comparator Product: The product or placebo used as a reference in the clinical trial. 2.37. Source Documents: Records such as hospital records, laboratory notes, memoranda, the volunteers' diaries or assessment checklists, drug dispensing records, recorded data obtained from automated instruments, copies thereof certified as accurate and complete after verification, photographic negatives, microfilm, X-ray films, and records kept in the laboratory and medico-technical departments participating in the trial are original documents.

2.38. Source Data: The entirety of the findings and observations belonging to the clinical trial and of the information belonging to other activities related to the clinical trial, contained in original records or in certified copies of original records. Source data are kept in source documents. 2.39. Clinical Trial: Refers to the clinical trial of medicinal products for human use, bioavailability studies and bioequivalence studies. 2.40. Clinical Trial Interim Report: A report on the evaluations made on the basis of the interim results of the trial and the analyses performed during the trial. 2.41. Clinical Trial Report: A written description of a trial conducted in volunteers for any therapeutic, prophylactic or diagnostic purpose, made by fully integrating the clinical and statistical descriptions, presentations and analyses of the trial into a single report. 2.42. Non-clinical Study: Biomedical studies not performed on human volunteers. 2.43. Coordinator: A physician or dentist selected from among the principal investigators in a multicentre trial, who is responsible for

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ensuring coordination between the principal investigators of these trial sites and the ethics committee, the sponsor, the legal representative if any, and, where necessary, between them and the Agency. 2.44. Blinding (Masking): A procedure whereby, during the trial, one or more of the parties involved in the trial, such as the principal investigator or investigator, the volunteer, or the monitor, does not know which investigational product has been administered to the volunteer. Single blinding generally refers to the volunteer being unaware, whereas double blinding generally refers to the volunteer, the principal investigator or investigator, the monitor and, in some cases, the data analysts being unaware of the treatment given. 2.45. Site Management Organization Service: The set of services provided to trial sites by a contract research organization, independently of the sponsor, at the request of the principal investigator, for the performance of tasks such as the organization of trial files and the preparation of volunteers for visits in carrying out trial procedures. 2.46. Case Report Form (CRF): A printed, optical or electronic document prepared for the recording, as defined in the trial protocol, of the data and other information belonging to each volunteer in the trial. 2.47. Approval (Ethics Committee Approval): The favorable decision of the ethics committee that the trial may be conducted at the relevant trial sites within the limits determined in accordance with good clinical practice and the relevant legislation. 2.48. Primary Endpoint: The most important endpoint in the trial, which provides primary data. 2.49. Randomization: The process of assigning volunteers to treatment or control groups by chance in order to reduce bias. 2.50. Site Coordinator: Refers to auxiliary clinical trial personnel who, provided that they are preferably graduates of faculties related to health sciences and science faculties, holding at minimum a bachelor's degree, are assigned to work at the trial site under the supervision and oversight of the principal investigator, to perform critical trial-related procedures or to carry out duties within the authority delegated by the principal investigator in relation to the trial. 2.51. Secondary Endpoint: An endpoint that is less important than the primary endpoint in the trial. 2.52. Endpoint: May be defined as a variable that is one of the primary interests of the trial. This variable may be related to efficacy and safety. An endpoint may be used synonymously with efficacy variable and safety variable, but it is not used synonymously with demographic variable.

2.53. Principal Investigator: A physician or dentist who has completed specialty or doctoral training in the field related to the subject of the trial, and who is responsible for the conduct of the trial at the relevant trial site. 2.54. Contract: A written, dated and signed agreement made between two or more involved parties, which sets out the arrangements for the delegation and distribution of the work to be undertaken and, where necessary, financial matters. The trial protocol may form the basis of the contract. 2.55. Contract Research Organization (CRO): An independent organization, working in compliance with the principles of good clinical practice, to which the sponsor has transferred all or part of its duties and functions related to the clinical trial by means of a written contract. 2.56. Standard Operating Procedures (SOPs): Detailed, written instructions established with the aim of providing guidance and support complementary to the principles of good clinical practice and the relevant legislation. 2.57. Impartial Witness: A person who, in cases such as the volunteer or his/her legal representative being unable to read, reads the informed consent form (ICF) and other written information to the volunteer during the process of informing the volunteer, who is not part of the trial team, who has no involvement in the trial, and who should not be influenced by the persons involved in the trial. 2.58. Auxiliary clinical trial personnel: A member of the trial team, other than a physician or dentist, who takes part in the clinical trial and who is assigned by the principal investigator or the sponsor to carry out work and procedures related to the clinical trial under the supervision and oversight of the principal investigator, 2.59. Audit: The systematic and independent examination of trial-related activities and documents, in order to determine whether the trial-related activities and the recording, analysis and accurate reporting of the data obtained from the trial have been carried out in accordance with the trial protocol, the sponsor's standard operating procedures, good clinical practice and the relevant legislation. 2.60. Audit Trail: Documentation that shows the course of

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events. 2.61. Audit Certificate: The document prepared by the person performing the audit, confirming that the audit has taken place. 2.62. Audit Report: A written evaluation prepared by the person performing the audit regarding the results of the audit.

3. FUNDAMENTAL PRINCIPLES OF GOOD CLINICAL PRACTICE The fundamental principles of good clinical practice are as follows: 3.1. Clinical trials shall be conducted in accordance with good clinical practice, which is based on the principles set out in the current version of the Declaration of Helsinki, the relevant legislation and ethical principles. 3.2. Before a clinical trial is initiated, the foreseeable risks that may arise from the trial shall be evaluated in terms of the anticipated benefits to be obtained by the volunteer and by society. However, where the fact that the benefits to be provided by the clinical trial are greater than the anticipated risks is at an acceptable level, the trial may be initiated and continued. 3.3. The health, rights and safety of volunteers are the most important considerations that must be taken into account. These considerations take precedence over the interests of science and society. 3.4. Clinical and non-clinical information on the investigational product shall be of a nature that adequately supports the clinical trial to be conducted. 3.5. Clinical trials shall be defined in a protocol that is in accordance with scientific rules, scientifically sound, and expressed clearly and in detail. 3.6. A clinical trial shall be conducted in accordance with the approved trial protocol. 3.7. The medical care provided to volunteers and the medical decisions made on behalf of volunteers shall be the responsibility of a qualified physician or dentist.

3.8. Every individual involved in conducting the trial shall be qualified by education, training, and experience to perform the tasks incumbent upon them. 3.9. Informed consent, given entirely of the persons' own free will, shall be obtained from all volunteers in accordance with the relevant legislation before the clinical trial is initiated. 3.10. Information relating to the clinical trial shall be recorded, processed, and retained in a manner that allows its accurate reporting, interpretation, and verification. 3.11. Records identifying the volunteers shall be protected, in accordance with the provisions of the relevant legislation, in a manner that respects the rules of privacy and confidentiality. 3.12. Trial products shall be manufactured, handled, and stored in compliance with the good manufacturing practices determined in accordance with the relevant legislation. These products shall be used in accordance with the approved trial protocol. 3.13. Quality systems that guarantee the quality of the trial in every respect shall be implemented in the trial. 4. ETHICS COMMITTEE 4.1. The ethics committee shall possess the qualifications necessary to evaluate the scientific, medical, and ethical aspects of the proposed trial. 4.2. The ethics committee shall have no fewer than seven and no more than fifteen principal members, and at least as many substitute members as the number of principal members, provided that at least one member is a person who is not a healthcare professional and one is a lawyer, and that the majority of its members are healthcare professionals educated at the doctoral or medical specialization level. 4.3. All ethics committee members shall, prior to joining the ethics committee, have received and documented basic training on good clinical practice (GCP) and clinical trials in accordance with current legislation. 4.4. When establishing the ethics committee, the members are expected, where possible, to display a distribution in proportions close to one another with respect to gender. 4.5. The ethics committee shall safeguard the health, rights, and safety of the volunteers participating in the trial and shall pay special attention to trials in which subjects who may be vulnerable and sensitive populations participate. 4.6. The ethics committee shall ensure that the information and documents required to be submitted in clinical trial applications are complete and compliant with the relevant legislation. 4.7. The ethics committee shall review the clinical trial application submitted to it within the timeframes specified in the relevant legislation and notify the applicant of its decision. 4.8. When notifying its decision, the ethics committee shall pay attention to the following matters, the decision format shall conform to the template published on the website of the TİTCK (Turkish Medicines and Medical Devices Agency), and it shall document these in writing: 4.8.1. The explicit title of the trial, 4.8.2. The list of documents reviewed, including, where available, their dates and version numbers, 4.8.3. The list of members, also indicating the fields of

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expertise of the ethics committee members, 4.8.4. If a favourable decision has been notified, the favourable decision and its date, 4.8.5. If an unfavourable decision has been notified, the unfavourable decision, its justification, and its date, 4.8.6. If there is a situation of terminating or provisionally suspending any previously given favourable decision, its justification and date. 4.9. The ethics committee shall review the qualifications of the principal investigator for the trial applied for and, where necessary, of the investigators, the coordinator, and the administrative representative, by making use of their curriculum vitae or other documents it requests.

