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DRAFT GUIDELINE ON PHASE 1 CLINICAL TRIAL CENTERS

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GUIDELINE ON PHASE 1 CLINICAL TRIAL CENTERS

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INTRODUCTION: In the process from the discovery of a human medicinal product to its licensing, numerous studies are conducted on the candidate molecule in both the preclinical and clinical phases. Preclinical studies generally aim to determine the pharmacodynamic, pharmacokinetic and toxicokinetic profile of the candidate molecule, as well as the pharmaceutical form to be used in human studies. Following the preclinical studies, clinical trials, in which the effects of the candidate molecule on humans are evaluated, are generally conducted in four consecutive phases. Phase 1, phase 2 and phase 3 clinical trials are conducted prior to licensing, while phase 4 clinical trials are conducted after licensing. Phase 1 clinical trials are studies in which the candidate molecule is administered to humans for the first time and which are generally conducted with a small number of healthy volunteers. Since no therapeutic benefit is expected for the volunteers (healthy or patient) participating in phase 1 clinical trials, in which the human medicinal product is administered to humans for the first time, the most important consideration is volunteer safety. In this context, phase 1 clinical trials may be conducted in places that are suitable for ensuring the safety of the persons to be studied, for the healthy conduct of the trial, for its follow-up and, where necessary, for emergency intervention; that possess personnel, equipment and facilities appropriate to the nature of the trial; and that are designed for conducting such trials. The Regulation on Clinical Trials, which entered into force upon its publication in the Official Gazette No. 28030 dated 19 August 2011, made the inspection and certification of the centers where phase 1 clinical trials are to be conducted mandatory, and the "Guideline on the Conduct of Good Clinical Practice Inspections Relating to Phase 1 Units" was published in August 2011. The first phase 1 clinical trial center inspection was carried out on 25 December 2011, and the clinical trial centers established for the purpose of conducting phase 1 clinical trials have been inspected periodically since 2011. The inspections carried out do not cover the entire hospital or hospital staff, or the studies conducted outside the inspected unit. Although some molecules or compounds to be tested on humans for the first time are "high risk," it should not be forgotten that serious adverse reactions may also occur in the later stages of a clinical trial. Furthermore, there are also risks arising from study procedures and/or those that may arise from licensed human medicinal products used as comparator products. For this reason, it is of vital importance that all centers where phase 1 clinical trials are conducted possess sufficient personnel and facilities to cope with emergency situations that may arise from the investigational product and/or study procedures. The guideline dated 21.06.2019 has been updated, within the scope of Article 36, Paragraph 2 of the Regulation on Clinical Trials of Human Medicinal Products, which entered into force upon its publication in the Official Gazette No. 32203 dated 27.05.2023, solely with respect to matters concerning phase 1 clinical trial centers to be conducted only with patient volunteers.

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1. Purpose: This guideline has been prepared with the aim of assisting sponsors, investigators and phase 1 clinical trial centers in the transition from preclinical studies to early-phase clinical studies, and of providing guidance for the inspection of the centers. 2. Scope: This guideline covers phase 1 clinical trials and the centers where such trials are to be conducted. 3. Legal Basis: This guideline has been prepared on the basis of Article 36, Paragraph 2 of the Regulation on Clinical Trials of Human Medicinal Products, which entered into force upon its publication in the Official Gazette No. 32203 dated 27.05.2023. 4. General Considerations: When designing early-phase clinical studies, the protection of volunteers must always be the primary priority, especially for the first administration of the investigational medicinal product to humans. Depending on the characteristics of the drug and the objectives of the development program, these studies may be conducted in healthy volunteers or in a selected patient population (with a medical condition or disease). These studies typically address one or more of the following: i. Estimation of the Safety and Tolerability of the Initial Dose: The first and subsequent administrations of the investigational medicinal product to humans generally aim to determine the tolerability of the dose range expected to be evaluated in subsequent clinical studies and the nature of the adverse reactions that may be expected. These studies typically include both single and multiple ascending dose administration. ii. Pharmacokinetics: The characterization of the absorption, distribution, metabolism and excretion of a drug continues throughout the development program, but initial characterization is an important early objective. Pharmacokinetic studies are particularly important for assessing the clearance of the drug and for predicting potential accumulation of the drug or its metabolites, interactions with metabolic enzymes and transporters, and potential drug–drug interactions. Some pharmacokinetic studies are generally conducted at later stages in order to answer more specific questions. For orally administered drugs, examining the effects of food on bioavailability is important for establishing food-related dosing instructions. Pharmacokinetic information should be obtained in subpopulations with potentially different metabolism or excretion, such as patients with renal or hepatic impairment, geriatric patients, children and ethnic subgroups (ICH E4, E7, E11 and E5, respectively). iii. Pharmacodynamics and Early Measurement of Drug Activity: Depending on the drug and the endpoint of interest, pharmacodynamic studies and studies relating drug levels to response (PK/PD studies) may be conducted in healthy or patient volunteers (with a medical condition or disease). If an appropriate measurement exists, pharmacodynamic data can provide early estimates of activity and effectiveness and can guide dosage and dosing regimen in subsequent studies.

