Medicinal Products for Human Use - TURKEY

Competent authority

Contact Details	**Contact Name 1** Ministry of Health - Turkish Medicines and Medical Devices Agency (TMMDA)/ Türkiye İlaç ve Tıbbi cihaz Kurumu (TITCK) **Contact Name 2** (Shortly referred to as Ministry or Agency) **Contact Name 3** Department of Clinical Drug Studies **Phone** +90 (312) 218 30 00 **Fax** 90 (312) 218 34 60 **Address** Söğütözü Mahallesi 2176. Sokak No:5 P.K. **ZIP/City** 06520 Çankaya/ANKARA **Country** Turkey (TR) **Web address** http://iegm.gov.tr **Additional Information** No local CA.
Trial Authorisation / Registration / Notification	**Regulatory and ethics bodies involved in approval process** Ministry of Health/ Competent Authority Ethics committee(s) **CA - Submission for authorisation mandatory for** Clinical trials conducted in humans, including studies to investigate bioavailability and bioequivalence, with drugs, medicinal and biological products, or herbal medicinal products, whether authorized or licensed, and for observational drug studies. **CA - Registration/ notification without approval required for** – **CA - Submission required to** National CA Relevant EC(s)
Submission of Application	**Responsible for study submission** –

	Entitled to study submission – **Prerequisites for submission** – **Guidance on submission of application available** Yes **Guidance on submission of application** Guideline Regarding Safety Reporting in Clinical Trials 2015. **Additional Information** Simultaneous application to the EC and the CA is possible, however, the EC’s positive opinion must be issued before CA’s approval can be requested.
Submission Format	**Format option(s)** – **Preferred format** – **Standard application form - Additional information** Standard application forms and cover letter samples for applicaton are posted on the Ministry’s website.
Language of Submission	**Language(s) of application** Turkish **Preferred language of application** – **English accepted** For some documents only, such as investigtors’s brochure and full trial protocol **Documents mandatory to be in official national language** –
Submission Fees	**Fees for trial submission mandatory** Yes **Fees** Application fees are mandatory and shall be paid for the application to the Ministry. Application fees are announced on the Ministry's website annually. Trials for academic purposes or specialty thesis are exempt from fees. **Waiver for academic (non-commercial) studies possible** Yes
Timelines Authorisation	**General timespan (max nr days)** 30 **Mode of approval (General)** – **ATMP/GMO trials (max nr days)** 60

	Mode of approval (ATMP/GMO trials) – **External expert advice required (max nr days)** – **Xenogeneic cell therapy (max nr days)** – **Mode of approval (Xenogeneic cell therapy)** – **Timespan counted from** Confirmation of formal completeness **Additional Information** The sponsor is granted a single opportunity to resubmit amendments upon request of the Ministry (Regulation on Clinical Trials of Medicinal and Biological Products 2014).
Amendments/ Substantial Amendments (SA)	**Notification mandatory for** – **Authorisation mandatory for** All clinical trials requiring authorisation by CA **Responsible for submission of SA** Sponsor **Standard notification form available** Yes **Standard notification form** A standard notification form and cover letter sample are posted on the Ministry's website. **Timeline for approval of SA (max nr days)** 30 From submission of the EC decision **Guidance on submission of SA available** Yes **Guidance on submission of SA** A comprehensive guideline providing detailed guidance on format, content and required appendixes of application as well as on the trial conduct (notification on amendments, trial termination etc.) is available (Guidance on The Format of Applications for the Clinical Trials of Medicinal and Biological Products [to The Ministry] 2014). **Additional Information** Amendments requiring a decision and approval are determined according to the Guideline for Good Clinical Practice (2014).
Safety Reporting	**Responsible for AE reporting to CA** Sponsor

	Sponsor must declare reportable events to National CA Relevant EC(s) Principal Investigator All investigators **Reportable AEs** SAE (Serious Adverse Event) SUSAR (Suspected Unexpected Serious Adverse Reaction) **SUSAR being life-thereatening or leading to death must be reported** Within a max of 7d upon first knowledge (+ 8d for additional information) **All other SUSARs** Within a max of 15d upon first knowledge **SAE /SADE must be reported** – **National standard reporting form available** Yes **Standard Reporting Form** Standard forms are posted on the Ministry’s website **Reporting format - Options** – **Preferred format** – **Annual safety report shall be provided by sponsor to** – **Guidance on AE reporting procedure available** Yes **Guidance on AE reporting procedure** A comprehensive guideline is available (Guideline Regarding Collection, Verification, and Submission of the Reports of Adverse Events/Reactions Occurring in Clinical Trials of Medicinal and Biological Products 2014). **Additional Information** Once a year, the sponsor will provide the ethics committee and the Agency with a listing of all suspected serious adverse reactions occurring during the trial, including information relevant to subjects’ safety, using the interim report form provided in the relevant guidelines to be issued by the Agency. In short-term studies or where necessary, the Agency may request a report earlier (Regulation on Clinical Trials of Medicinal and Biological Products 2014). **Investigator shall report SAE to** – **Reporting timeline** –
End of Trial	**End of trial declaration mandatory for** All clinical trials requiring authorisation by CA

