DECISION

No. 29/13.12.2010

on the approval of Regulations on the authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania

The Scientific Council of the National Agency for Medicines and Medical Devices, set up based on Minister of Health Order No. 1123/18.08.2010, reunited on summons of the NAMMD President in the ordinary meeting of 13.12.2010, in accord with Article 12(5) of Government Ordinance No. 734/2010 related to the organisation and operation of the National Agency for Medicines and Medical Devices, as amended, hereby adopts the following

DECISION

Art. 1. - The Regulations on the authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania are approved, according to the Annexes which are integral parts of this Decision.

Art. 2. - On the date of this Decision coming into force, the NMA Scientific Council Decision No. 11/26.06.2009 on approval of the Regulations on the authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania, approved through SCD No. 52/2006 shall be repealed.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,
Acad. Prof. Dr. Leonida Gherasim

ANNEX

REGULATIONS
on the authorisation by the National Agency for Medicines and Medical Devices of clinical trials/notification to the National Agency for Medicines and Medical Devices of non-interventional studies on medicinal products for human use in Romania

CHAPTER I
General principles

Art. 1. - (1) Clinical trials undertaken in Romania are authorised by the National Agency for Medicines and Medical Devices (NAMMD) in compliance with Law No. 95/2006 on healthcare reform, Title XVII – The medicinal product.

(2) Non-interventional studies are an exception to provisions of paragraph (1), as defined in the Norms relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, approved through Minister of Public Health Order No. 904/2006 on the approval of the Norms on the implementation of GMP rules in clinical trials carried out on medicinal products for human use, which shall be notified to the NAMMD.

Art. 2. - Clinical trials must be conducted in accordance with all regulations in force relating to clinical trials.

CHAPTER II
Clinical trial authorisation procedure

Art. 3. - (1) To start a clinical trial authorisation procedure, the applicant shall pay the clinical trial authorisation fee, established through Minister of Health Order in force concerning NAMMD fees.

(2) To perform the payment, at least 2 weeks in advance of submission of the application for clinical trial authorisation, the applicant shall submit to the Registry office a cover letter related to the payment in advance of the clinical trial fee accompanied by the filled-in clinical trial fee payment form.

(3) The fee is to be paid to the accounts published on the NAMMD website.

(4) The applicant is informed by e-mail on fee payment confirmation to the NAMMD.

Art. 4. - (1) Following the confirmation of the fee payment, the applicant may submit to the NAMMD an application for authorisation in the format shown in SCD No. 22/2010 on approval of the Guidance for the request for authorisation of a clinical trial on a medicinal product for human use, addressed to the competent authority, notification of substantial amendments and declaration of the end of the trial in Romania.

(2) At the same time with submission of the application, the applicant shall also forward a signed cover letter, on paper.

(3) On request, the documents mentioned in Annex 1, which is integral part of these regulations, shall be attached and forwarded in electronic format (on CD/DVD), structured in accordance with Annex 2.

Art. 5. – The assessment period starts on submission of the documentation (day 0).

Art. 6. - (1) The Clinical trials service or the Efficacy bureau of the National procedure department reviews the validity of all documents required under Annex 1 (validation) and in 10 days forwards to the applicant a letter of information on validation of the application.

(2) If the documentation submitted by the applicant is complete, the application is considered valid and the assessment period is continued.

(3) If the documentation submitted by the applicant contains the essential documents related to the study, but supplementations are however necessary, requests for supplementation of the documentation are made; the assessment period is discontinued until the date of submission of the required supplementations.

(4) If the documentation does not comprise the essential trial documents, the application for authorisation is refused.

Art. 7. – Documents under Art. 3 (2) must be drawn up in accordance with the provisions of SCD No. 22/2010.

Art. 8. – The documentation is submitted in either English or Romanian.

Art. 9. – The labelling of medicinal products used in clinical trials (investigational/reference/placebo products) is to be presented in Romanian or English (only for NAMMD use, for translation checking purposes); labelling for clinical trials shall only be done in Romanian, and if the sponsor/investigator is Romanian, the label is submitted in Romanian only.

Art. 10. It is recommended not to include substantial amendments to the main trial documentation after 50 days as of payment confirmation; in case such amendments are included, the time for assessment of the documentation should be prolonged.

