INVESTIGATOR’S BROCHURE

Add Clinical Trial Logo (if applicable)

IMP Name/Number:
EudraCT Number:
Sponsor Project ID Number:
Effective Date:
Version Number:

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The IB should be reviewed at least annually. More frequent revision may be appropriate depending on the stage of development and/or the generation of relevant new clinical or safety information.

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SIGNATURE PAGE

CI Signature:

__________________________________________  Date
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1. SUMMARY

This section should contain a brief (maximum of two pages) summary highlighting the significant points included in this document.

1.1. Introduction

Give a brief overview of the IMP/ATIMP and its indication.

1.2. Physical, Chemical and Pharmaceutical Properties

1.3. Nonclinical Data

1.4. Clinical Experience

2. INTRODUCTION

The Introduction should aim to provide a high-level overview of the investigational medicinal product and the setting in which it is being investigated. Information to be covered includes the generic and trade names of the drug product, its active ingredient(s), and the pharmacological class and position of the product being investigated within this class, especially potential advantages over other products within the class. This section should also summarise the rationale for investigating the investigational product, identifying anticipated prophylactic, therapeutic, or diagnostic indications, and provide an overview of the investigational approach as already conducted or intended.

2.1. Background

Briefly state the investigational medicinal product (IMP) chemical name, generic name (if approved) and trade name (if approved). List the active ingredients and confirm which pharmacological class the IMP is in. Briefly discuss its expected position within this class (i.e., the advantages it is expected to have over other products in that class).

Identify the anticipated prophylactic, therapeutic or diagnostic indication(s) that the IMP is being developed to address.

2.2. Rational for [Name product]

Briefly discuss the rationale for performing research with the IMP. Provide information on the general approach to be followed in developing/evaluating the IMP.

If appropriate, discuss other treatment options.
2.3. References

3. PHYSICAL, CHEMICAL AND PHARMACEUTICAL PROPERTIES AND FORMULATION

This is a brief section describing the chemical, physical, and pharmacological properties of the investigational product, in terms of the drug product and, where relevant, also the drug substance. The section should aim to provide the investigator with sufficient information on the investigational product so that potential risks associated with either the drug itself or any excipients can be assessed. This section should also provide information on storage and handling, including preparation steps needed prior to administration, such as reconstitution or dilution. Detailed instructions can be given in an IMP/ATIMP Management Plan or summary of drug arrangements (SODA) and referenced here.

3.1. Pharmaceutical Presentation

Describe the IMP substance. Give a brief summary of the relevant pharmaceutical properties.

3.2. Physical and Chemical Properties of the Drug Substance

Briefly describe the physical and chemical properties of the product.

3.3. Formulation Including Excipients

Describe the formulation to be used including the excipients. Justify the use of this formula if clinically relevant. Provide information on structural similarities to other known compounds.

3.4. Storage and Handling

Provide instructions for the storage and handling of the IMP in its dosage form.

3.5. References
4. NON-CLINICAL STUDIES

The study design and animal species or tests systems used should be stated. The summaries should also include, as applicable, information on the nature, frequency, and intensity of pharmacological or toxic effects, time to onset and duration of these effects, and reversibility of the effects. When a large number of non-clinical studies are available, it can be beneficial to provide the details of each study in a tabulated format, often in an Appendix, and then provide focused summaries of results and interpretations, supported by tables and figures, within the non-clinical section.

This section includes the results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies in a summary form. Examples of the information are:

<table>
<thead>
<tr>
<th>Species tested</th>
<th>Number/sex of animals per group</th>
<th>Unit dose</th>
<th>Dose interval</th>
<th>Route of administration</th>
<th>Duration of dosing</th>
<th>Duration of post-exposure follow-up</th>
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<th>Type of Study</th>
<th>Construct(s)</th>
<th>Test System</th>
<th>Administration Method</th>
<th>No./Group/Dose(s)</th>
<th>GLP Compliance</th>
<th>Testing Facility</th>
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Discuss the results of these studies including the following information:

- Nature and frequency of pharmacological effects.
- Severity or intensity of pharmacological effects.
- Time to onset of effects.
- Reversibility of effects.
- Duration of effects.
- Dose response.

If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed)
(a) Nonclinical Pharmacology

A summary of the pharmacological aspects of the investigational medicinal product and, where appropriate, its significant metabolites studied in animals should be included. For e.g., studies that assess potential therapeutic activity (e.g., efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions).