5. Facilities: 5.1. Healthy and Patient Volunteers: Centres where phase 1 clinical trials involving both healthy and patient volunteers are to be conducted shall have adequate space for the activities, equipment and personnel within the scope of the relevant study and shall, as a minimum, include the areas specified below. - Volunteer enrollment and screening areas, - An area for obtaining informed consent from volunteers individually, - Clinical area, - Rest and dining area, - Investigational product room, - Sample processing (centrifuge, etc.) and storage (freezer/deep freezer) area, - For centres not located within a hospital; an intensive care unit with "Level 1" or "Level 3" intensive care standards in terms of minimum equipment, personnel and service standards, - Areas for management and personnel, - Archive. Some of these areas may be combined in accordance with the workflow (e.g., the volunteer enrollment and screening areas and the area for obtaining informed consent from volunteers individually, the sample processing area with the sample storage area, or the rest area with the dining area). 5.2. Patient Volunteers: Centres where phase 1 clinical trials involving only volunteers with the medical condition or disease under investigation are to be conducted may be established within the clinic of the relevant department. Such centres shall possess the areas listed in Article 5.1. of this guideline; however, the clinical area and the rest and dining areas may be combined. The beds allocated within the clinic for the phase 1 clinical trial centre shall not be used for other purposes. However, where they are used due to force majeure, this matter shall be justified and appropriately documented. 5.3. General Characteristics: The layout, building and other general characteristics of

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centres where phase 1 clinical trials are to be conducted, whether involving both healthy and patient volunteers or only patient volunteers, are listed below. - Entrances to the centre shall be controlled and restricted, and entry/exit records shall be kept. - The facilities shall have adequate lighting and ventilation; the surfaces of floors, walls and work benches shall be easy to clean and disinfect. - Phase 1 clinical trials shall be conducted under conditions that ensure adequate safety for the volunteers, and the centre shall be appropriate to the potential risk of the study to be conducted. - Electricity shall be adequate and uninterrupted, and a backup power source shall be available. In addition, similar measures shall also be in place for water and medical gases (if any). - In addition to means of communication such as telephone, e-mail and fax, office equipment such as printers required for carrying out office activities shall be available. - Systems for the disposal of waste shall be available in accordance with the relevant legislation.

- Doors, corridors and lifts shall be wide enough to allow the transport of a volunteer on a stretcher in emergencies. - A system shall be established for easy identification of centre personnel, volunteers and visitors (badge, clothing in different colours, etc.). - The centre shall permit the sponsor to monitor the studies and to control (audit) the relevant areas, and shall provide a suitable office space for these activities. - There shall be a monitoring system to track the temperatures of areas and storage systems of key importance (investigational product room, archive, refrigerator, freezer/deep freezer, etc.), and records shall be kept. There shall be an alarm system that is triggered when the temperatures of these areas and storage systems exceed the established limits. The functionality of the alarm system shall be tested periodically and documented. - A list of the instruments and equipment used at the centre shall be prepared; their maintenance, repair and calibration shall be tracked and documented. - There shall be synchronized clocks in the areas at the centre where study-related activities are carried out. Furthermore, computer and hardware clocks shall also be synchronized with the system and/or with each other. 5.3.1. Volunteer Enrollment Area: - There shall be an enrollment area for informing volunteer candidates about the studies, recording them in the centre database, and similar procedures. 5.3.2. Volunteer Screening Area: - There shall be screening and physical examination areas where the necessary procedures will be carried out in order to assess the volunteers' suitability for the study. 5.3.3. Area for Obtaining Informed Consent from Volunteers Individually: - After oral and general information has been provided, the informed consent of a volunteer who decides to participate in the trial shall be obtained in a separate area designated for this procedure, where the volunteer can discuss the trial one-to-one with the investigator or an authorized physician and where the volunteer's privacy is also ensured. 5.3.4. Rest and Dining Area: - If the study protocol requires the volunteers to stay overnight at the trial site, there shall be a rest area where volunteers can spend their free time during their stay. - The rest areas shall be equipped with suitable activities for volunteers to spend their free time, and these areas shall be within the line of sight or under the supervision of centre personnel. - The dining area shall preferably be separate from the areas where clinical activities take place. However, the study protocol may require that meals be taken in the clinical area. In this case, a bedside meal table shall also be available. 5.3.5. Sample Processing and Storage Area: - There shall be a sample processing and storage area where the processing and storage activities of the materials collected from volunteers are carried out as defined in the study protocol.

- In cases where more than one trial is conducted simultaneously, the necessary measures must be taken to prevent any mix-up, contamination and cross-contamination in sample processing and storage areas. 5.3.6. Areas for Management and Personnel: - There must be areas necessary for personnel, such as changing rooms and lockers, staff room, toilets and showers. - Areas must also be established for the trial team, including quality assurance, principal investigator, investigator, site staff, etc., and administrative personnel. 5.4. Clinic If participants participating in the trial are required to stay/overnight at the trial site in accordance with the trial protocol; the site requires a clinical area with a number of beds appropriate to the number of participants, together with dining and rest areas as well as shower and toilet facilities. The number

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of beds required for the clinic depends on the protocol, the type of trial and/or the investigational medicinal product, and the admission times and duration of participants must be specified in the trial protocol. Regarding the clinical area: - If participants stay overnight at the site, there must be a changing room for them to change their clothes; and there must be a number of lockers consistent with the number of beds for personal belongings and clothing. - The beds used in the clinic must be wheeled and adjustable in height and inclination. The distance between beds must be wide enough to allow the passage of the emergency intervention cart/medical equipment. - The clinical trial area must be appropriately separated from routine clinical activities and other patients; participants' access to areas other than the clinical area must be restricted; and, while the trial is being conducted, there must be systems capable of detecting and recording participants' exits from the site. - Participants must not be allowed access to the kitchen, laboratory and office areas. The doors of such areas must be kept locked when not in use. Participants' access to areas other than the clinical area must be restricted. - In cases where more than one trial is conducted simultaneously; the necessary measures must be taken to prevent any disorder, confusion and contamination. - There must be a sufficient number of toilets, washbasins and showers designated solely for the use of participants. Trial staff must be able to open the door from the outside in an emergency. In addition, trial staff must be able to restrict and control access to the toilets in order to collect urine or feces samples when required. - There must be an alarm system to alert staff in medical emergencies. Alarms must be placed in every area designated for individuals' use (shower, toilet, bed, rest area, etc.). Furthermore, the functionality of this alarm system must be tested periodically and documented. - If participants are required to remain bedridden in accordance with the trial protocol, there must be an over-bed table so that they can eat their meals.