Art. 11. – NAMMD examination of an application for authorisation submitted in accurate and appropriate form is to be completed as soon as possible, in line with the deadline set in Minister of Public Health Order No. 904/2006.

Art. 12. – When the documentation is set up compliant with regulations in force and sufficiently substantiated, the NAMMD grants the authorisation for the performance of the clinical trial in the format mentioned in Annex 3, which is integral part of these regulations, according to the deadline set in Art. 39 of Minister of Public Health Order No. 904/2006.

Art. 13. - (1) If, following the assessment of the documentation, additional information or core clarifications to trial documentation is found necessary, the NAMMD notifies the applicant in writing.

(2) The deadline for assessment for clinical trial authorisation/refusal as specified in Minister of Public Health Order No. 904/2006 is extended with the time from applicant receipt of the notification to NAMMD receipt of the information required.

Art. 14. - If, following assessment of documentation, this is found not to be compliant with regulations in force and insufficiently substantiated, within the deadline provided in Minister of Public Health Order No. 904/2006, the applicant is notified the NAMMD about refusal of the authorisation, accompanied by an explanatory report.

Art. 15. - (1) The applicant may require revision of the refusal decision within 30 days as of issuance of the NAMMD decision; the application for revision must be accompanied by supporting documentation.

(2) The NAMMD examines the application and formulates an opinion within 30 days as of admission of the application for revision.

Art. 16. - (1) The authorisation is valid over the entire conduct of a clinical trial, approved by the NAMMD; the trial shall start within 1 year after the date of approval.

(2) The applicant informs the NAMMD about the trial onset in Romania (date of inclusion of the first patient/subject).

Art. 17. – The applicant submits to the NAMMD a copy of the National Ethics Commission/Institutional Ethics Commission opinion as soon as it becomes available.

Art.18. - A clinical trial may only start on condition the NAMMD has forwarded the authorisation for clinical trial conduct and after acquirement of the favourable opinion of the National Ethics Commission, in multicentre trials, or the Institutional Ethics Commission, in single-centre trials.

CHAPTER III
Procedure for amendment notification

Art. 19. – In accordance with Minister of Health Order No. 904/2006, after the onset of the trial, the sponsor may amend the clinical trial documentation.

Art. 20. - (1) The notification is mandatory only in case of substantial amendments (in accordance with SCD No. 22/2010).

(2) Immediate notification/submission of non-substantial amendments is not necessary (as under Minister of Public Health Order No. 904/2006).

Art. 21. - (1) To start an authorisation procedure for a substantial amendment, the applicant must pay the amendments assessment fee as established through the Minister of Health Order in force concerning the NAMMD fees.

(2) To pay the fee, the applicant submits a cover letter to the Registration bureau, accompanied by a filled-in amendment fee payment form, at least 2 weeks prior to the submission of the application for clinical trial authorisation.

(3) The applicant is informed via e-mail on confirmation of the payment to the NAMMD.

Art. 22. - (1) After the confirmation of the payment, the applicant submits to the NAMMD a notification in the format provided in SCD No. 22/2010 on approval of the Guideline on the request of authorisation of a clinical trial on a medicinal product for human use, addressed to the competent authority, the approval of substantial amendments and declaration of closure of a clinical trial in Romania.

(2) At the same time with the application, the applicant also submits a signed cover letter.

(3) On request, the documents mentioned in SCD No. 22/2010, section III.7, Form and content of the notification, are attached.

Art. 23. - (1) The amendments assessment period starts with submission of documentation (day 0).

(2) The NAMMD should respond to the notification of an amendment within 35 calendar days as of receipt of a valid notification.

Art. 24. - (1) The Clinical trials service and the Efficacy bureau of the National procedure department assess the notification validity.

(2) When the submission of the amendment is not considered valid (e.g. the dossier does not contain the necessary as per SCD No. 22/2010), the NAMMD informs the applicant within 10 calendar days of the aforementioned 35-day period, while stating the grounds for this decision.

Art. 25. – In case the documentation is set up in accordance with legal provisions in force and sufficiently substantiated, the NAMMD forwards the letter for amendment approval.

Art. 26. - (1) If, following assessment of the documentation, the NAMMD ascertains that additional information or essential clarifications to the documentation submitted are required, the NAMMD notifies the applicant in writing.

