

Guidance to the conduct of exploratory (phase 0) trials in Belgium (version 3, June 2016).

Introduction.

Since the introduction of exploratory clinical trials in Belgium experience has been gained in more than 70 studies. The revision of guideline ICH M3 has clarified the non-clinical requirements to support such studies. The circular letter (N° 596) of the Federal Agency for Medicines and Health Products (FAMHP) concerning GMP in early phase, now describes the manipulations of IMP's that can be done in units conducting early phase trials and how to apply for inspection. Therefore the guidance document of the FAMHP for the conduct of Exploratory Clinical Trials in Belgium dating from 2007 has been revised.

The number of new medicines that progress throughout the full development to a final market authorisation is low. The development of new medicines involves a lot of resources. Thus, the failure of many new medicines to progress to final marketing authorisation results in resources being diverted from the development of promising new medicines and therefore these may become available to the patients later than could have been the case or some promising new medicines may not at all become available to patients. If specific critical questions could be answered with data obtained in humans before starting a formal development project, a better documented decision to proceed or not with a full development program could be made. A lot of resources could thus be devoted to a more rational development of the most promising new products. Therefore there is a need for exploratory trials in humans. By definition an exploratory trial will result in providing an answer to a specific question with a limited human exposure in terms of dose, time and number of participants to the study. Exploratory studies will have no therapeutic or diagnostic intent. Without being limitative the goal of exploratory clinical trials can be:

- To confirm the presence of a biological pathway/mechanism in humans
- To establish if a new medicine possesses an acceptable pharmacokinetic profile at pharmacological doses
- To establish the validity of non-clinical disease models to human disease
- Characterize biomarkers of human disease and a pharmacodynamic response to a new medicinal product in minimally diseased patients
- Validate clinical models in healthy volunteers
- Correlate binding with effect and refine PK/PD modeling and simulation
- Compare human ADME or pharmacodynamic parameters across candidates
- Investigate potential for drug-drug interactions
- Evaluate binding affinity or metabolites produced in humans
- Establish the novelty of a potential therapeutic target in comparison to other established therapies.
- Identify differences between healthy volunteers and patients related to pharmacodynamic response sensitivity

The safety of the participants to such studies is paramount but without jeopardising their safety, the pre-clinical testing and the quality requirements for exploratory clinical trials may be less demanding than that normally expected for a phase 1 trial, because exposure will be limited and there will be no intent to reach doses that may cause toxicity. Because of the differences with “standard” phase 1 trials, guidance is given about the quality requirements and the pre-clinical data that are needed to

support exploratory trials, as well as the regulatory procedures to apply for exploratory trials

Procedure

An exploratory trial should be submitted as a phase 1 trial. In the EudraCT form the applicant should tick box E 7.1 and E 7.1.1 as well as E 7.1.3 (“other”). There the applicant should clearly indicate that an early phase exploratory trial application is submitted. Different products can be included in one clinical research protocol that will lead to answering a specific question, and the CTA can be filed under one EudraCT number. The internal treatment of the file will address the exploratory nature of the clinical trial application and therefore it must be clearly indicated why the trial will be exploratory in a covering letter. The aim of the trial or its place in the development program must also be explained in that letter. If there is experience in humans with similar substances (based on chemical or pharmacological similarity, nature of the biotechnological product etc.), this could be helpful in the evaluation of the expected safety of the trial and relevant data could be described in a separate section of the clinical trial application. In Belgium 15 calendar days are allowed for review of a clinical trial application in phase 1 as described by the law of May 7th 2004 concerning experiments on human beings (Wet inzake experimenten op de menselijke persoon - Loi relative aux expérimentations sur la personne humaine). The submission to the FAMHP must adhere to the standard Clinical Trial Application requirements as discussed in the European Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial and the Belgian Circular letter 575.