4.10. The ethics committee may request further information than that contained in the informed consent form (ICF) if it concludes that this would make a meaningful contribution to the rights, safety, and well-being of the volunteers. 4.11. Where a trial of non-therapeutic purpose is to be conducted with the consent of the volunteer's legal representative, the ethics committee shall pay particular attention to whether the proposed trial protocol or other documents sufficiently address the ethical considerations of the trial in question and whether they are compliant with the relevant legislation. 4.12. In cases where prior consent cannot be obtained, such as where the subject matter of the trial constitutes, with respect to the volunteer's health, a situation requiring emergency intervention and, at the time the intervention must be performed, the volunteer is unconscious and, in addition, a relative to provide consent on behalf of the volunteer or the volunteer's legal representative cannot be present either, the ethics committee shall determine whether the proposed trial protocol or other documents sufficiently address the ethical considerations of the trial in question and whether they are compliant with the relevant legislation. 4.13. The ethics committee shall review the amounts of the payments and the method of payment so that expenses that may arise from the volunteers' participation in the trial, such as transportation and meals, do not cause any coercion or have any negative impact on the volunteers. Payments to be made to volunteers shall not be contingent solely upon the volunteer's completion of the trial. 4.14. Where necessary, the ethics committee may request information on how the payment will be distributed among the volunteers. 4.15. The ethics committee shall ensure that information regarding expenses to be covered for the volunteers, such as transportation and meals, is included in the written informed consent form (ICF) and in the other written documents to be provided to the volunteers. 4.16. The ethics committee shall review and assess ongoing clinical trials at certain intervals, at least once a year, taking into account the degree of risk to the volunteers, through information and documents such as progress reports. 4.17. The ethics committee conducts an initial and continuing review of clinical trial applications. 4.18. Ethics committee members are obliged to observe the principle of confidentiality with respect to all information that comes to their attention. 4.19. Ethics committee members are prohibited from disclosing any documents and information that come to their attention relating to a clinical trial. Such documents and information shall be submitted only to authorized persons upon request by legally authorized persons or authorities. 4.20. Ethics committee members assume their duties by signing the confidentiality agreement and the conflict of interest declaration prepared by the TİTCK and published on the TİTCK's website. The said documents shall be renewed every year in January and in the event of any change in the declaration given, and shall be submitted to the TİTCK. 4.21. In order for ethics committees to operate in a standardized manner, their working procedures are determined by the TİTCK and published on the TİTCK's website. Ethics committees conduct their activities within the framework of these established standards. 4.22. The ethics committee shall operate in a manner compliant with the relevant legislation, good clinical practice (GCP), and standard working procedures, and shall record all its activities in writing. 4.23. Where necessary, the ethics committee may seek the opinion of expert persons from the relevant field and may invite such persons to meetings as advisors. Such persons are also required to sign the confidentiality agreement and the conflict of interest declaration prepared by the TİTCK and published on the TİTCK's

website. 4.24. Only those ethics committee members who participate in the ethics committee's reviews and deliberations shall vote, notify their decision, or make recommendations.

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4.25. Ethics committee members may vote or express opinions on matters relating to the trial if they are independent of the team of the clinical trial applied for or of the sponsor. An ethics committee member who has a relationship with the trial under review or a role in the trial may not participate in the ethics committee's deliberations and voting on that trial, and may not sign the ethics committee's decision. 4.26. The coordinator, administrative representative, principal investigator, investigator, sponsor, or the sponsor's legal representative may be invited to the ethics committee meeting for the purpose of providing information on any aspect of the trial. The coordinator, administrative representative, principal investigator, investigator, sponsor, or the sponsor's legal representative may not participate in the ethics committee's votes or decision notifications. 4.27. An up-to-date list containing the names and qualifications of the ethics committee members shall be maintained. 4.28. The ethics committee convenes with a two-thirds majority of the full membership and takes decisions by an absolute majority of the full membership. 4.29. The term of office of ethics committee members is two years, and members whose term of office has expired may be re-elected. 4.30. The membership of members who, during their term of membership, fail to attend three consecutive meetings or five non-consecutive meetings without a valid excuse shall terminate automatically. 5. PRINCIPAL INVESTIGATOR AND INVESTIGATOR 5.1. The coordinator, administrative representative, principal investigator, and investigators shall be qualified by education, training, and experience for the correct conduct of the trial. 5.2. The curriculum vitae of the coordinator, administrative representative, principal investigator, and investigators shall conform to the form published on the website of the TİTCK, and shall be up to date and signed. In the event of a request by the TİTCK, the ethics committee, or the sponsor, they shall substantiate these qualifications by providing documentary evidence. 5.3. A physician or dentist who has completed training in the specialty relevant to the subject of the trial and who is responsible for the conduct of the trial may serve as the principal investigator. The principal investigator must have completed a doctorate or a specialization. 5.4. Phase I clinical trials and bioavailability-bioequivalence studies are conducted by a suitable team possessing adequate training and experience in good clinical practice (GCP) and clinical trials, and by a pharmacologist who is a medical doctor and who has completed a specialization or a doctorate. 5.5. The coordinator, administrative representative, principal investigator, and investigators shall possess sufficient and detailed information on the trial products described in the current trial protocol and the investigator's brochure, and in the other sources of information provided by the sponsor. 5.6. The coordinator, administrative representative, principal investigator, and investigators shall be knowledgeable about good clinical practice (GCP), the current Declaration of Helsinki, and the relevant legislation, and shall comply with them. 5.7. The coordinator, administrative representative, principal investigator, and investigators are obliged to permit monitoring and auditing by the ethics committee or the sponsor, and inspection by the TİTCK or other relevant health authorities, in every matter relating to the trial, including the facilities where the trial is conducted and the documents relating to the trial. 5.8. Where necessary, the principal investigator, in order to assist in the conduct of the trial, ... the investigators, the clinical trial nurse and field staff, or auxiliary clinical trial personnel of appropriate qualifications, to the TİTCK and the ethics committee

...may delegate in accordance with the relevant legislation, provided that they are informed. He/she keeps records of the delegation lists of such persons. TİTCK (Turkish Medicines and Medical Devices Agency) may revoke this delegation, together with its justification. 5.9. The principal investigator should have a sufficient number of qualified personnel and adequate facilities to ensure that the trial can be conducted accurately and safely within the anticipated period. 5.10. The principal investigator should supervise the persons included in the trial team who undertake trial-related tasks at the trial site and who are delegated for this purpose in accordance with the relevant legislation. 5.11. Where the principal investigator obtains services from a team in order to perform trial-related duties, he/she should ensure that this team is appropriately qualified to carry out the said trial-related duties, and should implement procedures that ensure the integrity of the

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trial-related tasks performed and of any data obtained. 5.12. The coordinator, the administrative responsible person and the principal investigator should have sufficient time to conduct and complete the trial properly and within the designated trial period. Depending on the nature of the trial, the coordinator, administrative responsible person, principal investigator or investigators may conduct a certain number of trials simultaneously, provided that a valid justification is submitted. However, TİTCK (Turkish Medicines and Medical Devices Agency) or the ethics committee may impose restrictions in this regard, provided that the justification is stated. 5.13. The principal investigator should demonstrate the potential to enroll a sufficient number of eligible volunteers within the enrollment (recruitment) period. 5.14. The coordinator, administrative responsible person or principal investigator should ensure that the trial team is informed about the trial protocol, the investigational products and trial-related matters. 5.15. A qualified physician or dentist who is the principal investigator or an investigator is responsible for all trial-related medical or dental decisions. 5.16. The principal investigator or investigator and the trial site should ensure that adequate medical care is provided to the volunteer in the event of any trial-related adverse event, including clinically significant laboratory values, arising during or after the volunteer's participation in the trial. 5.17. The principal investigator or investigator should inform the volunteer where medical care is needed for an ongoing disease, as well as for other diseases arising during or after the trial and noticed by the principal investigator or investigator. 5.18. If there is another physician responsible for the volunteer's medical care and the volunteer consents to that physician being informed of his/her participation in the trial, it is recommended that the principal investigator or investigator provide the relevant physician with this information. 5.19. A volunteer is not obliged to state the reasons for his/her early withdrawal from the trial. However, the principal investigator or investigator may make a reasonable effort to ascertain the reason for the volunteer's withdrawal from the trial, provided that the volunteer's rights are respected. 5.20. Before initiating a trial, the coordinator, administrative responsible person or principal investigator should have obtained approval from the ethics committee and, for trials within the scope of the relevant legislation, authorisation from TİTCK (Turkish Medicines and Medical Devices Agency). 5.21. For trials requiring authorisation under the relevant legislation, for which the trial protocol has been approved by the ethics committee, the principal investigator or investigator should conduct the trial in accordance with the trial protocol authorised by TİTCK. 5.22. The coordinator, administrative responsible person or principal investigator and the sponsor should sign the trial protocol in order to confirm their mutual agreement. 5.23. The coordinator, administrative responsible person or principal investigator should not make any changes to the trial protocol without such changes being reviewed and approved in writing by the ethics committee and, for trials requiring authorisation under the relevant legislation, without the authorisation of TİTCK. However, where the protocol has been deviated from or a protocol change has been made in order to eliminate immediately emerging hazards, the ethics committee and TİTCK should be informed as soon as possible, together with the reasons therefor.

5.24. The coordinator, administrative responsible person, principal investigator or investigators should document any deviation from the approved trial protocol, together with the reasons therefor. It should be submitted upon request of the ethics committee or TİTCK. 5.25. The receipt, storage, distribution in accordance with the written request or the trial protocol, stock control, the procedures to be applied to the remaining amount and the record-keeping of the investigational products are under the responsibility of the principal investigator at each trial site where the trial is conducted. The principal investigator should preferably delegate these procedures to a pharmacist. 5.26. The person delegated by the principal investigator should keep records of the inventory of the investigational products held at the trial site, their use by the volunteers, and the return of unused products to the sponsor or their alternative disposal. These records should include the date, quantity, batch/serial number, expiry date, and the code numbers of both the investigational products and the trial volunteers. 5.27. The person delegated by the principal investigator should ensure that the investigational products are stored in accordance

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with the relevant legislation. 5.28. The principal investigator or investigator should keep records that appropriately document that the doses specified in the trial protocol have been administered to the volunteers, and should ensure that all investigational products received from the sponsor are reconciled with their consumption. 5.29. The principal investigator or investigator should ensure that the investigational products are used only in accordance with the approved trial protocol. 5.30. The principal investigator or investigator, or a suitably qualified person delegated by the principal investigator, should explain to the volunteers how to use the investigational products correctly and should check, at appropriate intervals, whether the volunteers are following the instructions properly. 5.31. If applicable, the principal investigator should implement the randomisation methods of the trial and ensure that the code is broken only in accordance with the trial protocol. In a blinded trial, the principal investigator should promptly document any premature unblinding and explain the reasons therefor to the sponsor. 5.32. The principal investigator, or an investigator who is a physician or a dentist, should comply with the rules specified in the relevant legislation and with ethical principles when obtaining and documenting the informed consent form (ICF). 5.33. The coordinator, administrative responsible person and principal investigator should ensure that the informed consent form (ICF) has been obtained from the volunteers participating in the trial before the trial is started. 5.34. The principal investigator should retain a wet-ink signed copy of the informed consent forms (ICF) in his/her own records. 5.35. The principal investigator should ensure that all data to be reported via the case report form and other required reports are reported to the sponsor accurately, completely and in a timely manner. 5.36. Data reported on the case report form that are based on source documents should be consistent with the source documents. In the event of any inconsistency, the reasons therefor should be explained. 5.37. Any correction or change to be made to a case report form should be dated and initialled, and the justification should be explained. This should not obscure the original data entry and should apply to both written and electronic changes. The sponsor should guide the principal investigator, or the investigator delegated by the principal investigator, in making such corrections. The sponsor should establish written procedures to ensure that documentation of any changes or corrections to be made to the case report forms is necessary and mandatory, and that such changes are always approved by the principal investigator or investigator. The principal investigator should retain records of the changes and corrections made.