Responsible for End of trial declaration

Sponsor

Regular Termination - Declaration timespan (max nr days)

90

Timespan counted from

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Early/premature Termination - Declaration timespan (max nr days)

15

Reasons for early termination shall be clearly stated

Yes

Standard Declaration form available

Yes

Standard Declaration form

A standard notification form and cover letter sample are posted on the Ministry's website.

Guidance on End of trial declaration available

Yes

Guidance on End of trial declaration

A comprehensive guideline providing detailed guidance on format, content and required appendixes of application as well as on the trial conduct (notification on amendments, trial termination etc.) is available (Guidance on The Format of Applications for the Clinical Trials of Medicinal and Biological Products [to The Ministry] 2014).

Additional Information

Premature termination: a description of measures to maintain treatment of subjects already enrolled in the study must be submitted.

Additional Information & Specifics

Additional Information

Documents provided by the Ministry are in Turkish. No official English translation is available. Unofficial English translations could be provided by Turkish Clinical Research Infrastructure Network (TUCRIN - tucrin.deu.edu.tr) upon request.

Ethics committee

Contact Details

Contact Name 1

Local ECs

Web address

https://www.titck.gov.tr/UnitsPageDescription.aspx?BirimId=CVgRV0Ms3dY=&KonuId=YvRiEmNsOw4=

Additional Information

A list of the ECs in Turkey is provided on the website of the Ministry of Health.

Ethical Review – General

Submission for Ethical review mandatory for

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Submission to CA and EC to be performed in the following order

In parallel

	Additional Information NB! Simultaneous application to the EC and the CA is possible; the EC’s positive opinion must be issued before CA’s approval can be requested **Regulatory and ethics bodies involved in approval process** –
Single-Centre Studies - Ethical Review	**Ethical approval (favourable opinion) to be obtained from** Any competent EC **Additional Information** The scientific and ethical approval will be obtained from any relevant EC in Turkey.
Multi-Centre Studies - Ethical Review	**Ethical approval (favourable opinion) required from** Lead EC (authorised to issue a single opinion) **Submission of application required to** Lead EC (authorised to issue a single opinion) **Additional Information** For multicentre clinical trials, it is sufficient to have a single EC decision.
Submission of Application	**Responsible for study submission** Sponsor **Entitled to study submission** – **Prerequisites for submission / approval** – **Guidance on study submission available** Yes **Guidance on study submission** A comprehensive guideline providing detailed guidance on format, content and required appendixes of application as well as on the trial conduct (notification on amendments, trial termination etc.) is available (Guidance on The Format of Applications for Clinical Trials to Ethics Committee 2014).
Submission Format	**Format option(s)** – **Preferred format** – **Standard application form available** Yes **Standard application form** Standard application forms and cover letter samples for applicaton are posted on the Ministry’s website. **Guidance on submission format available** Yes

	Guidance on submission format A comprehensive guideline providing detailed guidance on format, content and required appendixes of application as well as on the trial conduct (notification on amendments, trial termination etc.) is available (Guidance on The Format of Applications for Clinical Trials to Ethics Committee 2014).
Language of Submission	**Language(s) of application** Turkish English **Preferred language of application** – **English accepted** For some documents only, such as investigtors’s brochure and full trial protocol **Documents mandatory to be in official national language** –
Submission Fees	**Fees for Ethical review mandatory** Yes **Fees for Ethical review** Application fees are mandatory and shall be paid for the application to the EC. Application fees are similar to the ones announced on the Ministry's website, yet must be checked for each EC.
Timelines Ethical Review	**General timespan for single-centre studies (max nr days)** 15 **General timespan for multi-centre studies (max nr days)** 15 **ATMP/GMO trials (max nr days)** 60 **External expert advice required: Timespan (max nr days)** – **Xenogeneic cell therapy: Timespan (max nr days)** – **Timespan counted from** – **Additional Information** Submission is possible anytime. The sponsor is granted a single opportunity to resubmit amendments upon request of the Ministry (Regulation on Clinical Trials of Medicinal and Biological Products 2014). Approval from the EC for Bioavailability-Bioequivalence Studies will be obtained within 7 days after notification date
Amendments/ Substantial Amendments (SA)	**Ethical review mandatory for** Any substantial amendments **Responsible for notification of SA** Sponsor

Standard notification form available

Yes

Standard notification form

A standard notification form and cover letter sample are posted on the Ministry’s website.