(2) The assessment period until the approval/refusal of the amendment is extended with the time from applicant receipt of the request notification to NAMMD receipt of the information required.

Art. 27. – If, following assessment of documentation, this is found not to be compliant with regulations in force and not satisfactorily substantiated, this leads to refusal of the proposed amendment.

Art. 28. - (1) The applicant may require revision of the refusal decision within 30 days as of issuance of the NAMMD decision; the application for revision must be accompanied by supporting documentation.

(2) The NAMMD examines the application and formulates an opinion within 30 days as of receipt of the application for revision.

Art. 29. An amendment may only be implemented on condition the NAMMD has forwarded the approval of the amendment, when a favourable

opinion of the Ethics Commission concerning the amendment is not required or has already been granted.

CHAPTER IV
Importation of investigational medicinal products

Art. 30. - The notification of investigational medicinal products (IMPs) importation is performed in compliance with legislation in force.

CHAPTER V
Analysis of biological samples

Art. 31. - Analysis of biological samples collected during clinical trials may be carried out in certified or accredited laboratories in Romania or other countries.

Art. 32. - In case the analysis of biological samples is not performed in Romania, these shall be sent to another member states/the exportation in third countries shall be done in compliance with legal provisions in force.

CHAPTER VI
Good Clinical Practice (GCP) inspection

Art. 33. - GCP inspection is conducted in accordance with legal provisions in force.

CHAPTER VII
Requests concerning manner of trial subjects recruitment

Art. 34. - Recruitment of subjects for clinical trials conducted in Romania may only be done through physicians in hospitals or medical practices. Advertisements/Leaflets may be used, which may only be distributed in hospitals/medical practices; healthy volunteers may also be recruited by other means, except for the media.

CHAPTER VIII
Reporting of adverse reactions occurring in clinical trials

Art. 35. - It is the sponsor’s obligation to report to the NAMMD adverse reactions and other information according to provisions of SCD No. 26/2007 on the approval of the Guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use, occurring during clinical trials conducted at Romanian sites and NAMMD requests for electronic transmission, as posted on the EudraVigilance website.

Art. 36. – As per Minister of Public Health Order No. 904/2006, serious suspected unexpected adverse reactions, ending in death or life-threatening, are reported to the NAMMD by the sponsor only.

Art. 37. - Reporting of adverse reactions occurring in clinical trials conducted in Romania is done according to the form of the Council for International Organisations of Medical Sciences (CIOMS), 2nd version.

Art. 38. - In non-commercial studies, as defined in Minister of Public Health Order No. 904/2006, serious suspected unexpected adverse reactions are reported to the NMA by the investigator within the time frames mentioned in the provisions of SCD No. 26/2007.

CHAPTER IX
Requirements regarding investigator's qualification

Art. 39. – For compliance with provisions of Art. 13 of Minister of Public Health Order No. 904/2006 and of Art. 37 and 39 of SCD No. 39/2006 on qualification and training of the investigators, as well as on knowledge of and compliance with Good Clinical Practice (GCP) rules and of the legal provisions in the field, the investigator(s), sub-investigator(s) must demonstrate graduation from GCP training. The GCP graduation certificates become mandatory as of 1 January 2012.

Art. 40. - The application for clinical trial authorisation is accompanied by the form concerning qualification of each main investigator at the respective trial sites and their consent for participating in the clinical trial according to Annex 5, which is integral part of these Regulations.

Art. 41. - In case of non-commercial studies, the investigator who initiates the trial takes over the responsibilities of the sponsor.

CHAPTER X
Authorisation of institutions where clinical trials may be conducted

Art. 42. - Clinical trials may only be conducted in institutions authorised by the Ministry of Public Health, in accordance with provisions of Minister of Public Health Order in force on approval of Regulations for authorisation of units which may carry out clinical trials on medicinal products for human use.

Art. 43. - The authorisation is granted by the Ministry of Public Health on request by the interested institution, in compliance with legal regulations in force.

CHAPTER XI
Notification procedure for non-interventional studies

Art. 44. - Notification of non-interventional studies consists of submission by an applicant to the NAMMD of a notification address, set up according to

provisions of Annex 6, which is integral part of these Regulations, accompanied by the following documents:

- copy of the trial design;
- list of the sites where the trial will be conducted;
- information on the duration of the trial and the number of patients to be enrolled;
- list of the investigators containing their names, surnames and workplaces;
- trial endpoints:

a) The scientific endpoints of the trial must be clearly stated, as well as the relevance for the medical practice of the data obtained during the trial conduct;

b) The indicators for assessment of trial endpoints must be specified.