- Participants must, at all times and as far as possible, be visible to trial staff from several advantageous points in the clinical area and in their beds. 5.4.1. Medical Equipment: The medical equipment required for trial sites where Phase 1 trials are conducted may vary depending on the trial, the risks expected from the trial, and the measures to be taken to mitigate these risks. However, regarding the equipment used at the site: - A specific person must be responsible for the equipment, - All equipment must be regularly checked, maintained and calibrated (for systems that can be calibrated), and these procedures must be documented, - The manufacturers or subcontractors calibrating the equipment must provide a certificate guaranteeing that the calibration is performed in accordance with national standards, - All equipment must bear a label containing information relating to the equipment (name, brand/model, serial no, maintenance and calibration date, etc.). In addition, the medical equipment that may be required for Phase 1 sites is listed below, but is not limited to the following: - Equipment required for resuscitation and an emergency intervention cart, - Equipment for medical examination, - A monitoring system for the continuous monitoring of variables such as ECG, rhythm, oxygen saturation, blood pressure, pulse and temperature, - Electrocardiography, - Equipment for the processing of biological samples, - Refrigerator, freezer and deep freezer(s) for the storage of biological samples and, when required, the investigational medicinal product. 5.4.2. Medical Emergencies and Intervention: Phase 1 sites operating within or outside a hospital must, taking medical emergencies into consideration, appoint an intensive care specialist and/or an anesthesiology and reanimation specialist on a temporary or permanent basis. A Phase 1 site operating within a hospital must have reserved a sufficient number of beds in the intensive care unit. Phase 1 sites operating outside a hospital must, for trials to be conducted with low-risk investigational medicinal products, possess an intensive care unit complying with "Level 1" intensive care standards in terms of minimum equipment, personnel and service standards, and, for trials to be conducted with high-risk investigational medicinal products, an intensive care unit complying with "Level 3" intensive care standards. In addition to possessing an intensive care unit at "Level 1" intensive care standards for trials to be conducted with low-risk investigational medicinal products, Phase 1 sites operating outside a hospital must have a sufficient number of beds reserved in the intensive care unit at a

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tertiary healthcare institution and an agreement with that healthcare institution regarding the services to be provided. The site must have an emergency intervention cart, containing a sufficient quantity of appropriate equipment and medicines for use in medical emergencies, which can be easily and rapidly accessed. The contents of the emergency intervention cart may vary depending on the type of trial to be conducted and the potential anticipated risks. Within the scope of risk management and mitigation, the contents of the emergency intervention cart must be checked, approved and documented by an intensive care specialist or an anesthesiology and reanimation specialist. The equipment and medicines that may be included in the emergency intervention cart are listed below, but not limited to the following:

- Monitor, - Nasal cannulas, face masks and portable oxygen cylinders required for oxygen therapy - Airway equipment, - Transport ventilator - IV catheters, sets, tubes - Endotracheal tubes - Laryngoscope sets - Oral and nasal airways, - Suction system - Bag-valve mask (Ambu) - Defibrillator (preferably operable both on electricity and battery), - Transcutaneous cardiac pacing - Tracheostomy set and supplies, - Emergency medications together with IV fluids,

A member of staff shall be responsible for the emergency intervention trolley; it shall be checked periodically and also after each use in terms of quantity and expiry date, and records shall be kept. In the event of any medical emergency, study personnel shall have the following: - The telephone number of the sponsor's medical expert, - The method for reporting serious adverse events and the randomization code, - An alarm system for calling for help in a medical emergency (code blue, etc.), - Appropriate methods to intervene in medical emergencies with a high likelihood of occurrence, such as syncope, hypotension, anaphylaxis, and cardiopulmonary arrest, - The method of transferring the volunteer to hospital in a medical emergency.

All physicians and nurses on duty at the site shall receive training in basic life support or, where required, advanced life support, and shall hold valid certificates. If an intensive care specialist or an anaesthesiology and reanimation specialist experienced in resuscitation is a member of the research team and is present at the site during dosing and the follow-up period, it will be sufficient for the other personnel to have basic life support training.

All volunteers enrolled in the study shall be given a study identification card. The identification card shall contain the information that the individual has been enrolled in a clinical trial and a telephone number, reachable 24 hours a day, of the responsible investigator from whom study-related information may be obtained in emergencies.

In all areas allocated for use by volunteers, there shall be an alarm system to alert personnel in the event of any medical emergency, and the operability of this system shall be tested periodically and documented.

Site personnel shall be trained and prepared to detect any serious adverse event or reaction occurring in a volunteer and to provide emergency intervention. Drills shall be conducted using scenarios involving possible medical emergencies (cardiac arrest, anaphylaxis, cytokine release syndrome, etc.), and these drills shall be planned to include transfer to hospital/intensive care, peak hours in terms of hospital and transportation, and the night shift, and shall be repeated periodically. In addition, the situation of unblinding shall also be added to these scenarios.

Site personnel shall attend these trainings involving possible medical emergency scenarios, take part in various different scenarios (e.g. different events, places and times), and these processes shall be

documented and monitored. All matters relating to medical emergency scenario trainings shall be defined in a procedure. Any corrective/preventive action taken during a drill shall be followed up and documented.