Timeline Ethical review of SA (max nr days)

15

Guidance on submission of SA available

Yes

Guidance on submission of SA

A comprehensive guideline providing detailed guidance on format, content and required appendixes of application as well as on the trial conduct (notification on amendments, trial termination etc.) is available (Guidance on The Format of Applications for Clinical Trials to Ethics Committee 2014).

Additional Information

Amendments requiring a decision and approval are determined according to the 'Guideline for Good Clinical Practice (2013)'.

Safety Reporting

Reportable AEs

SAE (Serious Adverse Event)
SUSAR (Suspected Unexpected Serious Adverse Reaction)

Investigator shall report SAE to

Sponsor

Reporting timeline

Immediately (without delay)

Responsible for AE reporting to relevant EC(s)

Sponsor

SUSAR being life-thereatening or leading to death must be reported

Within a max of 7d upon first knowledge (+ 8d for additional information)

All other SUSAR must be reported

Within a max of 15d upon first knowledge

SAE/SADE must be reported

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Sponsor is obliged to notify all investigators of SAE/ SADE occurrence

Yes

National Standard Reporting form available

Yes

Standard Reporting Form

Standard forms are posted on the Ministry’s website.

Reporting format - Options

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Preferred reporting format

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	Provision of Annual safety report mandatory Yes **Guidance on AE reporting procedure available** Yes **Guidance on AE reporting procedure** A comprehensive guideline is available (Guideline Regarding Collection, Verification, and Submission of the Reports of Adverse Events/Reactions Occurring in Clinical Trials of Medicinal and Biological Products 2014). **National legal framework in place** Yes **Applicable national legal framework/ Reference** Regulation on Clinical Trials of Medicinal and Biological Products 2014 **Additional Information** Once a year, the sponsor will provide the ethics committee and the Agency with a listing of all suspected serious adverse reactions occurring during the trial, including information relevant to subjects' safety, using the interim report form provided in the relevant guidelines to be issued by the Agency. In short-term studies or where necessary, the Agency may request a report earlier (Regulation on Clinical Trials of Medicinal and Biological Products 2014).
End of Trial	**End of trial Declaration mandatory** Yes **Responsible for End of trial Declaration** Sponsor **Regular Termination - Declaration timespan (max nr days)** 90 **Timespan counted from** – **Early/premature Termination - Declaration timespan (max nr days)** 15 **Reasons for early termination shall be clearly stated** Yes **Standard Declaration form available** Yes **Standard Declaration form** A standard notification form and cover letter sample are posted on the Ministry's website. **Guidance on End of trial declaration available** Yes **Guidance on End of trial declaration** A comprehensive guideline providing detailed guidance on format, content and required appendixes of application as well as on the trial conduct (notification on amendments, trial termination etc.) is available (Guidance on The Format of Applications for Clinical Trials to Ethics Committee 2014).

National legal framework in place

Yes

Applicable national legal framework/ Reference

Regulation on Clinical Trials of Medicinal and Biological Products 2014

Additional Information

Premature termination: a description of measures to maintain treatment of subjects already enrolled in the study, shall be submitted to the Agency and the ethics committee

Additional Information & Specifics

Additional Information

NB! The EC's positive opinion must be issued before CA's approval can be requested.

An ethics committee is defined as 'a body established with the approval of the Agency to protect the rights, safety and wellbeing of human subjects by, among other things, expressing their scientific and ethical opinion on the methods and documents to be used to inform trial subjects and obtain their informed consent' (Regulation on Clinical Trials of Medicinal and Biological Products 2015).

A standard operating procedure for ECs is available (Standard Operating Procedure for Clinical Trials and Bioavailability-Bioequivalence Studies 2015).

Study specific Requirements

Sponsor

Sponsor - Definition available in national law

Yes

Sponsor - Definition (pursuant to national law)

Sponsor : 'an individual, institution or organization who takes responsibility for the initiation, conduct and/or funding of a clinical trial' (Regulation on Clinical Trials of Medicinal and Biological Products 2014).