Chemical and Pharmaceutical Data (CPD)

1 Chemical entities considered as investigational medicinal products

The quality evaluation will be done according to the guideline on the requirements to the chemical and pharmaceutical quality documentation concerning investigational medicinal products in clinical trials (CHMP/QWP/185401/2004 final), note for guidance on good manufacturing practice for active pharmaceutical ingredients (CPMP/ICH/4106/00), note for guidance on minimising the risk of transmitting animal spongiform encephalopathy via human and veterinary medicinal products (EMA/401/01) and Eudralex volume 4, annex 13 on the manufacture of investigational medicinal products.

The following information concerning the drug substance should be included in the IMPD of an exploratory CTA:

- Description of the drug substance, including physical and chemical characteristics
- Name and address of the manufacturer(s)
- General method of drug substance preparation (if control of any manufacturing step or intermediate has been identified as critical to the quality of the Drug Substance, tests and acceptance criteria for control should be briefly summarised)
- Acceptance limits (and a brief justification) and analytical methods used to assure the identity and purity of the drug substance. (information on the validation of the analytical methods would not be required at this stage unless multiple batches would be produced).
- Information to support stability of the drug product for the proposed clinical studies

Two different scenarios may exist with regard to the analytical characterisation of the drug substance:

A. The batch of active pharmaceutical ingredient for pre-clinical and clinical use is different.

In this case the similarity or representative nature of batches should be demonstrated by analytical controls (identity, purity, biologic potency, residual solvents and heavy metals. Structural aspects should be defined in some cases, e.g.: optical rotation (for chiral compounds), reducing/non-reducing electrophoresis (for proteins). In essence, a comparison of the new batch(es) with those used in toxicology testing should ensure that foreseeable risks have been appropriately covered by the pre-clinical program.

B. The batch of active pharmaceutical ingredient for pre-clinical and clinical use is the same.

In this case there is no need to prove similarity, the impurity profile is not needed unless purity is below 95%, optical rotation needs not to be reported. It should be noted that for future reference and comparison it may be advisable to have some data available. In case there are obvious problems during the toxicological qualification the impurity profile and the optical rotation may be determined as needed.

The following information on the drug product should be available:

- List of components used in the manufacture of the investigational product
- Quantitative composition of the drug product
- Name and address of the manufacturer
- GMP status of the manufacturer(s)
- Brief general description of the method of manufacture and packaging (include sterilization process for sterile products).
- If IMP's (e.g. solutions) are prepared on site, the Circular letter 596 should be applied.
- Acceptance limits (and brief justification) and analytical methods used to assure the identity, strength, and purity of the drug product. (information on the validation of the analytical methods would not be required at this stage unless multiple batches would be produced).
- Information to support stability of the drug product during the proposed clinical studies
- In case of parenteral administration sterility, amount of endotoxin and of particulate matter should be tested and reported.
- When the drug product is intended for inhalation, specific tests like particle size distribution measurement should be available.
- For testing requirements of any formulation, the PhEur or EU member state pharmacopea, the US pharmacopea or the Japanese pharmacopea should be consulted.
- Excipients should be listed in the PhEur or an EU member state pharmacopoeia, the US pharmacopoeia or the Japanese pharmacopoeia for the same route of administration and amount or they should appear on the GRAS (generally recognised as safe) list issued by FDA (<http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>). The use of novel excipients should be justified and the excipient should be fully characterised for the chemical, manufacturing and controls aspects as indicated by the EMA note for guidance on IMP's and any novel excipients should be adequately qualified through appropriate animal studies.

As a general rule, GMP procedures apply to the manufacturing of IMP's intended for clinical trials including exploratory trials (Eudralex volume 4, annex 13). This is also the case for radiopharmaceuticals (cfr. Eudralex volume 4, annex 3). Controls should be consistent with the stage of development of the drug product (ICH note for guidance Q7). For exploratory clinical trials it would for instance be acceptable that development labs and pilot plants would produce the relatively small quantities of product needed. It may be acceptable that facilities and equipment are appropriate, raw materials and intermediates are well described, the final active pharmaceutical ingredient and the drug product are well characterised, the documentation would be sufficient to trace the whole production process and that the personnel responsible for the production is sufficiently skilled and well trained to have an acceptable IMP for an exploratory trial.