In the event of a fire that may occur at the site, there shall be a fire evacuation procedure for the evacuation of volunteers. Fire extinguishers shall be checked regularly, and there shall be emergency exits and emergency lights. Periodic fire evacuation drills shall also be conducted and documented.

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The sponsor shall ensure that the relevant study is conducted at phase 1 sites that are compatible with the risk level of the investigational product in terms of personnel, facilities and equipment.

5.5. Investigational Product Room: In accordance with the relevant legislation, the receipt, storage, distribution in accordance with the written request or the research protocol, stock control, procedures for the remaining portion and record-keeping of investigational products are under the obligation of the responsible investigator (for other responsibilities regarding the investigational product, see GCP Guide articles 25-31). The responsible investigator may preferably designate a pharmacist for these procedures. In this context, the site shall have an investigational product room with controlled and restricted access, which only personnel authorized in matters relating exclusively to the investigational product are entitled to enter. Records of entries to/exits from the investigational product room shall be kept. The investigational product room shall have sufficient space appropriate for the studies being conducted. The requirements for the investigational product room will vary depending on the service to be provided within the scope of the study. In addition, there shall also be procedures and recording methods for the receipt, use, retrieval and destruction of the investigational product, including outside working hours and holidays.

Investigational products shall be stored in accordance with the specifications of the product and under the conditions stated in the instructions of the manufacturer/sponsor. The investigational product room: - Shall have sufficient space for separate storage of different investigational products, together with a quarantine area, - Shall be temperature and humidity controlled; shall also have an alarm system that will be activated in the event of deviation from pre-defined values, - Shall not be exposed to direct sunlight, - Shall be accessible only to authorized personnel.

In addition, stocks of appropriate medications shall also be kept for the management of commonly observed adverse events (such as headache and nausea), and events such as convulsions and low blood glucose levels, and clinical personnel shall be able to access these medications easily.

The sponsor is responsible for the appropriate packaging of the investigational product, its transport to the trial site, and for ensuring that transportation is carried out under appropriate conditions. The site shall document and retain information relating to the investigational product; dispatch, delivery, acceptance, storage, distribution, administration, investigational product accounting, and quantities returned or destroyed, and these processes shall be defined in the relevant procedure.

Where the randomization procedure is performed by the site, the processes relating to the generation, distribution, use and safekeeping of the randomization list shall be defined in a procedure. There shall be a written procedure to ensure the rapid identification of a 'blinded' investigational product in an emergency. The procedure shall be maintained throughout the study but shall be readily accessible; however, it shall not allow the blinding to be broken without detection

should not be administered. In addition, the procedures regarding unblinding in emergency situations, the training of relevant personnel and code-breaking drills should also be defined in the procedure. 5.6. Archiving: The trial site must have an archive area of appropriate size for the archiving of medical records and the trial master file; resistant to fire, with the necessary precautions taken against water and humidity, with the relative humidity ratio monitored, with rodent and pest control carried out, and appropriate for the activities conducted. Measures must be taken to ensure that only authorized personnel can access the archive and that access is restricted to persons other than these individuals. There must be a procedure regarding archive operations; entries to and exits from the archive (personnel and documents) must be recorded, the archiving period of documents related to the trial, including electronic data and raw study data, must be in compliance with the relevant legislation, and temperature and humidity values

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must be defined. There must be a fire/smoke detector in the archive area, and the functionality of the alarm system must be checked periodically. Essential documents (trial master file) are documents which, individually and/or collectively, permit the evaluation of the conduct of a trial and the quality of the data produced. These documents demonstrate the compliance of the responsible investigator or other investigators, the sponsor and the monitor with good clinical practice standards and the applicable regulatory requirements. Essential documents have been defined in the Good Clinical Practice Guideline (Article 12), and it has been specified which documents must be kept in the trial master file by both the investigator and the sponsor. Handwritten data entries must be clear, legible and indelible. Records for each activity must be made at the time the activity takes place. Furthermore, such records must allow the tracking of all important activities related to the trial. In the event that a modification is made to a data entry, such modification must not prevent the reading of the original information and must be signed and dated by the person making the modification. 5.7. Medical Laboratory: The facilities from which laboratory services are obtained, both for the screening of volunteers planned to be included in the trial and for the clinical tests to be performed within the scope of the trial, may be located within the hospital where the trial site is situated, or external services may be procured. The laboratories where biological samples will be analyzed must, at minimum: - Be licensed by our Ministry (for facilities within the country), - Have calibrations of the equipment used performed, quality control procedures applied, and maintenance carried out regularly, - Have procedures for the safe transfer of samples from the clinical area to the laboratory, and have the storage/transfer conditions during transfer documented, - Have a stock control procedure for tracking the expiry dates of reagents and consumables, - Have quality assurance and quality control systems, including an internal audit program, - Take the necessary measures for the protection of the personal data of volunteers, - Have a system for the archiving of source documents, including computer raw data.