Sponsorship mandatory

Yes

Co-Sponsor - Definition available in national law

No

Study Participants - Informed Consent (IC)

Standard IC form (ICF) available

Not specified

Informed Consent - Definition/ Requirements

Definition Informed consent form: 'a documented proof of consent, given based on detailed and comprehensible information about the study'

Prior to participation in the trial, the subject, or the subject's legal representative, will be informed by the principal investigator or by an investigator who is also a physician or dental practitioner fully knowledgeable in the subject matter of trial, sufficiently and in a manner comprehensible to the subject or the subject's legal representative, on the objective, methodology, expected benefits, foreseeable risks, challenges, and any aspects unfavorable to the subject's health or personal characteristics, as well as the conditions under which the study will be conducted and carried out, and that the subject is free to withdraw from the trial whenever the subject so wishes. The subject's consent will be obtained that he or she will be participating in the trial by his or her completely free will, and this will be documented on a Subject's Informed Consent Form.

Additional Information

Specific requirements for obtaining informed consent apply to vulnerable population (minors, incapacitated persons, etc).

Study Participants - Vulnerable Population

Minors / Children - Studies allowed

Yes
Special provisions apply

Specific provision

Where the subject matter of research is directly related to children or is a clinical condition that can be investigated only in children, or it is necessary to verify the applicability of adult data to children, it may be permitted to conduct a study in children.
If a child is capable of expressing assent, written consent of the child's parents, or custodian, where applicable, must be also obtained, in addition to the child's assent.
The ethics committee will be informed on the clinical, ethical, psychological and social aspects of the trial by a pediatrician who holds a doctoral or medical residency degree in pediatric dentistry, and give consideration to the protocol accordingly. An ethics committee cannot approve any clinical trial in children unless a favorable view for conducting the study in children has been given by a pediatrician. If deemed necessary for these trials, the opinion of a pediatrician or a pediatric dentist holding a doctoral or medical residency degree in a field relevant to the subject matter of the trial will be consulted, and the decision on whether or not to authorize the trial will be based on such opinion

Legal framework/Reference (Minors/Children)

Regulation on Clinical Trials of Medicinal and Biological Products 2014.
A detailed guideline is available (Guidance on Ethical Approaches for Clinical Trials Conducted with A Pediatric Population 2013).

Incapacitated persons - Studies allowed

Yes
Special provisions apply

Specific provisions

Where the subject matter of research is directly related to incapacitated persons or is a clinical condition that can be investigated only in incapacitated persons or all existing therapy options to treat the incapacitated person's condition have been exhausted, it may be permitted to conduct a study.

The ethics committee will be informed on the clinical, ethical, psychological and social aspects of the trial by a physician specialized in the subject matter being investigated, and give consideration to the protocol accordingly.

Legal framework / Reference (Incapacitated persons)

Regulation on Clinical Trials of Medicinal and Biological Products 2014

Emergency situations - Studies allowed

Yes
Special provisions apply

Specific provisions

Where the subject matter of research is directly related to persons unconscious or in intensive care, or is a clinical condition that can be investigated only in persons unconscious or in intensive care or all existing therapy options to treat their condition have been exhausted, it may be permitted to conduct a study in persons unconscious or in intensive care.

The ethics committee will be informed on the clinical, ethical, psychological and social aspects of the trial by a physician specialized in the subject matter being investigated, and give consideration to the protocol accordingly.
Written consent must be obtained of legal representatives or relatives of persons unconscious or in intensive care.

Written consent must be obtained of legal representatives or relatives of persons unconscious or in intensive care.

Emergency situation without prior consent of patient or proxy - Studies allowed

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Conditions allowing trial participation in emergency setting without prior consent

In the event a person unconscious or in intensive care or their legal representative or relatives cannot be reached to obtain their written consent, persons unconscious or in intensive care may be included in a trial, under the responsibility of the principal investigator or an investigator who is a medical doctor, provided the following requirements have been met:
a) The ethics committee must have given consideration to the proposed study protocol and other pertinent documents to determine whether the trial in question sufficiently meets ethical requirements.
b) In cases occurring suddenly, requiring urgent medical intervention and where existing therapy options have been completely exhausted, there is common medical view that the study will directly benefit persons unconscious or in intensive care.
If a person unconscious or in intensive care becomes capable of weighing the information provided to them and reaching a sound decision, they must be removed from the trial immediately if they wish to withdraw from the study at any stage, or refuse to take part in it (Regulation on Clinical Trials of Medicinal and Biological Products 2014).

Legal framework / Reference (Emergency Situation)

Regulation on Clinical Trials of Medicinal and Biological Products 2014

Pregnant or breastfeeding women - Studies allowed

Yes
Special provisions apply

Specific provisions

Where the subject matter of research is directly related to pregnant, puerperal or breastfeeding women or is a clinical condition that can be investigated only in pregnant, puerperal or breastfeeding women, it may be permitted to conduct a study in pregnant, puerperal or breastfeeding women.