Art. 45. - The clinical trial applicant is responsible for transmitting to the NAMMD the results of the non-interventional study, as well as for interpretation and statistical significance of results in one year as of trial ending.

Art. 46. - In case of non-interventional studies, the NMA does not request fees for activities undertaken.

Art. 47. - The NAMMD will maintain a separate database of non-interventional studies, also including the results of non-interventional studies carried out in Romania.

Art. 48. - In case the NAMMD has not made a written request to the clinical trial applicant concerning submission of additional necessary data in 60 days as of submission of the notification, the trial initiation notification is considered accepted and the trial may start.

ANNEX 1
to Regulations

DOCUMENTS
accompanying the application to the NAMMD for authorisation of a clinical trial

ESSENTIAL DOCUMENTATION

1. General information

1.1. Cover letter
1.2. Application form
1.3. Confirmation of EudraCT number receipt
1.4. If the applicant is different from the sponsor, a legal authorisation letter from the sponsor, empowering the applicant to act on behalf of the sponsor

2. Information on the protocol

2.1. Protocol containing all amendments
2.2. Summary of the protocol in Romanian
2.3. Opinion of the main investigator/coordinator on the ethical aspects of the trial

3. Investigator's Brochure (IB) or Document replacing the IB, in accordance with the content established in subsection II.6 of HCS 22/2010

4. Simplified Investigational Medicinal Product Dossier (IMPD), in accordance with the content established in subsection II.7 of HCS 22/2010

The Investigational Medicinal Product Dossier (IMPD) includes:
- Evidence of GMP compliance
- Examples of labels in Romanian and English

5. The MNI dossier, in accordance with the content established in subsection II.8 of SCD No. 22/2010

6. Information on the staff and facilities

6.1. Facilities made available for the trial (Authorisation of the health unit for the conduct of clinical trials, Consent of the health unit's director on conduct of the clinical trial)
6.2. CV of the coordinator-investigator in Romania (for multicentre trials)
6.3. CV of each investigator responsible for conducting the trial at Romanian investigational sites (main investigator)
6.4. Information about the support personnel (Form on main investigator's qualification)

7. Confirmation of payment

ADDITIONAL DOCUMENTATION

1. Copy of the Ethics Commission opinion, if available
2. Copy/summary of any scientific counselling
3. Copy of the EMA decision concerning agreement expressed concerning the PIP, as well as the opinion of the Paediatric Committee, if any
4. List of competent authorities (CA) in the EU to whom the application and the decision details have been submitted, when available
5. Information about all active clinical trials on the same IMP

ANNEX 2
to Regulations

◘ 1. General information

◘ 2. Protocol - related information

◘ 3. Investigator's brochure or IB accompanying document

◘ 4. Simplified Investigational Medicinal Product Dossier (IMPD),

◘ 5. MNI dossier

◘ 6. Information on the staff and facilities

◘ 7. Additional documents

ANNEX 3
to Regulations

MINISTERUL SĂNĂTĂȚII
AGENȚIA NAȚIONALĂ A MEDICAMENTULUI
ȘI A DISPOZITIVELOR MEDICALE
Str. Av. Sănătescu nr. 48, sector 1
011478 Bucureşti
Tel.: +40-21.317.11.02
Fax: +40-21.316.34.97

AUTHORISATION
for the conduct of the clinical trial

The National Agency for Medicines and Medical Devices, based on Art. 37 of Minister of Public Health Order No. 904/2006, hereby authorises conduct of the clinical trial according to Protocol No.:

EudraCT No.:

Title:

Sponsor:

Investigators:

Institution (trial site):

Remarks:

PRESIDENT,
.....

ANNEX 4
to Regulations

FORM
for reporting serious suspected adverse reactions

Suspected adverse reaction Protocol No. Notification No.

Investigational Medicinal Product Patient No.