5.38. The coordinator or principal investigator should keep, at each trial site, precise and accurate source information and trial records containing all relevant observations relating to the volunteers enrolled in the trial. Source data should be attributable, legible, original, accurate and complete. Changes made to source data should be traceable, should not obscure the original entry and should be explained where necessary. 5.39. The principal investigator should retain the trial-related documents in accordance with the relevant legislation and should take measures to prevent the accidental or premature destruction of the said documents. 5.40. Trial-related documents should be retained for at least fourteen years after the completion of the trial at all sites. However, where required by an agreement made with the sponsor, the said documents may also be retained for a longer period. When the period required for the retention of the documents has expired, it is the sponsor's responsibility to notify the principal investigator thereof. 5.41. The financial aspects of the trial should be documented in an agreement signed between the sponsor and the principal investigator. Where necessary, this agreement should also be made with the coordinator or the administrative responsible person. 5.42. The coordinator, administrative responsible person or principal investigator should provide monitors, auditors, the ethics committee, TİTCK or other relevant health authorities, and inspectors with direct access to trial-related records. 5.43. The coordinator, administrative responsible person or principal investigator should submit written summaries on the status of the trial to the institution where the trial is conducted, the ethics committee and TİTCK at least once a year, or more frequently upon request of the ethics committee and TİTCK. 5.44. The coordinator, administrative responsible person or principal investigator should promptly submit to the sponsor, the ethics committee and

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TİTCK their written reports on changes that will seriously affect the conduct of the trial or increase the risks to which the volunteers are exposed. 5.45. In the event of the emergence of new information that may adversely affect the health of the volunteers or the conduct of the trial, the coordinator, administrative responsible person or principal investigator should inform all relevant parties. 5.46. The principal investigator or investigator should comply with the timeframes specified in the relevant legislation for trial-related safety reporting and should fulfil his/her obligations. 5.47. The principal investigator, or an investigator to be delegated by him/her, reports all serious adverse events immediately to the sponsor, except for those for which the protocol or the investigator's brochure states that immediate reporting is not required. This urgent report is followed by a detailed written report. In the urgent report and in the subsequent follow-up reports, a single code number should be used for the volunteers participating in the trial. The volunteer's name and surname, personal identification information or address should not be used. 5.48. Adverse events or laboratory abnormalities identified in the trial protocol as critical for safety assessments should be reported to the sponsor by the principal investigator, or an investigator to be delegated by him/her, in accordance with the reporting requirements and within the timeframes specified in the trial protocol.

5.49. The principal investigator shall provide any additional information requested by the Turkish Medicines and Medical Devices Agency or the ethics committee regarding death cases, such as autopsy reports and medical records of cases resulting in death. 5.50. In the event of early termination or temporary suspension of the clinical trial for any reason, the principal investigator shall immediately inform the volunteers enrolled in the trial and ensure that appropriate treatment and follow-up are carried out. 5.51. If the principal investigator terminates or temporarily suspends the trial without the prior approval of the sponsor, the principal investigator shall immediately inform the institution where the trial is being conducted, the sponsor, and the ethics committee, and shall submit a detailed written explanation on this matter to the Turkish Medicines and Medical Devices Agency, the sponsor, and the ethics committee. 5.52. If the sponsor, the ethics committee, or the Turkish Medicines and Medical Devices Agency terminates or temporarily suspends the trial, the coordinator, administrative responsible person, or principal investigator shall inform the institution where the trial is being conducted along with the justification. 5.53. The principal investigator shall ensure that the institution where the trial is conducted, the ethics committee, and the Turkish Medicines and Medical Devices Agency have been informed after the completion of the trial. 5.54. All references to the principal investigator in this guideline also cover the coordinator.

6. SPONSOR 6.1. The sponsor is responsible for establishing written standard operating procedures, implementing and maintaining quality assurance and quality control systems in order to ensure that the trial is conducted, data is generated, documented, recorded, and reported in compliance with the trial protocol, the current Declaration of Helsinki, good clinical practice principles, and applicable regulations. 6.2. The sponsor is responsible for ensuring the agreement of all relevant parties to provide direct access to all trial-related sites, source data, and documents for monitoring and audits to be conducted by the sponsor, and for inspections to be conducted by the Turkish Medicines and Medical Devices Agency and relevant health authorities. 6.3. The sponsor shall ensure that it is stated in the trial protocol or in other written agreements that direct access to the source data of the trial will be provided and that monitoring, audits, and inspections related to the trial will be permitted. 6.4. In order to ensure the reliability and accurate processing of all data, quality control shall be applied at all stages related to data processing. 6.5. The sponsor shall implement a system to manage quality throughout the design, conduct, recording, evaluation, reporting, and archiving of clinical trials. 6.6. The sponsor shall focus its trial activities on ensuring the protection of volunteers and the reliability of trial results. Quality management encompasses clinical trial protocols, data collection tools and procedures, and the collection of information necessary for decision-making. 6.7. The methods used to guarantee and control the quality of the trial shall be proportionate to the risks inherent in the trial and the importance of the

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collected data. The sponsor shall ensure that each aspect of the trial is operationally feasible and shall avoid unnecessary complexity, procedures, and data collection. Protocols, case report forms, and other operational documents shall be clear, concise, and consistent. 6.8. All agreements between the sponsor and the principal investigator or other parties involved in the clinical trial shall be made in writing, either as part of the trial protocol or as a separate agreement.

6.9. The sponsor may transfer all or part of its trial-related duties to a contract research organization. The selection of the contract research organization is the responsibility of the sponsor. However, the ultimate responsibility for the quality and accuracy of the trial data always remains with the sponsor. The contract research organization shall implement quality assurance and quality control systems. 6.10. Any trial-related duty or function that has been transferred to and assumed by the contract research organization shall be specified in writing. 6.11. The sponsor shall ensure oversight of the trial-related duties and functions carried out on its behalf. 6.12. The sponsor remains responsible for any trial-related duty, except those specifically transferred to and assumed by the contract research organization. 6.13. All references to the sponsor in this guideline also cover the contract research organization, to the extent of the duties assumed by the contract research organization. 6.14. The sponsor shall work with appropriately qualified individuals for all stages of the trial process, including the design of the trial protocol and case report forms, the planning of analyses, and the analysis and preparation of the interim clinical trial report and the final clinical trial report. 6.15. The sponsor shall work with medical personnel who have the appropriate qualifications and who are prepared to promptly respond to questions or problems related to the trial. Where necessary, external consultants may be engaged for this purpose. 6.16. The sponsor shall work with appropriately qualified individuals to monitor the conduct of the trial, to process, verify, and perform statistical analyses of the data, and to prepare trial reports. 6.17. The sponsor may establish an independent data monitoring committee in order to periodically evaluate the progress of the clinical trial, including safety data and critical efficacy endpoints, and to make recommendations to the sponsor on whether to continue, modify, or terminate the trial. Working procedures shall be established for the independent data monitoring committee, and the independent data monitoring committee shall maintain records of all meetings it conducts. 6.18. The ethics committee or the Turkish Medicines and Medical Devices Agency shall request the establishment of an independent data monitoring committee from the sponsor where necessary. 6.19. When trial data is processed electronically or remote electronic data systems are used for trial data, the sponsor shall: 6.19.1. Ensure and document that the electronic data processing systems comply with complete, accurate, reliable, and consistent validation requirements that the sponsor must comply with, 6.19.2. Establish standard operating procedures for the use of these systems, 6.19.3. Ensure that these systems have a design that permits data changes in a manner that prevents the deletion of previously entered data, such as the documentation of data changes in the systems and the preservation of audit trails, data trails, and correction trails, 6.19.4. Maintain a security system that prevents unauthorized access to data, 6.19.5. Maintain a list of individuals authorized to make changes to the data, 6.19.6. Ensure and maintain adequate backup of the data, 6.19.7. Ensure that in the event of data modification during data processing, the original data and observations and the processed data remain comparable at all times, 6.19.8. Maintain the blinding, where applicable.

6.20. The sponsor shall use a volunteer code that has characteristics enabling the identification of each volunteer for the reported data. 6.21. The sponsor or other owners of the data shall retain all of the necessary documents belonging to the sponsor. 6.22. The sponsor shall retain all necessary trial-related documents concerning the sponsor in accordance with the applicable regulations of the countries where the product is approved or where the sponsor intends to submit an approval application. 6.23. If the sponsor suspends all or part of the clinical development process of the investigational product, the sponsor shall retain all trial-related documents for a period of at least fourteen years from the official termination of the trial. 6.24. If the sponsor suspends all or part of the clinical development process of the investigational product,

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the sponsor shall inform all investigators, the ethics committee, and the Turkish Medicines and Medical Devices Agency along with the justification. 6.25. Any transfer of data shall be notified to the ethics committee and the Turkish Medicines and Medical Devices Agency along with the justification. 6.26. The sponsor shall notify the principal investigator in writing of the requirement to retain documents or that retention is no longer required. 6.27. The sponsor is responsible for the selection of the principal investigator, investigators, and trial sites where the trial will be conducted. 6.28. For multicenter trials, the selection of the coordinator and the administrative responsible person is also the responsibility of the sponsor. 6.29. The sponsor shall provide the trial protocol and the current investigator's brochure to the coordinator, the administrative responsible person, the principal investigator, or the investigators before they sign the trial-related agreement, and shall allow the coordinator, the administrative responsible person, the principal investigator, and the investigators sufficient time to review them. 6.30. The sponsor shall ensure that the coordinator, administrative responsible person, principal investigator, or investigators enter into an agreement with the sponsor on the following matters and shall sign the trial protocol or an alternative document together with them to confirm this agreement: 6.30.1. To conduct the trial in accordance with good clinical practice, applicable regulations, and the trial protocol accepted by the sponsor, approved by the ethics committee, and authorized by the Turkish Medicines and Medical Devices Agency, 6.30.2. To comply with procedures related to data recording or reporting, 6.30.3. To permit monitoring, audits, and inspections, 6.30.4. To retain the documents that must be included in the principal investigator files, in accordance with the periods and conditions specified in the applicable regulations, until such time as the sponsor notifies that the documents are no longer needed. 6.31. The sponsor shall define and implement all of its trial-related duties and responsibilities before initiating the trial. 6.32. Where required by applicable regulations, the sponsor shall provide comprehensive legal and financial insurance for the principal investigator and investigators in accordance with the demands or needs arising from the trial, or shall compensate for any damage that may occur. 6.33. The sponsor shall specify in writing, in accordance with applicable regulations, how the costs of treatments to be provided for trial-related injuries that may occur as a result of complications arising from the trial will be covered. 6.34. When compensation is provided to trial volunteers, the method and form of compensation shall be in accordance with applicable regulations.