The clinical laboratory must participate in external accreditation (ISO 15189) or an interlaboratory comparison program in order to support the reliability of its results and to document the competence of the facility. If the clinical laboratory participates in an interlaboratory comparison program, the results obtained for each parameter studied in the laboratory must also be tracked and documented by the quality assurance department of the phase 1 trial site. Clinical laboratories may be inspected as part of the inspection of the phase 1 trial site or of a study-based inspection. For further information on clinical laboratory inspections, the "Guideline on the Conduct of Good Clinical Practice Inspections Related to Laboratories Participating in Clinical Trials of Medicinal Products" may be used as a reference. A procedure must be established for the transfer of samples to the clinical laboratory. Furthermore, since, in accordance with the applicable legislation, disclosing the identity information of the volunteers participating in the trial to parties other than the authorized authority/persons is not appropriate; the necessary measures must be taken in the processes of sending the samples belonging to volunteers to the clinical laboratory for analysis, invoicing, and communicating the results. A procedure must be established for sample management covering issues such as the collection, processing, evaluation of delayed and missed samples, labeling, monitoring, storage, and shipment of samples. The labeling, acceptance, and storage of samples, and the documentation of all these processes must ensure sample integrity and traceability. In addition, the relevant processes and operations, from the collection of blood to its shipment to the clinical laboratory and the receipt of laboratory results, must be traceable. A dated and approved list of the normal ranges of all relevant parameters studied in the clinical laboratory and, if available, the laboratory's accreditation certificate must be documented, and modifications must be tracked. A quality system must be implemented in the clinical laboratory, and rejection/acceptance criteria for samples and approval/modification authorities for results must be defined. Laboratory results and all related raw data must be retained by the clinical laboratory for the period defined in the applicable legislation. Data integrity requirements apply to all tests related to the trial; raw data

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must be adequately protected against modification or deletion. 6. Personnel: In accordance with the applicable legislation, phase 1 clinical trials must be conducted by a suitable team with adequate training and experience in good clinical practice, and by a physician-pharmacologist who has completed his/her specialty or doctorate. There must be a dated and approved organizational chart at the trial site showing the key positions and the personnel assigned to these positions. The organizational chart must be updated as necessary, and previous versions must be archived. Job descriptions must be created for all personnel working at the trial site, and responsibilities must be defined. Job descriptions must be dated and signed by the relevant personnel. For all personnel working at the trial site; information and documents related to personnel, such as curriculum vitae, training records, job descriptions, letter of acceptance of duty/confidentiality agreement, etc., must be tracked, updated as necessary, and archived. In addition, a form must be created showing the signatures and initials of all personnel included in the research team. For dosing days, the minimum number of personnel and their qualifications must be specified, and the measures to be taken in the event that key personnel are not present at the trial site on the study day must be defined. The volunteers'

all personnel responsible for the care and management of volunteers should receive basic life support training and/or advanced life support training (see 4.2.2), and this training should be repeated periodically. All new personnel, including part-time and temporary staff, should receive orientation training on general topics such as confidentiality, security, health, the use of procedures and centre policies, together with the relevant legislation. The methods related to the content and frequency of periodic trainings, the filing of training documents, the minimum qualifications of trainers in in-house trainings, measurement/assessment and the definition of the minimum passing level, the monitoring and documentation of trainings should also be defined in the relevant procedure. Periodic trainings that may be provided to personnel are indicated below (but are not limited to these): - Personnel and physicians responsible for volunteer care should receive regular training on resuscitation. - Drills should be conducted based on scenarios involving possible medical emergencies (cardiac arrest, anaphylaxis, cytokine release syndrome, etc.). When changes are made to procedures, personnel should be informed and trained. - Periodic trainings should be conducted on Good Clinical Practice and legislation.

7. Volunteers: For Phase 1 clinical trials to be conducted with healthy volunteers, processes related to the provision and management of volunteers should be defined. In this context, a volunteer database should be established for volunteers, and this database should, where possible, include a photograph of the volunteer. Volunteers should be given an identity card with a photograph, to be used during their stay at the centre. In order to document the volunteers participating in the trial, copies of the trial identity card and identity card (or driver's licence, etc.) of the volunteers participating in the trial should be archived in the trial file after the completion of the trial. Matters related to how multiple participation of volunteers in trials can be prevented (needle marks on the front of the elbow and low blood count results, etc.) should be defined in the procedure. The methods followed for verifying the medical history of volunteers, such as chronic disease/concomitant treatment etc., should also be defined in the procedure. Furthermore, warnings regarding participation in multiple trials simultaneously/concomitant treatment/medication use should be clearly included in the informed consent form. In order to prevent volunteers from bringing into the trial area materials not permitted under the trial protocol, such as cigarettes, food/beverages etc., volunteers should be screened, and infrastructure and procedures should be established for the identification of such materials by mutual signature and their return at the end of the trial. The number of beds in the wards should be compatible with the number of personal lockers allocated to volunteers. Processes related to payments to be made to volunteers, and methods related to obtaining informed consent and establishing a volunteer pool should be defined in the procedure. The volunteer database, access authorizations to volunteer data, and matters related to the protection of the confidentiality of volunteer data should be explained in the relevant procedures, and furthermore, when registering

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a volunteer in the database, a telephone number of the person to be contacted in emergencies should also be recorded, and the degree of relationship should be indicated.

8. Quality Management: The centre should have quality assurance and quality control systems in order to ensure that trials are conducted, documented and reported in accordance with the trial protocol, GCP, GMP and legal requirements. Detailed procedures compliant with national/international regulations should be established in order to ensure standardization in the work and operations carried out, covering all phases of the trial and all activities conducted at the centre. The quality assurance unit should be subordinate to the senior management of the centre; however, quality assurance personnel should also be independent of the trials conducted. The organizational chart and the activities conducted at the centre should be regulated within this scope. Quality assurance personnel should, as a minimum, have trainings on quality assurance systems such as Good Clinical Practice (GCP), quality management system, and internal audit. The quality assurance unit should, as a minimum, carry out the following: - To verify all activities carried out during the trial, - To ensure that quality management systems are followed, reviewed and updated, - To ensure that procedures are made available to personnel for use and are followed, - To check all data obtained from the trial in terms of reliability and traceability, - To plan and conduct internal audits at regular and defined intervals, and in this context, to monitor the necessary corrective actions, - To conduct surveys to evaluate outsourced services and service providers within the scope of the trial and to monitor the necessary corrective actions, - To report audit findings to the centre management and the principal investigator. - The quality management system should include root cause analysis, trend monitoring, all aspects of data integrity, and the implementation of appropriate corrective and preventive action (CAPA). With regard to procedure and document management; the current versions of procedures should be accessible in the relevant trial areas, old versions should be archived, they should be reviewed periodically, and changes should be communicated to personnel and training should be provided. The root cause of findings identified as a result of internal audits should be investigated. The centre management should be regularly informed about the activities carried out by quality assurance, their results and the necessary measures.