For the implementation of GMP in early phase clinical trials, reference is also made to the circular letter 596 that could be applicable to exploratory clinical trials.

2 Biotechnological products

In as far as applicable, the principles should be followed as outlined in the Guideline on the Requirements for Quality Documentation Concerning Biological Investigational Medicinal Products in Clinical Trials (EMA/CHMP/BWP/534898/2008). Generally speaking the guidelines

CPMP/BWP/328/99, CHMP/BWP/398498/2005, CHMP/BWP/2458/03, Eudralex 3AB1a, Eudralex 3AB2a, Eudralex 3AB3a, Eudralex 3AB4a, Eudralex 3AB5a, Eudralex 3AB6a and Eudralex 3AB7a are applicable with regard to all quality criteria for exploratory clinical trials using biotechnology products.

3 Investigational tools

It is conceivable that certain exploratory trials may involve products that are not intended to become medicinal products. These may be used to investigate the validity of a target in human disease, to evoke a response that could be validated as a biomarker or that could be used to investigate the effect of the exploratory medicine(s). In such cases, the investigational tool can be considered as a non-investigational medicinal product (NIMP) as defined in Eudralex volume 10, chapter III on clinical trials. For NIMP's, the Guidance on Investigational Medicinal Products (IMPs) and 'non investigational medicinal products' (NIMPs) should be followed.

4 Radiopharmaceuticals

In order to start a clinical study with radiopharmaceuticals in Belgium, approval should be obtained not only from the Federal Agency for Medicines and Health Products and the involved Ethics Committee(s) but also from the Federal Agency for Nuclear Control (FANC). Prior to submission of the clinical trial application to the Federal Agency for Medicines and Health Products and the involved Ethics Committee(s), the applicant of the clinical study should ensure that all activities related to the use of the radiopharmaceutical in the context of the clinical study (eg. transport, storage, manufacture, patient administration of the finished product, etc.) are fully covered by the appropriate licenses issued by the FANC (i.e. for every investigator site involved in Belgium). More information on the FANC can be found on the following website: <http://www.fanc.fgov.be/>

With regard to radiopharmaceuticals, the guidelines 3AQ20a and 3AQ21a apply in addition to the CHMP/QWP/185401/2004 guideline of the EMA and the general principles of the CHMP/QWP/306970/2007 guideline on radiopharmaceuticals.

Furthermore, reference is made to the FDA Guidance on PET drugs – cGMP (FDA, December 2009).

For PET radiopharmaceuticals which, under certain conditions, may be considered as a NIMP depending on the objectives of the PET study, more guidance can be found in the Q&A document of Eudralex Vol 10.

Pre-clinical testing: pharmacology, safety pharmacology and toxicology information

The pre-clinical requirements to conduct exploratory clinical trials are described in the ICH M3 guideline, revision 2. This guideline governs the requirements for the IMP's that are involved. When a biotechnological product is to be investigated, the preclinical requirements should not only be determined by the ICH M3 document, but

the ICH S6 guideline should also be consulted. The ICH M3 mentions 100 µg as a limit dose for the microdose trials. This is acceptable, but the potency and the molecular weight (in particular for larger molecules) should be taken into consideration when needed.

1 Investigational tools

If products will be used in an exploratory trial as investigational tools, in principle the same amount of testing will be required as if it were a candidate new drug substance. If this product is already well known and if sufficiently confirmed literature data are available this may however be superfluous. It should be considered whether it would be more important to determine acute effects and observe the animals during two weeks to detect delayed effects that may occur after a single exposure, rather than conducting a repeat dose toxicity study.