6.35. The financial aspects of the trial shall be documented in an agreement made between the sponsor and the principal investigator. Where necessary, this agreement shall also be made with the coordinator or the administrative responsible person. 6.36. Prior to initiating a clinical trial, the sponsor shall submit to the Turkish Medicines and Medical Devices Agency all applications required for review, acceptance, or authorization to commence the trial, in the appropriate format published on the Turkish Medicines and Medical Devices Agency website. All notifications made shall be dated and shall contain sufficient information to allow identification of the protocol. 6.37. During the initial application for the clinical trial, the sponsor is responsible for notifying the ethics committee and the Turkish Medicines and Medical Devices Agency of the number of volunteers planned to be enrolled from our country and the total target number of volunteers in the trial. In clinical trials, where the total target number of volunteers in the trial as notified at the time of application cannot be reached, the number of volunteers to be enrolled from our country may be increased. In order to increase the number of volunteers to be enrolled from our country, approval from the ethics committee and authorization from the Turkish Medicines and Medical Devices Agency shall be obtained, together with the justification and the current versions of the relevant documents such as insurance and budget. 6.38. In multicentre trials, the sponsor shall make a notification to the trial sites where the trial is being conducted, stating that the trial will also be conducted at these sites. This notification shall include the ethics committee approval of the trial, the authorization of the Turkish Medicines and Medical Devices Agency, a summary of the trial protocol, and the informed consent form (ICF). 6.39. When planning trials, the sponsor shall ensure that sufficient safety and efficacy data have been obtained

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which, based on the data to be obtained from non-clinical studies or clinical trials, will support the determination of the route of administration, dosage, duration of use, and the study population to be examined for the investigational product. 6.40. The sponsor shall update the investigator's brochure as significant new information becomes available. 6.41. The sponsor shall ensure that the investigational product is suitable for the trial phase, is manufactured in accordance with the applicable good manufacturing practice (GMP) rules, and, where blinding is used, is coded and labelled in a manner that maintains the blinding. In addition, the labelling shall comply with the relevant legislation. 6.42. The sponsor shall provide acceptable storage conditions and storage periods for the investigational product, the fluids and methods required for the preparation of the product, and, where available, the devices required for the infusion of the product. The sponsor shall inform all parties concerned. 6.43. The sponsor shall ensure that the investigational product is packaged in a manner that prevents contamination and unacceptable deterioration during transport and storage. 6.44. In blinded trials, the coding system for the investigational product shall include a mechanism that allows rapid identification of the products in the event of a medical emergency while preventing the breaking of the blind. 6.45. Where significant formulation changes are made to the investigational or comparator product during a clinical trial, the sponsor shall obtain, before the new formulation is used in clinical trials, the results of the additional studies necessary (e.g., stability, dissolution rate, bioavailability) to assess whether these changes significantly alter the pharmacokinetic profile of the product. 6.46. The sponsor is obliged to supply investigational products to the principal investigator and the trial sites. 6.47. In order to be able to initiate the trial, the sponsor shall under no circumstances supply investigational products to the trial site before obtaining ethics committee approval and the authorization of the Turkish Medicines and Medical Devices Agency.

6.48. Following the manufacture or importation of the investigational product, its storage, distribution, and delivery to the trial site in accordance with the specifications of the product, the maintenance of these conditions at the trial site, the collection of unused products from the trial site and the ensured return or appropriate destruction thereof, and the keeping of records of this entire process are obligations of the sponsor. 6.49. The sponsor shall ensure that the instructions to be followed by the principal investigator, and by the person(s) designated by the principal investigator, regarding the handling and storage of investigational products, together with the procedures for their documentation, are set out in written agreements. The methods in question shall ensure the safe receipt, handling, and storage of the product, its administration to volunteers, the retrieval of unused product from volunteers, and the return of unused products to the sponsor or their disposal or destruction in an alternative manner permitted by the sponsor and compliant with the relevant legislation, in accordance with the relevant legislation. 6.50. The sponsor shall ensure that investigational products are supplied to investigators in a timely manner. 6.51. The sponsor shall ensure the operation of a system for the retrieval of investigational products and for the documentation of this retrieval process (e.g., retrieval of defective product, retrieval of products remaining after completion of the trial, retrieval of products past their expiry date). 6.52. The sponsor shall ensure the operation of a system for the disposal of unused investigational products and for the documentation thereof. 6.53. The sponsor shall take measures to ensure that the stability of the investigational products throughout their period of use is confirmed. 6.54. The sponsor shall ensure that sufficient quantities of the investigational products used in the studies are retained in order to re-confirm their specifications where necessary, and that records are kept of the analyses of batch samples and of their specifications. As retaining sufficient quantities for sample analyses from the batches of investigational products (including comparator arm medicinal products) that are placed on the market in our country and that will be procured from the market for use falls, pursuant to the relevant legislation, under the responsibility of the manufacturer, the sponsor conducting the clinical trial may not be held responsible. 6.55. The sponsor shall retain the samples, to the extent permitted by stability, until the study data are complete or for the period required by the applicable licensing conditions (for

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whichever of these covers the longer period), in accordance with the relevant legislation, at its facility abroad or within the country. 6.56. The sponsor shall ensure that it is stated in the protocol or other written agreements that direct access to source data or documents relating to trial-related monitoring, auditing, ethics committee review, and inspection by the Turkish Medicines and Medical Devices Agency or the relevant health authorities is provided to the coordinator, the administrative responsible person, the principal investigator, and the investigators. 6.57. The sponsor shall ensure that all volunteers give their written consent to direct access to their original medical records for trial-related monitoring, auditing, and inspection. 6.58. The sponsor is responsible for the continuous safety evaluation of investigational products. 6.59. When findings emerge that would adversely affect the conduct of the trial or the safety of volunteers, and that may also alter the favourable opinion regarding the conduct of the trial, the sponsor shall inform the coordinator, the administrative responsible person, all principal investigators and investigators, the trial sites, the ethics committee, and the Turkish Medicines and Medical Devices Agency.

6.60. The sponsor shall expedite the reporting of all adverse reactions that are both serious and unexpected to the coordinator, the administrative responsible person, all principal investigators and investigators, and, where necessary, to the ethics committee and the Turkish Medicines and Medical Devices Agency. 6.61. The sponsor shall submit all safety updates and periodic reports to the Turkish Medicines and Medical Devices Agency in accordance with the relevant legislation. 6.62. The sponsor shall ensure that the trial is adequately monitored. 6.63. The sponsor shall monitor the trial in order to ensure the protection of the rights and health of volunteers, that the reported trial data are accurate, complete, and verifiable against source documents, and that the trial is conducted in accordance with the currently approved trial protocol, good clinical practice (GCP), and the relevant legislation. 6.64. The sponsor may conduct audits, independent of and separate from routine monitoring or quality control functions. The purpose of this is to evaluate whether the trial is being conducted in accordance with the trial protocol, standard operating procedures, good clinical practice (GCP), and the relevant legislation. 6.65. The sponsor shall select, to conduct the audit, individuals who are independent of the clinical trial and the data collection systems. 6.66. The sponsor shall ensure that the education and experience of the auditors are sufficient to conduct the audit appropriately. The qualifications of the auditors shall be documented. 6.67. The sponsor shall conduct audits of clinical trials and systems in accordance with written procedures setting out what is to be done, how, and at what frequency, and the format and content of audit reports. The audit report submitted to the Turkish Medicines and Medical Devices Agency or the relevant health authorities shall contain the importance of the trial, the number of volunteers in the trial, the type and degree of complexity of the trial, the level of risk to volunteers, and the outcomes identified. In addition, the observations and findings of the auditors shall be documented. In order to preserve the independence and value of the audit process, the Turkish Medicines and Medical Devices Agency or the relevant health authorities should not routinely request audit reports. The Turkish Medicines and Medical Devices Agency or the relevant health authorities may access the audit report during an inspection, on a case-by-case basis, in the event of serious non-compliance with good clinical practice (GCP) or during a judicial case or investigation. 6.68. Where sponsor personnel, the coordinator, the administrative responsible person, the principal investigator or investigators, or persons involved in the trial fail to comply with the trial protocol, the standard operating procedures, good clinical practice (GCP), or the relevant legislation, the sponsor shall take immediate action to remedy this non-compliance. 6.69. If, as a result of monitoring or auditing, serious or persistent non-compliance on the part of the coordinator, the administrative responsible person, the principal investigator or investigators, or persons involved in the trial is identified, the sponsor shall terminate the participation of these persons in the trial and shall immediately inform the Turkish Medicines and Medical Devices Agency and the ethics committee of this situation. 6.70. In the event of the early termination or temporary suspension of a trial, the

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sponsor shall notify the principal investigator, the ethics committee, and the Turkish Medicines and Medical Devices Agency of the termination or temporary suspension and the reasons thereof. 6.71. When the trial is completed or terminated early, the sponsor is responsible for the preparation of the clinical trial reports and for their submission to the ethics committee and the Turkish Medicines and Medical Devices Agency. 6.72. In multicentre trials, in addition to ensuring that the case report forms are designed to include the data required for all trial sites, the sponsor shall ensure that additional case report forms designed to collect additional data are provided to the investigators collecting the additional data.