9. Risk Assessment and Risk Management: In Phase 1 clinical trials, risks that may arise from the investigational product and/or the trial design and methodology should be minimized. The risks in question should be assessed in all respects before each clinical trial, in particular during the transition from preclinical studies, where uncertainties regarding the tolerability and safety of the investigational product are greatest, to first-in-human exposure studies. The risk assessment process should include the assessment of risks related to the investigational product, clinical procedures, volunteer safety and rights, and the reliability of trial results. In this context, processes related to the assessment and management of risks should be defined in a procedure at the Phase 1 clinical trial centre. In addition, matters such as how the risk assessment will be documented, the review of the risk assessment (e.g. continuous monitoring and updating when necessary), and who is responsible for the follow-up and documentation of compliance with risk management should also be defined in the procedure.

All aspects of the phase 1 clinical trial, including data obtained from preclinical studies, should be reviewed, assessed, and monitored by individuals with appropriate technical, scientific, and clinical expertise established by the site, as part of risk assessment and risk management, starting from the proposal stage and throughout the duration of the study; appropriate risk mitigation activities should be recommended and monitored. Matters that may be considered in the risk assessment process are set out below, but are not limited to the following: - All matters relating to the investigational medicinal product (IMP), such as its class, novelty, species specificity, mechanism of action, potency, dose/concentration relationship for efficacy and toxicity, administration, and route of delivery, - The design of the study, - Whether the data provided are sufficient to calculate the starting dose or any dose escalation, and whether these data were generated within the framework of a quality system, - Starting dose calculations, dose escalation

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proposals, stopping criteria, - Maximum exposure and dose, - Transition from single dose to multiple doses, - Assessment of participants and interventions, - The data/documents used in the risk assessment process, the version and status of these documents (draft/final), - The availability of any specific antidote or emergency treatment, - The adequacy of the site and its personnel in terms of possible medical emergencies, - Scenarios for a specific emergency situation, Additional personnel and resources (e.g. specific training, expertise, facilities, etc. for the conduct of the studies). The risks identified after the evaluation of every aspect of the trial and the measures to be taken to mitigate these risks should be documented. 9.1. Risks Arising from the Investigational Medicinal Product (IMP): Due to the scientific uncertainties arising from the nature of innovative medicines, the ESG (Expert Scientific Group on Phase I Clinical Trials) report states that it is not possible to compile an exhaustive list of all possible risk factors related to investigational medicinal products (IMPs) and their targets. Therefore, the assessment of risks or hazards that may arise from the investigational medicinal product (IMP) should be case-based and scientifically grounded. Nevertheless, the ESG report provides examples of certain agents that carry a high risk of harming volunteers during first exposure studies and of factors that require special attention. These are: - Any agent whose effects may cause serious physiological disturbances to vital body systems, - Agonistic or stimulatory effects, - New agents or new mechanisms of action with no prior experience, - Species specificity that makes preclinical risk assessment difficult or impossible, - The potency of the agent (for example, compared to a natural ligand), - Multifunctional agents (e.g. bivalent antibodies, FcR binding domains), - Cell-associated targets (cell surface targets that activate signaling pathways), - Targets that 'by-pass' normal control mechanisms, - Immune system targets, - Targets in systems with potential for large biological amplification in vivo.

In the risk assessment of an investigational medicinal product (IMP) in first-in-human exposure studies, in addition to the factors expressed above, other factors, some of which may become more significant in the future, must also be taken into account. Examples of these include: - Agents with a target that is not present in animal models, - Combination products; for example, retroviral vectors in gene therapy (even if the components have previously been used in humans, the new combination may create a new risk), - 'Bio-similars' that differ significantly from the innovative product (e.g. post-translational modifications), - Vaccines with novel adjuvants; in particular, those that direct the antigen to signaling molecules on the surface of immunocytes, or those designed to stimulate proinflammatory cytokine production from lymphocytes, or antigen-presenting cells, - Significant changes in the route of administration, posology, or formulation of an agent. When the sponsor has new safety/toxicological data relating to the investigational medicinal product (IMP), it should immediately inform the responsible investigator, and clear and detailed responsibilities should be explicitly stated in the contract to be concluded between the parties. 9.1.1. Agents Other Than the Investigational Medicinal Product (IMP): In clinical trials, agents other than the investigational medicinal product (IMP) are also used, such as comparator products or rescue medications. The risks of each of these for the volunteer, as well as the risks when combined with the investigational medicinal product (IMP), should also be assessed. 9.1.2. Risk Management for the Investigational Medicinal Product (IMP): Risk management related to the investigational medicinal product (IMP) includes the determination of an appropriate starting dose, dose escalation, and administration of the doses. 1. Starting Dose: In a first-in-human exposure study, the calculation of the starting dose is a central factor affecting the safety of the volunteers in the study. There are two different methods recommended for determining the starting dose: - NOAEL (No Observed Adverse Effect Level) - MABEL (Minimal Anticipated Biological Effect Level) If different safe starting dose values are obtained by different methods, the lowest value should be taken as the starting dose. 2. Dose Escalation: As a general rule, the dose/toxicity or dose/response relationship observed in preclinical studies should guide two dose levels in dose escalations, depending on which is steeper. Dose escalation should be performed only after all data obtained from previous doses have been carefully evaluated. Dose adjustments may occur only after reviewing all relevant data (e.g. safety data, PK data if available)

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and discussing with the sponsor (dose escalation, reduction, or no change). It should be clearly stated in the relevant procedure that the trial will not continue until the approval of the Agency and the Ethics Committee is obtained for exceeding the limits foreseen for dose escalation or for a significant change in the protocol. Nevertheless, stopping rules must be clearly defined in the protocol.