The ethics committee will be informed on the clinical, ethical, psychological and social aspects of the trial, particularly with regard to fetal or infant health, by a physician specialized in the subject matter being investigated, and give consideration to the protocol accordingly.

Legal framework / Reference (Pregnant or breastfeeding women)

Regulation on Clinical Trials of Medicinal and Biological Products 2014

Data Protection

Notification to DP Authority/ Ombudsmann is mandatory

No

	Approval/ authorisation required No **Specific notification timelines before operations start** – **Language of notification** – **Notification format** – **Additional Information** Confidentiality: Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a volunteer's identity. The confidentiality of records that could identify volunteers should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirements. The monitors, auditors, the Ethics committee, Turkey Pharmaceuticals and Medical Device Agency and the other relevant health authorities will have direct access to the original medical records of the volunteer, but such information will be kept confidential. Pursuant to the applicable regulation requirements, the records directly identifying the volunteer will be kept confidential, they will not publicly disclosed and the identity of the volunteer will be still kept confidential even if results of the trial are published (Guideline for Good Clinical Practice 2014). Clinical trials conducted in humans, including studies to investigate bioavailability and bioequivalence, with drugs, medicinal and biological products, or herbal medicinal products, whether authorized or licensed, and for observational drug studies will be entered in a public register, respecting the privacy of personal information (Regulation on Clinical Trials of Medicinal and Biological Products 2014). **Legal framework (on safeguarding the collection, handling, recording, keeping and/or processing of any clinical trial related data and patient files)** –
Insurance	**Liability insurance or alternative arrangements for damages mandatory for** – **Responsible for covering insurance** Sponsor **Additional Information** To secure the subjects against harms from the clinical trial, insurance meeting regulatory requirements must be provided to subjects who take part in clinical trials, except observational drug studies and Phase IV clinical studies (Regulation on Clinical Trials of Medicinal and Biological Products 2014). A comprehensive guideline is available (Guidance on Insurance Coverage for Clinical Trials 2013).
Quality Assurance/ Quality Control (QA/QC)	**Monitoring** Optional

Audit by sponsor

Optional

Standard Operating Procedures (SOPs)

Optional

National legislation

General Information: Applicable Legislation & Conventions

Official website providing relevant national legislation available

Yes

Official website providing relevant national legislation

Ministry of Health - Turkish Medicines and Medical Devices Agency TMMDA/Türkiye İlaç ve Tıbbi cihaz Kurumu TITCK

Official governmental legal database available

Yes

Official governmental legal database

The Official Gazette web page: T.C. Resmî Gazete

Clinical Trials on IMPs in Humans

Applicable national regulations

National Act on Medicinal Products

Transposition of (CT) Directive 2001/20/EC (or comparable national legal framework)

Regulation on Clinical Trials of Medicinal and Biological Products (previously titled Regulation on Clinical Trials), No. 29041 of the Official Gazette, June 25, 2014

Transposition of (GCP) Directive 2005/28/EC

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Additional Information

ad Regulation on Clinical Trials of Medicinal and Biological Products 2014: This Regulation is issued based on Supplemental Article 10 of Fundamental Law #3359 dated 07.05.1987 on Health Services and Articles 27 and 40 of Decree Law #663 on the Organization and Mandate of the Ministry of Health and Its Subordinate Agencies, and is aligned with Directives 2001/20/EC and 2005/28/EC concerning Good Clinical Practice, constituting a part of European Union’s legislations governing medicinal products. Retrospective studies are not covered by this regulation.

Please refer to the 'Guideline for Good Clinical Practice (2014)' for general principles regarding clinical trials. Guidelines on other relevant topics are also provided by the Ministry.

An overview on the current legislation related to the conduct of clinical trials in Turkey has been recently published and is publicly available:
Ilbars H. Clinical Trials in Turkey. Turk J Haematol 2013;30:111–114.

Definition

IMP/IMP Study

IMP - Definition available in national law

Yes

IMP - Definition

'a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial' (Regulation on Clinical Trials of Medicinal and Biological Products 2014).

IMP Study - Definition

Clinical Trial: 'any investigation in humans intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more investigational medicinal products, or to identify any adverse reactions to one or more investigational medicinal products or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal products with the object of ascertaining their safety and efficacy'

Additional Information

Observational drug study is defined as 'an epidemiological study to collect data on a medicinal product, spontaneously prescribed to patients undergoing treatment in the indications using the posology and route of administration, for which the product has been approved in Turkey according to the current diagnostic and therapeutic guidelines of the Ministry' (Regulation on Clinical Trials of Medicinal and Biological Products 2014).