6.73. The responsibilities of the coordinator, the administrative responsible person, the principal investigators, the investigators, and the other persons involved in the trial should be documented by the sponsor before the trial commences. 6.74. The provision of information to the coordinator, the principal investigators, and the investigators regarding adherence to the protocol and compliance with the uniform set of standards established for the evaluation of clinical and laboratory findings, as well as the completion of case report forms, should be ensured by the sponsor, and records thereof should be maintained. 6.75. The sponsor should ensure communication among the principal investigator, the coordinator, the administrative responsible person, the investigators, and the other persons involved in the trial who participate in the trial. 6.76. The sponsor should ensure that the trial is appropriately monitored. 6.77. The responsibilities of the sponsor and the trial-related parties regarding the use of computerized systems should be clear, and users should be trained by the sponsor on the use of these systems. 6.78. When changes are made to computerized systems, such as software upgrades or the transfer of data, the sponsor should ensure the integrity of the data, including any data that describe the context, content, and structure of the data. 6.79. The sponsor should develop a systematic, prioritized, and risk-based approach to the monitoring of clinical trials. 7. QUALITY MANAGEMENT 7.1. All parties involved in the trial team are responsible, within the scope of the duties and authorities specified in this Guideline, for the establishment and implementation of the quality management system. 7.2. The quality management system should include a risk-based approach as described below: 7.2.1. During the protocol development stage, the sponsor should identify those processes and data that are critical to ensuring the protection of volunteers and the reliability of the trial results. 7.2.2. Risks to critical trial processes and data should be identified. Risks should be assessed both at the system level (e.g., standard operating procedures, computerized systems, personnel) and at the clinical trial level (e.g., investigational product, trial design, data collection and recording). 7.2.3. The identified risks should be evaluated by taking into consideration the following: 7.2.3.1. the likelihood of errors occurring, given the existing risk controls, 7.2.3.2. the impact of such errors on the protection of volunteers and data integrity, 7.2.3.3. the extent to which such errors can be detected. 7.2.4. The sponsor should determine which risks need to be mitigated or can be accepted. Risk mitigation activities may be incorporated in the design and implementation of the protocol, in oversight plans, in agreements defining the roles and responsibilities among the parties, in systematic measures to ensure adherence to standard operating procedures, and in training on processes and procedures. Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables and the statistical design of the trial, in order to identify systematic issues that may affect volunteer safety or data integrity. The detection of deviations from the predefined quality tolerance limits should trigger an assessment to be performed to determine whether any action is needed. 7.2.5. Quality management activities should be documented to facilitate risk review and continuous improvement during the conduct of the clinical trial, and should be communicated to the trial-related parties. 7.2.6. Taking into account evolving knowledge and experience, the sponsor should regularly review the risk control measures that will ensure the implemented quality management activities are effective and appropriate.

7.2.7. The sponsor should describe the quality management approach implemented in the trial and summarize in the clinical study report any important deviations from the predefined

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quality tolerance limits. 8. MONITOR AND MONITORING ACTIVITIES 8.1. Monitors should be appointed by the sponsor. 8.2. Monitors should be adequately trained in good clinical practice (GCP) and clinical trials, and should possess the scientific or clinical knowledge required to monitor the trial appropriately. 8.3. The qualifications of the monitor should be documented. 8.4. Monitors should be thoroughly familiar with the investigational products, the trial protocol, the written informed consent form (ICF), other written information to be provided to volunteers, the sponsor's standard operating procedures, good clinical practice, and the applicable regulatory requirements. 8.5. In determining the scope of monitoring, the sponsor should take into consideration issues such as the purpose, design, size, and complexity of the trial, the degree of blinding, and the endpoints. 8.6. Monitoring should generally be conducted on site before, during, and after the trial. However, depending on the nature and risks of the trial, monitoring may also be conducted remotely through electronic systems or applications. 8.7. In accordance with the sponsor's requirements, monitors perform the following activities where relevant and necessary to the trial and the trial site: 8.7.1. Undertaking the role of communication between the sponsor and the coordinator, the administrative responsible person, the principal investigator, or the investigators, 8.7.2. Verifying that the principal investigator and the investigator have appropriate qualifications and resources, ensuring that these remain appropriate throughout the trial, and ensuring that the staff and facilities, including the laboratory and equipment, are safe and adequate for the conduct of the trial and continue to remain appropriate throughout the trial, 8.7.3. It is necessary to verify that the investigational products meet the following conditions: 8.7.3.1. that storage periods and conditions are acceptable, 8.7.3.2. that investigational products are available in sufficient quantities throughout the trial, 8.7.3.3. that investigational products have been administered only to volunteers eligible to receive them, at the doses and for the durations specified in the trial protocol, 8.7.3.4. that volunteers have been provided with the necessary instructions regarding the proper use, handling, storage, and return of the investigational products, 8.7.3.5. that the receipt, use, and return of the investigational products at the trial sites are appropriately controlled and that documentation thereof is available, 8.7.3.6. that the arrangements concerning unused investigational products at the trial sites comply with the applicable regulatory requirements. 8.7.4. Ensuring that the principal investigator and the investigators comply with the approved trial protocol and, if any, all approved amendments, 8.7.5. Ensuring that written informed consent has been obtained from all volunteers before they participate in the trial, 8.7.6. Ensuring that the principal investigator and the investigators have received the current investigator's brochure, all documents necessary for the trial, and all trial supplies that will be needed for the proper conduct of the trial and for compliance with the applicable regulatory requirements, 8.7.7. Ensuring that the coordinator, the administrative responsible person, the principal investigator, and the investigators fulfill all their obligations specified in the trial protocol and documented in written agreements between the sponsor and the principal investigator, and that they do not delegate these duties to unauthorized persons,

8.7.8. Ensuring that the principal investigator and the investigator who is a physician or dentist enroll only eligible volunteers in the trial, 8.7.9. Ensuring that the dates on which volunteers are enrolled in the trial are reported, 8.7.10. Ensuring that source data and other trial records are accurate, complete, up to date, and maintained, 8.7.11. Ensuring that the principal investigator and the investigator who is a physician or dentist submit all required reports, notifications, applications, and information, and that these documents are accurate, complete, prepared in a timely manner, legible, dated, and identify the trial, 8.7.12. Checking the accuracy and completeness of case report form (CRF) entries, source data, and other trial-related records against one another, 8.8. The monitor should specifically ensure that the following have occurred: 8.8.1. that the data required by the trial protocol are accurately reported on the CRFs and are consistent with the source data, 8.8.2. that any change in dose or treatment is duly documented for each of the volunteers, 8.8.3. that adverse events, concomitant medications, and intercurrent illnesses are reported in accordance with the trial protocol and on the CRFs, 8.8.4. that visits not

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undertaken by the volunteers and tests and examinations not performed are clearly reported on the CRFs, 8.8.5. that, in the case of the withdrawal or discontinuation of enrolled volunteers from the trial, the situation is reported on the CRFs and the necessary explanation is provided, 8.8.6. that the principal investigator and the investigator who is a physician or dentist are informed of any error, omission, or illegibility in the completion of the CRFs, 8.8.7. that appropriate corrections, additions, or deletions are made, that they are dated, that explanations are provided where necessary, and that they are made by the principal investigator or through an investigator authorized to make the original CRF changes, 8.8.8. that safety reports are duly reported to TİTCK (Turkish Medicines and Medical Devices Agency), the ethics committee, and the sponsor as specified in the applicable regulations, 8.8.9. that the principal investigator maintains the essential documents, 8.8.10. that, in the event of deviations from or violations of the trial protocol, the standard operating procedures, good clinical practice, and the applicable regulatory requirements, these are reported to the principal investigator and that steps are taken to prevent the recurrence of the identified deviations or violations. 8.9. The monitor should comply with the sponsor's written standard operating procedures, the applicable regulatory requirements, and the procedures specified by the principal investigator for monitoring a specific trial. 8.10. The monitor should submit a written report to the sponsor following each visit to the trial site or other communication regarding the trial. The report should state the date, the trial site, the name of the monitor, the name of the principal investigator, and the names of the other persons contacted. The reports should include a summary of the monitor's observations, the findings the monitor considers significant, deviations, deficiencies, conclusions, actions taken or to be taken, and the monitor's statements to ensure compliance.

8.11. The monitoring report being reviewed and followed up by the sponsor shall be documented by a person designated by the sponsor. 9. TRIAL PROTOCOL AND PROTOCOL AMENDMENTS The content of the trial protocol shall generally consist of the topics specified below. However, trial site-specific information may be specified on separate protocol pages or in a separate agreement, and some of the information listed below may be included in other documents referenced in the protocol, such as the investigator's brochure: 9.1. Trial protocol title, protocol number and date, 9.2. Amendment number and date for protocol amendments, 9.3. Name and address of the sponsor and, if different from the sponsor, the monitor, 9.4. Name and title of the person authorized to sign the trial protocol and protocol amendments on behalf of the sponsor, 9.5. Name, title, address and telephone numbers of the sponsor's medical adviser or, where appropriate, dentist for the trial, 9.6. Name and title of the investigator(s) responsible for conducting the trial and the address and telephone numbers of the trial sites, 9.7. Name, title, address and telephone numbers of the appropriately qualified physician or dentist responsible for all trial-related medical or dental health decisions, 9.8. Address(es) of clinical laboratory(ies) and other medical or technical departments and/or institutions involved in the trial, 9.9. If available, the name and description of the investigational product(s), 9.10. A summary of findings from non-clinical studies that may be clinically pertinent, and findings from clinical trials relevant to the trial, 9.11. A summary of the known and potential risks and benefits, to participants, known at the time, 9.12. A description and justification for the route of administration, dosage, dosage regimen and treatment period(s), 9.13. A statement that the trial will be conducted in accordance with the trial protocol, good clinical practice and the applicable regulatory requirement(s), 9.14. A description of the population to be studied, 9.15. References to literature and data that are relevant to the trial and that provide background for the trial, 9.16. A detailed description of the objectives and purpose of the trial, 9.17. The scientific integrity of the trial and the credibility of the data obtained from the trial depend substantially on the trial design. A description of the trial design should include the following: 9.17.1. A specific statement of the primary endpoints and, if available, secondary endpoints to be measured during the trial, 9.17.2. A description of the type and design of the trial to be conducted, and a schematic presentation of the trial design, methods and stages, 9.17.3. A description of the measures to be taken to minimize or prevent bias, 9.17.4. A

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description of the trial treatments and the dosage and dosage regimen of the investigational product(s), 9.17.5. A specification of the dosage form, packaging and labelling of the investigational product(s), 9.17.6. A description of the expected duration of participation and a description of the entire trial including any follow-up period for participants, if available, 9.17.7. A description of the stopping rules or completion criteria for the trial for the individual participant for individual parts of the trial and for the entire trial, 9.17.8. If available, methods of accounting for the use of the investigational product,