2 Radiopharmaceuticals

The evaluation of radiopharmaceuticals should address both general parameters of the medicinal product and radiation dosimetry aspects. Guidelines with regard to the dosimetry and all necessary precautions related to the use of radiopharmaceuticals should always be observed, also in an exploratory clinical trial. It should also be justified why no alternatives to radiopharmaceuticals can be used. It is not the intention of this guidance document to consider the use of radiopharmaceuticals that will be administered as radiotherapy.

Knowledge of the toxicology of the ligand per se is the first aim of pre-clinical safety testing and therefore safety studies may be conducted with unlabelled compound.

Choice of animal species

The selection of the animal species to be used in the non-clinical experiments should be justified. This is particularly important if only one species can be used. For the study of “off-target” toxicity, the rat and the dog would be convenient as they would allow the use of established routine procedures and this would have the advantage of a large database of experimental data for comparison being available. If the target of the candidate drug substance(s) would be known and already studied in humans, and therefore “on target” untoward effects would be known, the rat and the dog would be the normal choice to cover any “off-target” adverse effects. Obviously, in vitro metabolism data may confirm this choice or may lead to the proposal of an alternative, based on the comparability of the metabolism of the substance in humans and animals.

When the target is new and not previously studied in humans, it should be assured that the target is present and operational in at least one of the animal test species that are used for safety testing. Otherwise, potential “on target” adverse effects would not be detected in non-clinical tests. It might be less likely that species specific expression would be a major issue for a medicinal product of chemical origin, and it can be anticipated more often if the product is of biotechnological origin. In those cases where species specificity hampers the study of target related adverse effects, “off target” toxicity may still be determined when using routinely used animal species for safety testing, but alternative models like genetically engineered animals and animal homologues may be envisaged to study potential “on-target” effects. It should be

ascertained that the tissue expression, second messenger mechanisms etc. are comparable in the animal and the human in case genetically engineered animals would be a realistic testing possibility. In the case that animal homologues of a human target would be used, consideration should not only be given to the similarity of molecular targets (second messengers, nature of the effect, tissue distribution) but when the substance is produced by biotechnological means also to the production process and possibly resulting impurity profiles.

By using human cell lines and animal cell lines or organs in vitro that contain the target, it should preferably be known whether the potency of the test compound(s) would be similar, higher or lower in humans and the species used for safety testing. This may allow to calculate starting and maximal doses for the clinical trial more precisely by adjusting for species differences and may allow the use of a more realistic safety factor than the arbitrarily chosen ones to take species differences into account.

Often it is well known to what extent homology exists between a human and animal target in terms of for instance amino acid composition. It is however not clear to what extent such homology can predict functional differences. The use of in vitro data to compare animals and humans may make the question obsolete how much homology between both is sufficient to reliably extrapolate from the one to the other or at least represent valuable additional information. The potency of a test compound, its maximal effect and the type of response as well as the second messengers involved in the response could all be of value to enhance the predictability of the experimental data. Which in vitro data are required should be determined on a case by case basis and it should be justified why the data used are relevant to sufficiently predict responses in humans.

Starting dose

There are two well accepted ways of estimating a safe starting dose that could be applicable to exploratory clinical trials. One is the estimation of a Minimal Anticipated Biological Effect Level (MABEL) and the other is the use of 1/50th of the NOAEL in the most sensitive species.

If the mechanism of action of the medicinal product(s) to be used in the trial is well known, the pharmacological activity and the target-related or structure-related adverse effects are well known. Hence “off-target” toxicity may be of more concern than “on-target” activity. The 1/50th of the NOAEL after scaling (mg/m²) may be most realistic of the two approaches for calculating the starting dose in this case.

If the product(s) to be investigated in an exploratory clinical trial have a new mechanism of action or if they are biotechnology-derived products, the MABEL approach may be the safest possibility.

There are various parameters that can be used for estimating MABEL. One is to model the occupancy of the target with different doses, another is to test effects on human tissues ex-vivo and a third possibility is to use data from a carefully qualified animal model. Dose- or concentration- response data should be taken into account. A literature review of the effects of other relevant molecules may also be useful. It is common practice to take into account a safety factor of ten to allow for species differences and inaccuracies to the calculation.