(b) Pharmacokinetics and Product Metabolism in Animals

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. Addresses the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

Biodistribution and vector shedding studies may be discussed in this section.

(c) Toxicology

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

Single dose;
Repeated dose;
Carcinogenicity;
Special studies (e.g., irritancy and sensitization);
Reproductive toxicity;
Genotoxicity (mutagenicity).

4.1. Non-clinical Test Material

State what material was used in the nonclinical studies and what form that material took.

4.2. Good Laboratory Practice

Specify which studies were conducted to GLP. Where studies have not been conducted to GLP explain the justification for this and whether the studies were conducted in the spirit of the principles of GLP/GLP like conditions.
4.3. Non-clinical Pharmacology

4.3.1. Non-clinical Pharmacology Studies Performed

4.3.2. Pharmacokinetics and Product Metabolism in Animals

4.4. Toxicology

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4.4.5. Other Toxicity Studies

4.5. Non-clinical Assessment of Safety

Provide summary and assessment of findings from non-clinical studies.

4.6. References

5. EFFECTS IN HUMANS

This section should include a thorough discussion of the effects of the Investigational Medicinal Product in humans. A summary of each completed clinical trial should be provided as well as any additional information obtained through alternative methods e.g., experience during marketing.

If clinical data from studies with similar products is relevant the data can be presented in this section.

ICH E6 specifies that information should be summarised on the ‘pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities’.

This section may be very brief if this is a First Trial in Man (FTIM) trial with little clinical data available.

5.1. Clinical Overview

Provide a summary of clinical studies conducted to date (if applicable)
5.2. Clinical Studies Conducted with IMP/ATIMP

5.2.1 Pharmacokinetics and Product Metabolism in Humans

- Summary of metabolism, absorption, plasma protein binding, distribution and elimination.
- Bioavailability of the IMP (absolute and/or relative).
- Differences in pharmacokinetic profile in population subgroups such as the elderly, renal impairment etc.
- The effect of food on the pharmacokinetic profile.
- The effect of other drugs on the pharmacokinetic profile. It is particularly important to investigate drugs known to affect the cytochrome P450 (CYP) pathway as well as drugs commonly co-prescribed for the condition being investigated.

5.2.2 Safety and Efficacy

- Summary of the safety profile of the IMP and its metabolites.
- Pharmacodynamics profile of the IMP and its metabolites.
- Summary of the efficacy of the IMP and its metabolites.
- Dose response summary.
- Tables to summarise adverse drug reactions (ADRs).
- Discuss the important differences in ADR incidence and patterns across subgroups or indications.
- Describe the possible risks and anticipated ADRs in future studies based on the current experience with the IMP.
- Describe any precautions that should be taken or special clinical monitoring that should be performed.

5.2.3 Marketing Experience

- List those countries where regulatory approval has been granted or rejected. List those countries where the IMP is currently being marketed and has been withdrawn from the market. Discuss any additional information gained through the marketing process.

If there have been no clinical studies conducted to date with the ATIMP/IMP state....

There have been no clinical trials with [name of product] to date. A first-in man, Phase 1/2 trial is due to commence xxxxx.
5.3. **Existing Clinical Data from Other Clinical Studies**

Add any data available from other relevant clinical studies using a similar IMP/ATIMP. Provide details on the IMP/ATIMP and how it differs from the IMP to be tested.

5.4. **References**

6. **SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR**

For first-time-in-man IBs, state that no data are available on the relationship of AEs to administration of the IMP, because no studies have yet been conducted in human subjects. For IMPs in early phase development, state that limited data are available on the relationship of AEs to administration of the IMP, because clinical experience is limited. In this case, state that the guidance for the investigator is based on nonclinical data and on the results of any Phase I/II studies.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the IMP. Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that are based on previous human experience and on the pharmacology of the investigational product.

This section should include risks related to the IMP, as well as critical raw materials, excipients, conditioning regime, procedures related to the IMP and its administration.

The following subheadings may be helpful, but do not all need to be included if not relevant.

6.1. **Summary of pre-clinical and clinical data**

6.2. **Dosage and Method of Administration**

6.3. **Contraindications**

This section can contain the exclusion criteria for the trial or/or any specific contraindications known the protocol.

[name of product] must be administered according to protocols approved by UCL.

