|  |
| --- |
| **Eligibility criteria for a fast-track process [1]** |
| **Early CT** | [ ]  Yes [ ]  No |
| **Paediatric oncology and hematology**  | [ ]  Yes, specify age range :[ ]  No |
| **Rare disease** | [ ]  Yes [ ]  No |

**[1] non-eligibility criteria (for information) especially:** healthy volunteer, complex design, ATMP

|  |
| --- |
| **Clinical trial identification** |
| **Title** |  |
| **Sponsor** |  |
| **EudraCT number** |  |
| **CPP concerned (if identified)** |  |
| **Protocol** | **Date/version :**  |

|  |
| --- |
| **Study documentation** |
| **Name IMP [2]****dosage, pharmaceutical form** | Chemical | Biological | **Document** | **Submitted****Version & date** | **Last authorized by ANSM****Version & Date*****(If applicable)*** |
| IMP1 | **[ ]**  | **[ ]**  | IMPD (Quality) |  |  |
| IB |  |  |
| IMP2 | **[ ]**  | **[ ]**  | IMPD (Quality) |  |  |
| IB |  |  |
| IMP3 | **[ ]**  | **[ ]**  | IMPD (Quality) |  |  |
| IB |  |  |
| IMP4 | **[ ]**  | **[ ]**  | SmPC |  |  |

**[2] tested, comparator and placebo**

*(Duplicate as necessary)*

| **Clinical trial information** |
| --- |
| **Active Substance** | **Code & [INN] :**  |
| **Study treatments** Description of planned therapeutic schemes  |

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **IMP** | **Starting Dose** | **Maximum Daily dose** | **Route of administration** | **Schedule** | **Maximal treatment duration** |
| Therapeutic scheme 1 : |
| IMP1 |  |  |  |  |  |
| IMP2 |  |  |  |  |  |
|  |  |  |  |  |  |
| Therapeutic scheme 2 : |
| IMP3 |  |  |  |  |  |
| IMP4 |  |  |  |  |  |
|  |  |  |  |  |  |

*(Duplicate as necessary)* |
| **Study population & Contraception** | **Study Population : [ ]** male [ ]  female**Age range :****Description of contraceptive measures** and justification in case of non-compliance with current recommendations issued by the CTFG :

|  |  |  |  |
| --- | --- | --- | --- |
| **IMP** | **T ½*****(half-life of elimination)*** | **Profile*****(genotoxic, teratogen)*** | **Type and duration of contraception *(women and men)*** |
|  |  |  |  |
|  |  |  |  |

*(Duplicate as necessary)*Justification in case of non-compliance with current recommendations issued by the CTFG:  |
| **Study plan** |  |
| **Scientific advice** | **Has a scientific advice been given for the IMP or trial? : [ ]** Yes [ ]  No(by the EMA or another competent authority of the EU or a third country)**Are there discrepancies between the submitted protocol and the recommendations provided in the scientific advice?:**  **[ ]** Yes [ ]  NoIf yes, please justify : |
| **Pediatric investigation plan** | **Is the trial part of a paediatric investigation plan (PIP) submitted to the EMA?**  **[ ]** Yes [ ]  No**Are there discrepancies between the submitted protocol and the PIP?**  **[ ]** Yes [ ]  NoIf yes, please justify : |
| **ICH S9** | [ ]  Yes [ ]  NoIf Yes, please indicate if the trial covers several indications/pathologies and if all are S9 : |

|  |
| --- |
| **Quality section** |

|  |
| --- |
| 1. **Active substance (Section S of IMPD)**
 |

* 1. **Generalities**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **#** | **Questions** | **Yes** | **No** | **If yes, specify** |
| 1 | Has the active substance a monograph ? | [ ]  | [ ]  | If yes, specify: [ ]  Ph. Eur. [ ]  a Pharmacopoeia of an EU MS[ ]  USP/JP |
| 2 | How the suitability of the monograph has been shown with regard to the implemented process?  |  |  | Indicate the relevant pages of the IMPD (S.2.2):  |
| 3 | Has the Active substance a valid CEP\* | [ ]  | [ ]  | If yes: * CEP No.:
* Holder:
* special tests/limits, re-test period, TSE information, if relevant, should be indicated:
 |
| 4 | Is the active substance of an authorised drug product in the EU from the same manufacturer using the same process? | [ ]  | [ ]  | If yes, indicate the authorised drug product : |
| 5 | Is the active substance described in an ASMF\* already submitted to ANSM and accepted in support of a given drug product? | [ ]  | [ ]  | If yes, ASMF number :  |
| 6 | **None of the above (full S Section)** | [ ]  |  |  |

**\* Biologicals are not concerned with**

* 1. **Manufacture (S.2)**

**Control of Materials (S.2.3)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **#** | **Questions** | **Yes** | **No** |  |
| 1 | Is there any material of animal or human origin used in the process? | [ ]  | [ ]  | If yes, fill viral safety section. |