9.17.9. Maintenance of trial treatment randomization codes and procedures for their breaking, 9.17.10. Identification of data to be recorded directly on the case report forms (i.e., no prior written or electronic record of data) and data to be considered as source data. 9.18. Inclusion criteria for participants in the trial, 9.19. Exclusion criteria for participants in the trial, 9.20. Withdrawal criteria for participants from the trial and methods describing the following: 9.20.1. When and how participants will be withdrawn from or taken out of the trial, 9.20.2. The type and timing of data to be collected for withdrawn or discontinued participants, 9.20.3. Whether and how participants will be replaced, 9.20.4. The follow-up of participants withdrawn from or discontinued from the trial. 9.21. The treatments to be administered, including the name of all products, dosages, dosage schedule, route of administration, the treatment period(s) for each investigational product treatment, trial treatment group and trial arm, including follow-up periods for participants, 9.22. Permitted and prohibited medications and treatments (including rescue medication) before and after the trial, 9.20.3. Whether and how participants will be replaced, 9.20.4. The follow-up of participants withdrawn from or discontinued from the trial. 9.21. The treatments to be administered, including the name of all products, dosages, dosage schedule, route of administration, the treatment period(s) for each investigational product treatment, trial treatment group and trial arm, including follow-up periods for participants, 9.22. Permitted and prohibited medications and treatments (including rescue medication) before and after the trial, 9.23. Methods for monitoring participant compliance, 9.24. Specification of efficacy parameters, 9.25. Methods and timing for assessing, recording and analyzing efficacy parameters, 9.26. Safety assessment: 9.26.1. Specification of safety parameters, 9.26.2. Methods and timing for assessing, recording and analyzing safety parameters, 9.26.3. Procedures for eliciting and reporting adverse events and intercurrent illnesses, and methods for recording them, 9.26.4. How and for how long participants will be followed up after adverse events. 9.27. Statistics: 9.27.1. A description of the statistical methods to be employed, including the timing of planned interim analyses, 9.27.2. The number of participants planned to be enrolled in the trial, 9.27.3. In multicenter trials, the number of participants anticipated to be enrolled at each trial site, 9.27.4. The reason for the selection of the sample size, including reflections on the power of the trial and clinical justification, 9.27.5. The level of significance to be used, 9.27.6. Criteria for terminating the trial, 9.27.7. Procedures for accounting for missing, unused or spurious data, 9.27.8. Procedures for reporting deviations from the original statistical plan (any deviations from the original statistical plan should be described and justified in the protocol or, where appropriate, in the final report), 9.27.9. The selection of participants to be included in the analyses (e.g., all eligible participants, evaluable participants, randomized participants, participants who have received the investigational product).

9.28. The identification of any individuals or organizations/institutions having direct access to source data, 9.29. A description of the ethics considerations related to the trial, 9.30. Data processing and record keeping, 9.31. Financing and insurance, if not addressed in a separate agreement, 9.32. Publication policy, if not addressed in a separate agreement, 9.33. A specification of the arrangements to ensure that participants will have access to interventions identified as beneficial during the trial after the trial is over. 10. INFORMED CONSENT FORM 10.1. In obtaining and documenting informed consent from participants, the ethical principles that have their origin in the current Declaration of Helsinki, good clinical practice and the applicable regulatory requirement(s) should be complied with. 10.2. The written informed consent form to be provided to participants who will take part in the trial must have been approved by the ethics committee

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and authorization must have been obtained from the Turkish Medicines and Medical Devices Agency before the trial commences. 10.3. The written informed consent form to be provided to participants should be revised in light of newly obtained information relevant to the participant's consent. Any revised informed consent form must be approved by the ethics committee and authorization must be obtained from the Turkish Medicines and Medical Devices Agency before use. The participant or the participant's legally acceptable representative must be informed immediately when new information that may affect the participant's willingness to continue in the trial is obtained. The sharing of such information must be documented. 10.4. The responsible investigator or any person involved in the trial should not unduly influence or coerce the participant to participate or to continue in the trial. 10.5. None of the oral information or written documents regarding the trial, including the written informed consent form, should contain any provision or statement that would waive or appear to waive any of the participant's or the legally acceptable representative's legal rights, or any provision or statement that would release or appear to release the responsible investigator, any person involved in the trial, the institution, the sponsor or their representatives from liability for negligence. 10.6. The participant or the legally acceptable representative should be informed about all pertinent aspects of the trial. 10.7. The language used in oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the participant or the legally acceptable representative or an impartial witness. 10.8. Before informed consent is obtained, the participant or the legally acceptable representative should be given ample opportunity and time to enquire about details of the trial and to decide whether or not to participate. All questions about the trial should be answered to the satisfaction of the participant or the participant's legally acceptable representative by the person providing the information. 10.9. The written informed consent form should be signed and personally dated by the participant or, where applicable, the participant's legally acceptable representative and by an impartial witness who did not participate in the informed consent discussion, and by the investigator who is a member of the trial team who conducted the informed consent discussion and who is a competent physician or dentist, with the first name and surname being written in the person's own handwriting, before the participant participates in the trial. Each page of the written informed consent form should be initialed by the participant or, where applicable, the legally acceptable representative and the impartial witness, and by the investigator who is a member of the trial team.

10.10. If the volunteer or the volunteer's legal representative is unable to read or write, or if the volunteer is visually impaired, the entire informed consent discussion shall be conducted in the presence of an impartial witness who is not a member of the trial team. In this case, after the written informed consent form (ICF) and other written information to be provided to the volunteer have been read out or explained to the volunteer or the volunteer's legal representative, after the volunteer or the legal representative has orally consented to the volunteer's participation in the trial, and, where applicable, after these persons have signed and dated the consent form, an impartial witness shall sign and date the consent form. By signing the consent form, the witness attests and certifies that the information contained in the consent form and the other written information were accurately explained to the volunteer or the volunteer's legal representative, that they were understood by the volunteer or the legal representative, and that informed consent was given by the volunteer or the legal representative of his/her own free will.

10.11. The informed consent discussion, the written informed consent form (ICF) provided to volunteers, and other written information shall include, as a minimum, explanations relating to the following subjects:

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10.11.1. That the study is a trial,

10.11.2. The purpose of the trial,

10.11.3. The treatments to be administered in the trial, and the probability of random assignment of volunteers to trial groups for the different treatments,

10.11.4. All procedures to be followed or performed on the volunteer, including invasive procedures to be performed during the trial,

10.11.5. The responsibilities of the volunteer,

10.11.6. The experimental aspects of the trial,

10.11.7. The foreseeable risks or discomforts to which the volunteer (and, where the trial is to be conducted in pregnant or nursing women, the embryo, fetus, or nursing infant) may be exposed,

10.11.8. That, with regard to the benefits reasonably to be expected from the trial, the volunteer is informed of this circumstance where no clinical benefit is intended for the volunteer,

10.11.9. The alternative procedures or treatment regimens that may be available to the volunteer, and their potential benefits and risks,

10.11.10. The compensation to be provided to, or the treatments to be made available for, the volunteer in the event of a trial-related injury,

10.11.11. Information regarding expenses, such as transportation and meals, to be covered for the volunteers,

10.11.12. That participation of the volunteer in the trial is voluntary and that the volunteer may refuse to participate in, or withdraw from, the trial at any time he/she wishes, without being subject to any penalty or sanction and without forfeiting any of his/her rights,

10.11.13. That monitors, auditors, the ethics committee, the Turkish Medicines and Medical Devices Agency (TİTCK), and other relevant health authorities may have direct access to the volunteer's original medical records, that this information will be kept confidential, and that, by signing the written informed consent form (ICF), the volunteer or the volunteer's legal representative authorizes such access,

10.11.14. That, in accordance with the relevant legislation, records identifying the volunteer will be kept confidential and will not be disclosed to the public, and that, in the event of publication of the results of the trial, the identity of the volunteer will remain confidential,

10.11.15. That the volunteer or the volunteer's legal representative will be informed in a timely manner when new information relevant to the subject matter of the trial and capable of affecting the volunteer's willingness to continue participation in the trial is obtained,

10.11.16. The telephone numbers of the persons whom the volunteer may contact at any time in order to obtain further information about the trial, about his/her rights, or about any adverse event related to the trial,

10.11.17. The circumstances or reasons that would require the termination of the volunteer's participation in the trial,

10.11.18. The anticipated duration of the volunteer's participation in the trial,

10.11.19. The approximate number of volunteers expected to participate in the trial.

10.12. Prior to participation in the trial, the volunteer or the volunteer's legal representative shall be provided with a copy of the signed and dated written informed consent form (ICF) and a copy of the other written information provided to the volunteer. During the volunteer's participation in the trial, the volunteer or the volunteer's legal representative shall be provided with a copy of the signed and dated updates to the consent form and a copy of any changes made to the written information provided to volunteers. One copy of these informed consent forms shall be retained by the principal investigator, and the other copy shall be retained by the volunteer.

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10.13. Where the clinical trial is one in which the volunteer can be enrolled in the trial only with the consent of the volunteer's legal representative, the volunteer shall also be informed about the trial to the extent of his/her capacity of comprehension and, where possible, the written informed consent form shall be assented to, signed, and dated by the volunteer personally.

10.14. Except in the circumstances specified in Article 10.15, a non-therapeutic trial (a trial in which there is no anticipated direct clinical benefit to be obtained by the volunteer) shall be conducted only on volunteers who are able to give consent personally and who are able to sign and date the written informed consent form.

10.15. Non-therapeutic trials may also be conducted on volunteers whose legal representative has given consent, provided that the following conditions are fulfilled:

10.15.1. That the objectives of the trial cannot be met by means of a trial in volunteers who are able to give informed consent personally,

10.15.2. That the foreseeable risks to which the volunteers will be exposed are low,

10.15.3. That the potential negative effects on the health of the volunteer are minimized and low,

10.15.4. That the trial is not prohibited by law,

10.15.5. That approval is obtained from the ethics committee regarding the participation of such volunteers and that the written favorable opinion covers this matter.

Unless there is a justified exceptional circumstance, such trials shall be conducted on patients having a disease or condition targeted by the investigational product. Volunteers participating in such trials shall be closely monitored and shall be withdrawn from the study if they experience discomfort in any way.

10.16. In order to protect the rights, safety, and well-being of the volunteer and to ensure compliance with the relevant legislation, in emergency situations where it is not possible to obtain the volunteer's prior consent, the written consent of the volunteer's legal representative, if any, shall be requested. In cases where the volunteer's legal representative is not present, the conditions specified in the trial protocol — previously approved by the ethics committee and previously authorized by the Turkish Medicines and Medical Devices Agency (TİTCK) with regard to the volunteer's participation in the trial — shall be complied with. Thereafter, the volunteer or the volunteer's legal representative shall be informed about the trial as soon as possible, and the written consent of the volunteer or the legal representative shall be obtained regarding the continuation of the volunteer's participation in the trial or the volunteer's withdrawal from the trial of his/her own will.