Exposures in animals at therapeutically active doses and exposures in animals at NOAEL could be used also to calculate a starting dose, using estimated exposures in humans based on modelling.

It should also be noted that in early phase trials and in particular for exploratory trials there is still a relative lack of pharmacokinetic data. Therefore it may be difficult to calculate a MABEL value very precisely. Whereas additional safety factors could be used to take into account such uncertainties it is generally not recommended that this would be done extensively as a substitute for achievable pre-clinical data outlined in earlier sections. First, it is not always clear what the safety factor should be to increase the default factor of 10. Using arbitrarily chosen factors is no guarantee that safety is indeed sufficiently safeguarded and may on the other hand quickly lead to unrealistically high safety factors. It may be more realistic in some cases to obtain the necessary data that could reduce the uncertainty and that would enable a more accurate extrapolation from animals to humans than to keep increasing the margin of safety.

Maximal dose

The PK data obtained in humans at lower doses should allow to accurately predict when exposures will be reached that could result in reactions of a critical magnitude. A maximal dose capping based on a real exposure can thus be proposed. The response observed in humans in previous cohorts during the exploratory clinical trial should be taken into account before dose escalations. Obviously, an adverse clinical response that occurs in clinical testing would mean that the maximally allowed exposure for an exploratory clinical trial has been reached. If a sufficient pharmacological response is observed that allows to answer the question that was the reason to undertake the exploratory trial, the maximally needed dose may be considered to have been reached. Escalation of the dose above any of these limits would generally not be acceptable in an exploratory clinical trial, unless the observed dose-limiting effects are reflecting an interaction with the primary pharmacological target. An escalation of the dose may then be acceptable on condition that the effects are not serious or severe, and that they are monitorable and reversible. It should also be considered that an effect that is dose limiting to normal volunteers may not be dose limiting for patients: therapeutic effects in the latter may be untoward in the former, sensitivity may be different between normal volunteers and patients, some mechanisms may play a role in the one and not in the other etc. Maximal acceptable doses may thus be dependent on the type of subjects.

General clinical and ethical requirements

The safety of participants in first-in-human trials can be improved by careful consideration of the risks associated with it and by pro-actively managing those risks. In this context, the guideline to mitigate risks in first in human clinical trials should be applied (EMA/CHMP/SWP/28367/07). Several key issues should be taken into account.

A. Study participants:

Subject intended to be enrolled into a clinical study should be appropriate to answer the specific questions to be addressed in the study. Depending on these questions, the subjects can be either healthy volunteers or patients, preferably with minimal disease and in stable condition. The Informed Consent process should ensure a detailed communication of all potential risks and documented verification of the participants' comprehensive understanding of the involved risks and the

safe-guards, including the indemnity conditions in case of short- and long-term health damage. Exploratory CTA studies should not be performed in pediatric patients and pregnant or lactating women.

B. Site of the clinical trial

Although expCTA studies should present fewer potential risks than do traditional phase I studies because the maximal dose is limited, a thorough knowledge of existing guidelines on eIND/expCTA studies is required to be able to make a correct judgment of the risks involved and to evaluate the preclinical dossier in collaboration with the competent authority, ethics committee and pharmaceutical company. Therefore, expCTA studies should only be performed by trained investigators who have acquired the necessary expertise in conducting early clinical drug trials (i.e. phase I-II) under well controlled circumstances. Expedited CTA studies should take place in well equipped clinical facilities and be conducted by medical staff with appropriate level of training and experience in early clinical drug development. Training in Good Clinical Practice (GCP), safety training and Basic Life Support should be considered mandatory for investigator and site personnel.

End of the exploratory phase and initiation of further development

An exploratory clinical trial should try to answer a specific question or group of questions that will allow to decide on bringing one or more compounds to development or to further pursue a target in discovery and development research. This means that the investigational plan should be clearly outlined at the moment of submission, and clinical stopping points for each of the compounds or the target tested should be provided. When the original questions are answered the exploratory clinical trial should be ended. Amendments could be submitted within the context of an exploratory clinical trial if this is deemed necessary, but if these amendments are intended to extend the trial beyond the original objectives, this must first be discussed with the FAMHP and the ethics committee that is concerned with the trial.