I. Information on the adverse reaction

<table>
<tr><td>1.Patient’s initials</td><td>1.Country</td><td colspan="3">2.Birthplace</td><td>2.a. Age</td><td>3. Sex</td><td colspan="3">4.-6. Manifestation of the adverse reaction</td><td></td></tr>
<tr><td></td><td></td><td>Day</td><td>Month</td><td>Year</td><td></td><td></td><td>Day</td><td>Month</td><td>Year</td><td rowspan="2">8-12
Fill in accordingly:
[ ] Death
[ ] Life-threatening
[ ] Prolonging hospitalisation
[ ] Invalidating
[] Congenital disorders/cancer</td></tr>
<tr><td colspan="10">7.Reaction’s description (including relevant outcomes/laboratory testings)</td></tr>
<tr><td colspan="10"></td><td>[ ] Other important requirements</td></tr>
</table>

II. Information about the suspected investigational medicinal product

<table>
<tr><td colspan="2">14.Name of the investigational medicinal product</td><td>20. The adverse reaction has subsided after the discontinuation of the trial
[ ] Yes [ ] No</td></tr>
<tr><td>15. Daily dose</td><td>16. Route of administration</td><td>21. The adverse reaction has reoccurred after the second administration of the investigational medicinal product [ ] Yes [ ] No</td></tr>
<tr><td colspan="2">14.Name of the investigational medicinal product</td><td>20. The adverse reaction has subsided after the discontinuation of the trial
[ ] Yes [ ] No</td></tr>
</table>

15. Daily dose	16. Route of administration	21. The adverse reaction has reoccurred after the second administration of the investigational medicinal product [ ] Yes [ ] No
14.Name of the investigational medicinal product		20. The adverse reaction has subsided after the discontinuation of the trial [ ] Yes [ ] No
15. Daily dose	16. Route of administration	21. The adverse reaction has reoccurred after the second administration of the investigational medicinal product [ ] Yes [ ] No
17. Administration indication(s)		
18. Period of administration (from/until)	19.Duration of the administration	

III. Concomitant indication and history

22. Concomitant medication and administration dates (excluding that meant for treatment of the reaction)
23. Other relevant anamnesis data (such as diagnosis, allergic reactions, pregnancy etc.)

IV Information about the sponsor and the investigator

24.a. Name and address of the sponsor		24.b. Name of the investigator
24.c. Date of receipt by the sponsor	25.a. Type of information [ ] Initial [ ] Sequential	25.b. Manner of informing the sponsor
Date of notification	Date of receipt	[ ] Additional information is to be attached

Sponsor’s signature

ANNEX 5
To Regulations

FORM
for main investigator/coordinator qualification and arrangements made for participation in the clinical trial

Investigational medicinal product ……..... Protocol No. .....…

Name of the main investigator/coordinator .....….....

Investigator's address ……...….....…….

…….……

Curriculum Vitae/summary: ..... Attached YES [ ]

Qualification (profession) …….…….....

Experience in clinical trials: .....

Experience with other medicinal products relevant to the proposed trial

…….....

Involvement in other clinical trials:

Time necessary for this protocol:
Availability of subjects suitable for the clinical trial:
I hereby accept to participate as main investigator/coordinator in the clinical trial mentioned:
I hereby agree to allow control of all documents:
I hereby agree to allow access to basic documentation:
I hereby agree to sign the commitment form and conduct the trial according to the approved protocol, in compliance with the revised Helsinki Declaration of Human Rights and Good Clinical Practice in Romania.
During the trial, the following will participate as sub-investigators :

Signature Date.....

(day/month/year)

Title

Monitor

(Name)

ANNEX 6
to Regulations

NOTIFICATION

on conduct of a non-interventional study in Romania

To

THE NATIONAL AGENCY FOR MEDICINES AND MEDICAL DEVICES

APPLICANT **SPONSOR** ☐ **INVESTIGATOR** ☐ **CRO*** ☐

Name and surname

Profession

Institution

Address

Telephone/Fax number

*) Contract research organisation

We are hereby notifying you on conduct of a non-interventional study for a medicinal product authorised for marketing in Romania:

Title of the clinical study:

.....

- Country

Information about the investigational medicinal product

- Trade name/code
- Active substances
- CTA code
- Pharmaceutical form
- Doses
- Route of administration
- Manufacturer

This notification is accompanied by:

- Copy of the study design
- Study endpoints
- List of the sites where the study is conducted;
- Information about the study duration and number of patients to be enrolled.
- List of investigators containing the names and surnames of the investigators and their workplaces