10.17. In clinical trials to be conducted on children, if the child has the capacity to express assent, in addition to the child's own assent, the written consent of the child's mother and father, or of the guardian if the child is under guardianship, shall be obtained after they have been informed in accordance with the relevant legislation.

10.18. In clinical trials to be conducted on persons in intensive care and with impaired consciousness, written consent shall be obtained after the legal representative, if any, or otherwise the relatives have been informed in accordance with the relevant legislation. If none of them can be reached, the person may be included in the trial under the responsibility of the principal investigator or of an investigator who is a physician or a dentist.

10.19. Ethics committee approval and authorization from the Turkish Medicines and Medical Devices Agency (TİTCK) must also be obtained for other information and documents to be provided to volunteers besides the informed consent form (ICF).

10.20. Changes may be made to the patient cards and patient diaries used in authorized and ongoing studies, provided that the Turkish Medicines and Medical Devices Agency (TİTCK) and the ethics committee are notified. However, the Turkish Medicines and Medical Devices Agency (TİTCK) or the ethics committee may request a correction regarding these changes, together with the justification.

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11. INVESTIGATOR'S BROCHURE

11.1. The investigator's brochure is a compilation of the clinical and nonclinical data pertaining to the investigational product(s). In this guideline, the limits of the minimum information to be included in the investigator's brochure are delineated, and recommendations regarding its design are provided.

11.2. The purpose of the investigator's brochure is to provide information to the principal investigator and to other persons involved in the trial, thereby enabling them to understand the rationale for many key features of the trial protocol — such as dose, dose frequency or dose interval, methods of administration, and safety monitoring methods — and to ensure compliance therewith.

11.3. The investigator's brochure also provides insight to support the clinical care of volunteers throughout the clinical trial. The information should be presented in a concise, plain, impartial, and balanced manner, without a promotional intent, and in such a way that a potential investigator can understand it and make an impartial risk-benefit assessment regarding the suitability of the trial.

11.4. A medically qualified person may participate in the process of amending the text of the investigator's brochure; however, this shall be approved in the investigator's brochure by the disciplines that generated the described data.

11.5. The type and scope of the available information in the investigator's brochure are expected to vary depending on the stage of development of the investigational product.

11.6. If the investigational product is licensed in our country, a comprehensive investigator's brochure may not be necessary. Where the Turkish Medicines and Medical Devices Agency (TİTCK) grants permission, the package leaflet, the summary of product characteristics, the instructions for use, or the labelling of the product may be a suitable alternative, provided that current, comprehensive, and detailed information is included on all matters relating to the investigational product that may be of importance to the principal investigator. If a product licensed in our country is being studied for a new use, an investigator's brochure relating to this new use shall be prepared.

11.7. The investigator's brochure shall be reviewed at least annually and revised at the required frequency in accordance with the sponsor's written procedures. Depending on the stage of development and the emergence of relevant new information, frequent amendments or updates may be necessary. However, these new pieces of information shall be submitted to the ethics committee for approval. If these are changes that need to be reflected in the informed consent form (ICF) or in the trial protocol, authorization from the Turkish Medicines and Medical Devices Agency (TİTCK) must be obtained in addition to ethics committee approval.

11.8. The sponsor is obligated to ensure that the principal investigator is provided with a current investigator's brochure. In a trial sponsored by an investigator, the investigator shall determine whether the investigator's brochure is provided by a commercial manufacturer. If the investigator's brochure is provided by the investigator, this person shall provide the necessary information to the trial team.

11.9. The investigator's brochure shall contain a title page and a confidentiality statement:

11.9.1. Title page: The sponsor's name, the identity of each investigational product (trial number, chemical name, or approved generic name, if legally permitted, and

(trade names if requested by the sponsor). In addition, it is recommended that an edition number be provided and that reference be made to the number and date of the previous edition. 11.9.2. Confidentiality Statement: The sponsor may wish to make a statement indicating that the investigator's brochure is a confidential document that will be used only for informational purposes by the investigator, the study team, the ethics committee, and the Turkish Medicines and Medical Devices Agency. 11.10. The investigator's brochure should consist of the following sections, and in each of them, where applicable, references to the relevant literature should be provided. 11.10.1. Table of Contents: An example of the table of contents section is provided in

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Article 11.12. 11.10.2. Summary: A brief summary (preferably not exceeding two pages) should be provided, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information that is important for the clinical development stage of the investigational product. 11.10.3. Introduction: A brief introduction should be written explaining the chemical name of the investigational product(s) (and, once approved, their generic and trade names), all active ingredients it contains, the pharmacological class of the investigational product(s) and their expected position within this class (e.g., its advantages), the rationale for conducting research with the investigational product(s), and the intended prophylactic, therapeutic, or diagnostic indications. Consequently, the introduction should present the general approach to be followed in the evaluation of the investigational product. 11.10.4. Physical, Chemical, and Pharmaceutical Properties and Formulation: The substances contained in the investigational product (including chemical or structural formulae) should be described, and a brief summary of the relevant physical, chemical, and pharmaceutical properties should be provided. In order to ensure that appropriate safety measures are taken throughout the trial, the formulations used, including excipients, should be described and, if clinically relevant, justified. Information on the storage and handling of dosage forms should be provided. Structural similarities to other known compounds should be stated. 11.10.5. Nonclinical Studies: The results of all significant, relevant nonclinical pharmacological, toxicological, pharmacokinetic, and metabolism studies of the investigational product must be presented in summary form. This summary should include the method used, the results, and a discussion of the significance of the findings regarding the investigated therapeutic effects and the adverse or undesirable effects in humans. When appropriate, the information presented should also include, if known, the following: 11.10.5.1. The animal species tested, 11.10.5.2. The number of animals in each study group and their sex, 11.10.5.3. The unit of the administered dose (e.g., mg/kg, ml/kg), 11.10.5.4. The dose range, 11.10.5.5. The route of administration, 11.10.5.6. The duration of dosing, 11.10.5.7. Information on systemic distribution, 11.10.5.8. The duration of follow-up after exposure, 11.10.5.9. The findings obtained, including the following: 11.10.5.9.1. The nature and frequency of pharmacological or toxic effects, 11.10.5.9.2. The severity or intensity of pharmacological or toxic effects, 11.10.5.9.3. The time to onset of the effects, 11.10.5.9.4. The reversibility of the effects, 11.10.5.9.5. The duration of the effects, 11.10.5.9.6. The dose-response relationship. Where appropriate, table format or lists should be used in order to clarify the presentation.

In the following sections, the most important findings obtained from the studies should be discussed, including the dose-response relationship of the observed effects, their significance for humans, and any side effect that should be examined in humans. Where appropriate, the findings on effective and non-toxic doses in the same animal species should be compared (the therapeutic index should be discussed). The significance of this information for the dose recommended for humans should be stated. Where possible, comparisons should be made in terms of blood/tissue levels rather than on an mg/kg basis. a) Nonclinical Pharmacology: A summary of the pharmacological properties of the investigational product and, where appropriate, of its significant metabolites studied in animals should be included in the investigator's brochure. The summary in question should include studies evaluating the potential therapeutic efficacy (e.g., efficacy models, receptor binding, and specificity) and safety (e.g., special studies evaluating pharmacological effects other than the intended therapeutic effect). b) Pharmacokinetics and Product Metabolism in Animals: The pharmacokinetics, biotransformation, and elimination of the investigational product in all animal species studied should be summarized. The discussion of the findings should include the absorption of the investigational product and its metabolites, their local and systemic bioavailability, and their relationship to the pharmacological and toxicological findings in the animal species. c) Toxicology: A summary of the toxicological effects found in the relevant studies conducted in different animal species should be presented under the headings of single dose, repeated dose, special studies (e.g., irritation and sensitization), reproductive toxicity,

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genotoxicity, mutagenicity, and carcinogenicity. 11.10.6. Effects in Humans: The known effects in humans should be discussed comprehensively, including information on the pharmacokinetic properties, metabolism, pharmacodynamic properties, dose-response relationship, safety, efficacy, and other pharmacological properties of the investigational product(s). Where possible, a summary of each completed clinical trial should be provided. In addition, findings on any use of the investigational product(s) other than the findings obtained from clinical trials (e.g., experience gained during marketing) should also be presented. 11.10.7. Pharmacokinetics and Product Metabolism in Humans: If available, a summary of the information related to the pharmacokinetics of the investigational product(s) should be provided, including the following: 11.10.7.1. Pharmacokinetic properties (metabolism, absorption, plasma protein binding, and elimination where appropriate), 11.10.7.2. The bioavailability of the investigational product using the reference dosage form (absolute or relative bioavailability where possible), 11.10.7.3. Population subgroups (e.g., in terms of sex, age, and individuals with impaired organ function), 11.10.7.4. Interactions (e.g., product-product interactions and interactions with food), 11.10.7.5. Other pharmacokinetic data. 11.10.8. Safety and Efficacy: Safety information obtained from previous studies in participants (volunteers) with the investigational product(s) (and, where appropriate, their metabolites), and information on their pharmacodynamic properties, efficacy, and dose-response relationship should be presented in summary form, and the significance of this information should be discussed. If a large number of clinical trials have been completed, presenting the safety and efficacy summaries in subgroups by indication ensures that the data are presented clearly. For all clinical trials (including those for all indications studied), adverse reactions must be summarized in tabular form. Differences in adverse reaction

patterns/incidences between indications or subgroups should be discussed. The investigator's brochure should describe the probable risks and adverse reactions that may be anticipated on the basis of previous experience with the investigational product and other products. It should also describe the precautions to be taken or the special monitoring to be performed as part of the use of the products in the trial. 11.10.9. Marketing Experience: The investigator's brochure should identify the countries where the investigational product has been marketed or approved. Any significant information obtained from the marketed use of the product (e.g., formulations, dosages, routes of administration, and adverse product reactions) should be summarized. The investigator's brochure should also identify the countries where the investigational product has not been approved/licensed for marketing or has been withdrawn from the market/license. 11.10.10. Summary of Data and Guidance for the Investigator: This section should provide a general discussion of the clinical and nonclinical data and, where possible, summarize the information obtained from various sources on the different properties of the investigational product(s). In this way, the most informative interpretation of the available data can be presented to the responsible investigator, and an assessment of their implications for future clinical trials can be enabled. Where appropriate, published reports on related products should be discussed. In this way, the responsible investigator(s) can be enabled to anticipate adverse reactions or other problems in clinical trials. The overall objective of this section is to ensure that the probable risks and adverse reactions, the specific tests, observations, and precautions that may need to be taken for the clinical trial are clearly understood by the investigator. This should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Based on previous experience obtained in humans and on the pharmacological effects of the investigational product, guidance should also be provided to the investigator on the recognition and treatment of probable overdose and adverse reactions. 11.11. An example of the title page of the investigator's brochure is provided below: Name of the sponsor Product Study number Name(s): chemical name, generic name (if approved) Trade names (if legally permitted and if requested by the sponsor) Edition number of the investigator's brochure Date of issue of the investigator's brochure Edition number and date of the previous edition replaced by the investigator's brochure 11.12. An

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example of the table of contents of the investigator's brochure is provided below: Confidentiality statement (optional) Signature page (optional)

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Summary
Introduction
Physical, chemical, and pharmaceutical properties and formulation
Nonclinical studies
Nonclinical pharmacology
Pharmacokinetics and product metabolism in animals
Toxicology
Effects in humans
Pharmacokinetics and product metabolism in humans
Safety and efficacy
Marketing experience
Summary of data and investigator's guide
References to publications and reports: these should be placed at the end of each section.
Annexes (if any)

12. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF THE CLINICAL TRIAL

12.1. Essential documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the principal investigator or investigators, sponsor, and monitor with good clinical practice standards and with the applicable regulatory requirements.