Once the decision can be taken to proceed with one or more compounds into formal development, this decision should be clearly communicated when submitting a next clinical trial application. Since an exploratory trial is designed to answer very specific questions with limited testing, it should be ascertained that the complete package of pre-clinical testing that would normally be expected to support development according to ICH M3 and, for biotechnological products, ICH S6 should be available before starting a clinical trial aiming at further development (longer duration, higher doses, therapeutic intent etc.). Obviously the data that were obtained during the exploratory phase can be used and pre-clinical data that were obtained to support the exploratory trial may be completed to meet the requirements to support further development.

Scientific advice

Less pre-clinical testing is required to support exploratory clinical trials in comparison with classical phase 1 trials (ICH M3 Rev 2). Thus relatively limited data will be available and it should be ascertained that these will be sufficient to support a trial. Targets may involve mechanisms that were never explored in humans, which may lead to an unexpected response in humans. Therefore, the sponsor has the possibility

to ask for Scientific and Technical (i.e. regulatory) Advice at the FAMHP. If a sponsor is planning a study involving a new target according to the exploratory trial paradigm, the sponsor is advised but not required to start a Scientific Advice procedure prior to the formal exploratory CTA submission.

In the start up phase of the exploratory clinical trials, a pre-submission procedure was used. Since now a possibility to ask Scientific and Technical advice exists, the pre-submission procedure for exploratory clinical trials is considered obsolete and should no longer be used.

References

Guideline on strategies to identify and mitigate risks for first-in human clinical trials with investigational medicinal products.

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Production and quality control of medicinal products derived by recombinant DNA technology. Eudralex 3AB1a

Quality of biotechnological products: analysis of the expression construct in cells used for production of rDNA derived protein products. Eudralex 3AB2a

Production and quality control of cytokine products derived by biotechnological processes. Eudralex 3AB3a

Production and quality control of monoclonal antibodies. Eudralex 3AB4a

Note for guidance on quality of biotechnological products: stability testing of biotechnological/biological products. Eudralex 3AB5a

Gene therapy product quality aspects in the production of vectors and genetically modified somatic cells. Eudralex 3AB6a

Use of transgenic animals in the manufacture of biological medicinal products for human use. Eudralex 3AB7a

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Radiopharmaceuticals. Eudralex 3AQ20a

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CHMP/QWP/306970/2007 guideline on radiopharmaceuticals

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Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals. EMA/ CHMP/ICH/302/95. Revision 1.

Note for guidance on genotoxicity: specific aspects of regulatory genotoxicity tests for pharmaceuticals. EMA/CPMP/ICH/141/95

Note for guidance on genotoxicity: a standard battery for genotoxicity testing of pharmaceuticals. EMA/CPMP/ICH/174/95

List of abbreviations

ADME	Absorption, Distribution, Metabolism, Excretion
CPD	Chemical and Pharmaceutical data
CTA	Clinical Trial Application
EMA	European Medicines Agency
EudraCT	Database of all clinical trials commencing in the European Community (http://eudract.EMA.europa.eu/)
expCTA	Exploratory Clinical Trial Application
eIND	Exploratory Investigational New Drug Application
FAMHP	Federal Agency for Medicinal and Health Products in Belgium
FANC	Federal Agency for Nuclear Control in Belgium
FDA	Food and Drug Administration in the US
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRAS	Generally Recognised As Safe
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
MABEL	Minimal Anticipated Biological Effect Level
NIMP	Non-Investigational Medicinal Product
NOAEL	No Observed Adverse Effect Level
PhEUR	European Pharmacopea
PET	Positron Emission Tomography
PK/PD	Pharmacokinetics/Pharmacodynamics