The reviewed data and the decisions taken regarding dose adjustments (dose increase, decrease, or no change) must be clearly documented. The decision to increase the dose must be approved by the sponsor and the principal investigator; this decision and the approvals must be clearly documented before the participant (volunteer) is dosed.

3. Administration of Doses: The number of participants dosed, the interval between dosings, the participant cohorts, and the monitoring period between dosings will vary depending on the investigational medicinal product (IMP), the route of administration of the IMP, and the type of the study.

In the case of a high-risk investigational medicinal product, the first dose in any cohort: must be administered such that only one participant receives the active investigational medicinal product (they must not be randomized to placebo). The participant dosed in this manner must be closely observed for at least 24 hours by a nurse, the principal investigator and, where necessary, an intensive care specialist or an anesthesia and reanimation specialist experienced in resuscitation, and this process must be documented. Furthermore, unless there is a clear scientific justification and/or a risk-proportionate basis for administering an IMP to be given intravenously by rapid injection, it must be administered by slow infusion. The protocol must include details regarding the infusion rate and duration.

9.2. Risks Arising from Clinical Procedures: The clinical procedures to be performed within the scope of the study must be assessed taking into account standard practices and procedures. For example, if an invasive procedure such as a biopsy is a normal practice for standard treatment/care, its inclusion in the study protocol does not constitute an additional risk for the participants. However, if it is performed solely pursuant to the clinical trial protocol and is not part of standard care/treatment, it will constitute an additional risk.

For the management of risks arising from clinical procedures, the following must be assessed: - The qualifications, experience, and training of the personnel with respect to the clinical procedures to be performed, - The need for special facilities or equipment for the performance of the procedure, - The need for additional monitoring activities to identify problems and take preventive measures in order to protect the participants (volunteers).

9.3. Risks Arising from Failure to Obtain Appropriate Informed Consent: Pursuant to the relevant legislation; where the ethics committee is satisfied that the benefit to be obtained outweighs the risks likely to arise from the research, the research may be initiated after the approval of the ethics committee and the permission of the Agency have been obtained, provided that informed consent is duly obtained with due regard to personal rights. The research is conducted only for as long as these conditions continue. A person wishing to volunteer to participate in the research, or their legal representative, must, before the research begins, be adequately informed, in a manner they can understand, by the principal investigator or an investigator from the research team, about the purpose and methodology of the research, its expected benefits, foreseeable risks and discomforts, aspects that are unsuitable with regard to the person's health and personal characteristics, the conditions under which the research will be conducted and continued, and the fact that they have the right to withdraw from the research at any time they wish.

In studies to be conducted on child participants, persons with a certain degree of mental impairment, and patients in intensive care and/or with impaired consciousness, the process of obtaining informed consent must be handled with care and must comply with the provisions of the relevant legislation. Individuals volunteering for the study must be given sufficient time to read the informed consent form (ICF), to discuss with their family and friends, and, if necessary, to ask

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questions to the site staff.

9.4. Risks Arising from Failure to Protect Personal Data: For the participant databases created by the site, or within the scope of the study, personal data (Republic of Türkiye ID number, full address, telephone number, date of birth, medical history, etc.) are collected from participants (volunteers) or volunteer candidates.

The collection, management, and transfer of personal data must be carried out in compliance with the relevant legislation. Access to personal data must be granted only to authorized person(s), and the necessary measures for this purpose must have been taken. Furthermore, a participant has the right to request the removal of their personal data from the site database.

9.5. Risks Regarding the Reliability of Study Results: The data collected during the study must be complete, consistent, and accurate. Data must be: - Attributable – It must be documented who performed an activity and when, - Legible – Data must be readable throughout their life cycle, - Contemporaneous – The activity must be documented at the time it is performed, - Original – Data must be the raw/source data or a certified true copy, - Accurate – Data must be accurate, true, complete, valid, and reliable, - Complete – All data collected to obtain the necessary information must be documented, including any test, repeat test, or re-analysis, - Consistent – Data must be created in a reproducible manner, - Enduring – Data must be recorded in appropriate and approved systems capable of storing them for the period defined in the relevant legislation, - Available – Data must be accessible for review and audit (inspection) for the period defined in the relevant legislation.

Furthermore, risks arising from the design of the study, such as inclusion criteria, randomization, treatment, masking, outcome measures, and the follow-up process, together with risks arising from data collection methods and matters relating to the trial site, may affect the reliability of the study results.

The foreseeable risks within the scope of the relevant study, including but not limited to those listed above, must be identified and appropriate risk mitigation activities must be carried out. The necessary quality control procedures must be applied in a manner appropriate to the volume of data to be collected and the speed of data collection.

10. Miscellaneous and Final Provisions Entry into Force: This guideline enters into force on the date of its approval. Execution: The President of the Agency executes the provisions of this Guideline.