6.4. **Special Warnings and Special Precautions for Use**

[name of product] is intended for investigational use only by selected Investigators familiar with information in this Investigator’s Brochure and experienced in conducting clinical studies.
6.5. Interactions

6.6. Use during Pregnancy and Lactation

6.7. Undesirable Effects

Detail significant known and potential risks with the product and discuss how this is being mitigated.

For ATIMPs the following should be considered to be included:

- Information obtained from on-going risk analysis based on existing knowledge of the type of product and its intended use including risk associated with the application method (e.g. surgery, concomitant medication, associated devices);
- Information on the risks due to product failure;
- Information on short and long term safety issues particular to ATIMPs such as infections, immunogenicity/immunosuppression and malignant transformation as well as those related to medical devices for combined ATIMPs.

6.8. Overdose

Possible wording for First Time In Man (FTIM) Trial....

No data from clinical studies are available regarding overdose of [name of product].

6.9. Drug Abuse and Dependency

Possible wording for FTIM Trial....

No studies have been conducted to evaluate the potential for abuse and dependence. Based on the mechanism of action and pharmacological activity, however, there is no evidence to suggest that [name of product] has potential for abuse or dependence.

6.10. Use and Handling

For ATIMPs provide information on the product safety handling, containment and disposal.

Example of wording for GM material...

This IMP contains genetically-modified material. Local biosafety guidelines applicable for gene therapy products should be followed. Instructions for the preparation of the infusion solutions will be provided in the IMP management plan.
6.11. **Reference Safety Information (RSI) for Assessment of Expectedness of Serious Adverse Reactions**

- This safety section should contain a clear list or table of expected serious adverse reactions (SARs) indicating severity and frequency for each listed SAR. The expected SARs should be listed using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms, such as for example Common Terminology Criteria for Adverse Events [CTCAE].

- The table of expected SARs should contain columns for ‘Date added to IB’ and ‘Date removed from IB’ to assist with safety reporting.

- This section should be limited to expected SARs only. All observed adverse reactions including non-serious adverse reactions, suspected SARs that have occurred only once, and fatal and life-threatening SARs that are considered unexpected should not be included in this section but described in the Summary of data and guidance for the investigator section.

- Example Expected Serious Adverse Reactions tables shown below.

- The frequency of adverse reactions reported as in the table below are derived from previous clinical trials and are defined using the following convention: very common (>1/10), common (> 1/100 to <1/10), uncommon (> 1/1,000 to <1/100), rare (> 1/10,000 to <1/1,000), very rare (< 1/10,000) not known. Use this convention where sufficient numbers of subjects have been exposed to the IMP/ATIMP.

- During the early stages of product development, the number of observed ‘suspected SARs’ for each ‘expected SAR’ should be provided, together with the number of patients exposed, see example below:

- Table of Serious Adverse Reactions for [Enter compound number/Name] considered expected for safety reporting purposes.

<table>
<thead>
<tr>
<th>SOC</th>
<th>SARs</th>
<th>Number of subjects exposed (n) = 328</th>
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<tbody>
<tr>
<td></td>
<td>All SARs</td>
<td>Occurrence of fatal SARs</td>
</tr>
<tr>
<td></td>
<td>n* (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>Diarrhoea</td>
<td>25 (7.6)</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td>ALT increase</td>
<td>12 (3.6)</td>
</tr>
<tr>
<td></td>
<td>AST increase</td>
<td>9 (2.7)</td>
</tr>
<tr>
<td>Cardiovascular disorders</td>
<td>Myocarditis</td>
<td>33 (10.0)</td>
</tr>
</tbody>
</table>
n = number of subjects who have experienced the SAR

If there are expected life-threatening or fatal SARs listed in this RSI section, the number of suspected life-threatening and fatal suspected SARs that have occurred should be included as in the table above.

Alternatively possible wording for FTIM Trial....

There have been no related adverse reactions to date and therefore, there are no SARs currently classed as expected. As there are no expected SARs, any serious AEs deemed to be unexpected and related to (IMP/ATIMP name) for the proposed Phase I/II study will be reported as per Directive 2001/20/EC and the CT-3 guidance as a Suspected Unexpected Serious Adverse Reaction (SUSAR). No SARs are considered expected by the sponsor for the purpose of expedited reporting of SUSARs and identification of SUSARs in the “Cumulative summary tabulation of serious adverse reactions” in the DSUR for the IMP.

6.12. Other Potentially Clinically Relevant Information for the Investigator

6.13. References