12.2. Timely provision of these documents to the relevant parties may ensure the successful management of the trial by the coordinator, administrative responsible, principal investigator, investigators, sponsor, and monitor.

12.3. These documents are also reviewed as part of the process demonstrating the validity of the conduct of the trial and the integrity of the data collected, in the sponsor's independent audit function, and in inspections carried out by the Turkish Medicines and Medical Devices Agency.

12.4. The documents to be prepared are grouped into three sections according to the stage of the trial at which they will normally be generated: before the clinical phase of the trial commences, during the conduct of the clinical phase of the trial, and after completion or termination of the trial.

12.5. The purpose of each document is explained. It is specified whether these documents are to be filed in the files of the principal investigator, the sponsor, or both. Some of the documents may be combined, provided that individual elements are easily identifiable.

12.6. The trial master files should be prepared at the beginning of the trial, both at the principal investigator's site and at the sponsor's. At the close of the trial, the monitor should review both the principal investigator's and sponsor's files and confirm that all necessary documents are in the appropriate files before a closure is performed.

12.7. Any or all of the documents addressed in this guideline may be subject to, and made available for, audit by the person conducting the audit on behalf of the sponsor, and inspection by the Turkish Medicines and Medical Devices Agency or the relevant health authority.

12.8. The sponsor and the principal investigator should maintain a record of the location(s) where their respective essential documents are stored. The archiving system should ensure identification, retrieval, and access to the documents.

12.9. Depending on the activities conducted, individual trials may require additional documents not specifically identified in the list of essential documents. The sponsor or principal investigator should include these as part of the trial master file.

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12.10. The sponsor should ensure that the principal investigator has control of and continuous access to the case report forms reported to him/her by the principal investigator. The sponsor should not have exclusive control over these data. When a copy is used in place of an original document, the copy in question should meet the requirements of certified copies.

12.11. Before the clinical phase of the trial commences, at least the following documents should be prepared and filed before the trial formally begins:

12.11.1. Investigator's Brochure, for the purpose of documenting that relevant and current information about the investigational product has been provided to the investigator,

12.11.2. Signed trial protocol and amendments and CRF, if available, for the purpose of documenting the agreement of the investigator and the sponsor to the trial protocol, amendments, and CRF (a draft CRF may also be acceptable; however, ethics committee approval of the final version of the CRF must be obtained before the first enrollment of a volunteer is performed),

12.11.3. Informed consent form (ICF), for the purpose of documenting that written information has been provided to volunteers to support their ability to give fully informed consent, and that measures for volunteer recruitment for the trial are appropriate and not coercive; advertisements, if any other written information is used to recruit volunteers for the trial,

12.11.4. Financial aspects of the trial,

12.11.5. Insurance statement, if required,

12.11.6. Agreements signed between the relevant parties,

12.11.7. Ethics committee approval,

12.11.8. Turkish Medicines and Medical Devices Agency authorization, when required in accordance with the applicable legislation,

12.11.9. Curriculum vitae of the coordinator, administrative responsible, principal investigator, and investigators,

12.11.10. Normal values or ranges of the tests specified in the trial protocol, and documentation relating to the laboratory, if available,

12.11.11. Label for the investigational product prepared in accordance with the applicable legislation,

12.11.12. Instructions for handling of investigational products, if not included in the trial protocol or the Investigator's Brochure, for the purpose of documenting the instructions required for appropriate storage, packaging, distribution, and disposal of investigational products and trial-related materials,

12.11.13. Shipping records for investigational products and trial-related materials, for the purpose of documenting the shipment dates, batch numbers, and method of shipment of investigational products and trial-related materials,

12.11.14. Certificate of analysis for the shipped investigational product,

12.11.15. Unblinding procedures in blinded trials,

12.11.16. Randomization list,

12.11.17. Pre-trial monitoring report, for the purpose of documenting that the trial site is suitable for the trial.

12.12. During the conduct of the clinical phase of the trial, in addition to the essential documents already available, at least the following documents should be added to the files as evidence of any new relevant information as it becomes available:

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12.12.1. Updates to the Investigator's Brochure,

12.12.2. Revisions to trial-related documents made during the course of the trial, such as the trial protocol, ICF, CRF,

12.12.3. Ethics committee approval and Turkish Medicines and Medical Devices Agency authorization for amendments made, if required,

12.12.4. Changes to the coordinator, administrative responsible, principal investigator, or investigators,

12.12.5. Changes to the normal values or ranges of the tests specified in the trial protocol and documentation relating to the laboratory, if available,

12.12.6. Monitoring reports,

12.12.7. Other significant communication notes excluding trial site visits (such as notes of telephone conversations, meeting notes),

12.12.8. Signed ICFs obtained in accordance with the applicable legislation, source documents,

12.12.9. Signed, dated, and completed CRFs,

12.12.10. CRF corrections,

12.12.11. Safety reports,

12.12.12. Volunteer screening log,

12.12.13. Volunteer identification code list,

12.12.14. Records relating to the use of investigational products in accordance with the trial protocol, for the purpose of documenting this,

12.12.15. Signature page, for the purpose of documenting the signatures and initials of persons authorized to make entries or corrections on the CRF.

12.13. After completion or termination of the trial, in addition to the documents specified in 12.11. and 12.12., at least the following documents should be added to the files:

12.13.1. Records at the trial site relating to the investigational product, accounting documentation for the use of the investigational product,

12.13.2. Documentation relating to the destruction of investigational products in accordance with the provisions of the applicable legislation,

12.13.3. Completed volunteer identification code list,

12.13.4. Final trial close-out monitoring report,

12.13.5. Documentation of audits and inspections performed, if any,

12.13.6. Documentation of an unblinding event, if one has occurred,

12.13.7. Final report to be submitted to the ethics committee and the Turkish Medicines and Medical Devices Agency,

12.13.8. Clinical trial report.

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13. OTHER PROVISIONS

13.1. Where only an extension of the term of insurance documents previously approved by the ethics committee and authorized by the Turkish Medicines and Medical Devices Agency is to be made, without any change to any of the insurance conditions, it is sufficient to inform the ethics committee and the Turkish Medicines and Medical Devices Agency.

13.2. For the purpose of assisting in the conduct of the trial, an investigator, clinical trial nurse, field staff, monitor, clinical trial pharmacist, or a qualified person may be appointed, provided that the Turkish Medicines and Medical Devices Agency and the ethics committee are informed. However, the Turkish Medicines and Medical Devices Agency or the ethics committee may cancel such appointment with justification.

13.3. In the event of a change of the principal investigator involved in a clinical trial that has previously obtained ethics committee approval and Turkish Medicines and Medical Devices Agency authorization, a change may be made provided that the Turkish Medicines and Medical Devices Agency and the ethics committee are informed. However, the Turkish Medicines and Medical Devices Agency or the ethics committee may cancel such appointment with justification.

13.4. In international multicenter clinical trials, for documents such as Investigator's Brochure amendments, protocol amendments, and ICF amendments that will not be implemented in our country and do not contain safety report information, it is sufficient to inform the ethics committee.

13.5. For the purpose of conducting a clinical trial, the CRF should be submitted at the initial application for ethics committee approval and Turkish Medicines and Medical Devices Agency authorization, and approval and authorization should be obtained. However, for subsequent amendments to be made to the CRF, it is sufficient to inform the ethics committee.

13.6. For certain technical changes that do not affect the validation of electronic CRFs (such as version changes of a nature that do not alter the quality and quantity of data, such as changes that facilitate the completion of data in a CRF version approved by the ethics committee and the Turkish Medicines and Medical Devices Agency, that enable the system to automatically generate a question in case of incorrect data entry, or interface changes to the software used), it is sufficient to inform the ethics committee.

13.7. In multicenter clinical trials, a single ethics committee decision is sufficient. The said ethics committee decision should be obtained from the ethics committee located at the place where the coordinating center is situated; if there is no ethics committee there, the decision should be obtained from the relevant ethics committee at the location nearest to the coordinating center among the centers included in the trial. In single-center clinical trials, the decision should be obtained from the ethics committee located at the place where the trial is conducted; if there is no ethics committee, the decision should be obtained from the relevant ethics committee at the location nearest to the trial site.

14. ENTRY INTO FORCE This Guideline enters into force on the date of its approval.

15. EXECUTION The President of the Agency executes the provisions of this Guideline.

REVISION HISTORY Revision No. Revision Date Rationale and Explanations 00 29.12.1995 An update was made before the establishment of the quality management system. 01 28.01.2009 An update was made before the establishment of the quality management system. 02 28.05.2010 An update was made before the establishment of the quality management system. 03 10.12.2010 An update was made before the establishment of the quality management system. 04 06.12.2011 An update was made before the establishment of the quality management system. 05 23.08.2011 An update was made before the establishment of the quality management system. 06 17.04.2013 An update was made before the establishment of the quality management system. 07 15.07.2014 An update was made before the establishment of the quality management system. 08 13.11.2015 An update was made before the establishment of the quality management system. 09 01.02.2024 An update was made due to a change in the Regulation.

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