REVISION HISTORY Revision No Revision Date Justification and Explanations 01 15.11.2022 Harmonized with the guideline template determined within the scope of the Agency's quality system. 02 01.08.2023 1. Within the scope of the legislative amendment, the "Legal Basis" section has been revised. 2. The "General Provisions" have been revised. 3. Minimum physical space requirements for centers where only studies involving patient volunteers will be conducted have been added to the section "5. Facilities". 4. Considering only studies involving patient volunteers, the matter of restricting the access of volunteers to areas other than the clinical area has been added to the section "5.4. Clinic". 5. An addition has been made to the quality assurance job description in the section "8. Quality Management". 6. The matters of "Entry into Force" and "Execution" have been added under the heading "10. Miscellaneous and Final Provisions".

Annex-1. Related References: 1. ABPI, 2012, Guidelines for Phase I Clinical Trials 2. MHRA Phase I Accreditation Guidance (Final 28-Oct-15) 3. MRC/DH/MHRA Joint Project, 2011, Risk Adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products 4. Early Stage Clinical Trial Taskforce, 2006, Joint ABPI/BIA Report 5. TSO, 2006, Expert Scientific Group on Phase I Clinical Trials 6. WHO TRS No: 996 Annex 9 7. US Food and Drug Administration, 2005, Guidance for Industry: Estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers 8. International Conference on Harmonisation, Guidance on Non Clinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for pharmaceuticals, M3(R2). 9. International Conference on Harmonisation, Note

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For Guidance On Toxicokinetics: The Assessment Of Systemic Exposure In Toxicity Studies, S3A 10. International Conference on Harmonisation Preclinical Safety Evaluation Of Biotechnology-Derived Pharmaceuticals, S6(R1).

Annex-2. Sample List of Procedures: The procedures listed below are shared for the purpose of establishing a general framework; phase 1 sites are required to establish their own procedures so as to cover all activities carried out at the site in accordance with their workflow processes. In this context, some of the processes expressed below may be combined, some processes may be addressed separately, or new processes may be added. A. Procedures Related to Clinical Processes: 1. Acceptance of trials and signing of the clinical trial agreement with the sponsor, 2. Preparation of the study protocol and protocol amendments (in cases where the study protocol is prepared by the site) 3. Preparation of the investigator's brochure (for trials without a sponsor), 4. Procedure for obtaining approval from the Ethics Committee and TİTCK (Turkish Medicines and Medical Devices Agency) for the study (for trials without a sponsor) 5. Volunteer database (including its validation), 6. Volunteer management (management, selection and evaluation of volunteers) 7. Preparation of the informed consent form (ICF) (for trials without a sponsor), 8. Obtaining consent from volunteers, 9. Admission of volunteers to the site and hospitalization procedures, 10. Study management group study procedures/principles, duties and responsibilities, 11. Risk assessment and mitigation in phase 1 clinical trials, 12. Dose selection and dose escalation for phase 1 clinical trials, 13. Administration of doses and stopping rules, 14. Providing protocol training to the study team; the duties, responsibilities and delegation of responsibilities of the study team, 15. Conduct of the phase 1 clinical trial, 16. Conduct of other clinical trials (if deemed necessary), 17. Pharmacy room management and pharmacy room requirements, 18. Acceptance, storage, distribution, accountability, return or destruction of the investigational medicinal product (IMP), 19. Preparation of standard meals, presentation to volunteers and monitoring thereof, 20. Insertion and removal of IV cannulas in volunteers, 21. Administration of the investigational product to volunteers, 22. Recording, evaluation and reporting of adverse events/reactions occurring during the study, 23. Discharge procedures of volunteers from the site, 24. Procedure for making payments to volunteers, 25. Resting area and monitoring of these areas during volunteers' stay at the site, 26. Management of suppliers, 27. Selection and appointment of expert/consultant physicians for the conduct of study-related activities, 28. Preparation of the study report (for trials without a sponsor), 29. Use and maintenance of the intensive care unit and emergency trolley, 30. Management and maintenance of the clinical facility, 31. Separation and storage of samples,

32. Procedure for the use, maintenance and calibration of equipment used at the site, 33. Maintenance of temperature and humidity recorders; recording of temperature and humidity values 34. Ensuring line cleaning before and after distribution of the investigational product, 35. Management of medical emergencies, provision of basic and advanced life support, transfer to intensive care, 36. Code breaking/unblinding, training of relevant personnel and code breaking rehearsal, 37. Case report form, data collection and completion of case report forms, 38. Preparation and review of the case report form (for trials without a sponsor), 39. Preparation of the trial master file (TMF) (for trials without a sponsor) 40. Recording and reporting of protocol deviations/violations, 41. Monitoring of the study by the sponsor, 42. Procedures for the entry and exit of volunteers to and from the site, 43. Use and maintenance of the emergency call system, 44. Collection of blood samples from volunteers, 45. Numbering of samples collected from volunteers, 46. Measurement of vital signs and physical examination, 47. Transfer of serum/plasma samples to the clinical laboratory, 48. Abnormal laboratory results, B. Procedures Related to the Quality System: 1. Procedure for writing procedures, 2. Preparation, publication, distribution, collection and archiving/destruction of quality documents, 3. Quality management, 4. Control of changes, 5. Corrective/preventive actions, 6. Internal and external audits, 7. Notification of nonconformities and violations, 8. Audit of service providers, 9. Audit of the study report, 10. Regulatory authority inspections and sponsor audits, C. General Procedures: 1. Control and disposal of medical waste, 2. Personnel training, 3. Medical records and source data, 4. Procedure for archiving documents and

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retrieving them from the archive, 5. Management of emergencies (flood, earthquake, etc.), 6. Maintenance and control of fire alarm systems, 7. Pest control, 8. Validation of computerized systems (if any) 9. Electronic signature and system access control (if any), 10. Backing up, restoring and archiving of electronic data, 11. Controlled access to the relevant areas of the site, 12. Installation, labeling, use and maintenance of equipment used at the site,

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