* 1. **Characterisation (S.3)**

**Impurities (S.3.2)**

| For chemical substance |
| --- |
| **Impurity** | **Impurity name XX /code** | **Impurity YY/ code** | **Impurity ZZ / code** |
| **Structure / origin** |  |  |  |
| **Maximum daily dose of the active substance** | MDD | MDD | MDD |
| **Impurity claimed limit** |  |  |  |
| **Structure / origin** |  |  |  |
| **NC Tox study number & NC Tox lot number** |  |  |  |
| **Range of impurity levels found in NC Tox batches** |  |  |  |
| **HED\* (of impurity) at NOAEL***Indicate species* |  |  |  |
| **Range of impurity levels found in clinical batches** |  |  |  |
| **Justification** | e.g. qualification in NC studies | e.g. qualification in NC studies | e.g. TTC according to ICH M7 |
| **Limit of detection\*\*****Limit of quantification\*\*** |  |  |  |
| **If available** |
| **Exposure of animals** (plasmaAUC&Cmax) *if applicable*-at NOAEL-at highest dose | - XXX- YYY |  |  |
| **Safety margin based on calculated/****Extrapolated exposure of human at the highest dose (at the claimed limit)** |  |  |  |

\*HED: Human equivalent dose, MDD: maximum daily dose, \*\* LOD and LOQ of the analytical procedure used for determination of the impurity

| For biological substance |
| --- |
| **Impurities** | **Limit of Detection (LOD)/ quantification (LOQ)** | **Estimation of clearance, if cleared** | **Range of levels in clinical batches (per container)** | **Maximum amount for the highest clinical dose for an adult of 70 kg, a child of x Kg** | **Risk-based assessment (e.g. PDE, ICH M7…or any other non clinical/clinical justification** |
| **Process related impurities (including antifoam….)** | Impurity X |  |  |  |  |  |
| Impurity Y… |  |  |  |  |  |
|  |  |  |  |  |  |
| **Product related impurities****…** |  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

* 1. **Control of Active Substance (S.4)**

**Batch Analyses**

| **#** | **Questions** | **Yes** | **No** |
| --- | --- | --- | --- |
| 1 | Will the presented clinical batches be used in this clinical trial | [ ]  | [ ]  |
| 2 | Will other batches be used in this clinical trialIf yes, indicate batch numbers | [ ]  | [ ]  |
| 3 | Confirm that all batches are representative of the process intended to be used in this Clinical trial | [ ]  | [ ]  |

* 1. **Stability (S.7)**

|  |  |  |
| --- | --- | --- |
| **#** | **Questions** | **Specify** |
| 1 | What is the proposed retest period/ shelf life for biologicals | Months :Storage conditions : |
| 2 | What is the duration of long term stability studies? | Months :Study Conditions : |
| 3 | What is the duration of accelerated stability studies? | Months :Study Conditions: |
| 4 | Other conditions | The conditions studied : |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **#** | **Questions** | **Yes** | **No** | **Specify if necessary** |
| 5 | Is the container used during the stability studies identical to the container closure system described in section 3.2.S.6 | [ ]  | [ ]  |  |
| 6 | Is the retest period/shelf life for biologicals proposed based on extrapolation | [ ]  | [ ]  |  |
| 7 | Is an extension protocol of the shelf-life in accordance with the GL EMEA/CHMP/BWP/534898/2008 provided | [ ]  | NA [ ]  |  |
| 8 | **Are trends or OOS results observed**  | [ ]  | [ ]  | For which attributes and which storage conditions: |
| 9 | Have forced degradation studies been conducted | [ ]  | [ ]  |  |
| 9.1 | If Forced degradation studies were conducted, have any specific storage conditions to be applied | [ ]  | [ ]  | If yes, specify the precaution for storage: |

|  |
| --- |
| 1. **Finished product (Section P of IMPD)**
 |

* 1. **Manufacture (P.3)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **#** | **Questions** | **Yes** | **No** | **NA** |
| 1 | Did Media fill runs cover the worst case conditions of the aseptic process | [ ]  | [ ]  | [ ]  |

* 1. **Excipients (P.4)**

| **#** | **Questions** | **Yes** | **No** | **NA** |
| --- | --- | --- | --- | --- |
| 1 | Is there any non-pharmacopoeia excipient used in the formulation? | [ ]  | [ ]  |  |
| 2 | Is there any novel excipient used in the formulation? | [ ]  | [ ]  |  |
| 3 | Is there any non-pharmacopoeia excipient however used in other type of products such as cosmetics? | [ ]  | [ ]  |  |
| 4 | Is there any excipient of animal or human origin present?  | [ ]  | [ ]  |  |
| 5 | Is BSE/TSE risk is addressed?[Fill the viral safety section if applicable] | [ ]  | [ ]  | [ ]  |
| 6 | Is there any excipient with known effects (EMA/CHMP/302620/2017)?  | [ ]  | [ ]  |  |

\*for definition of novel excipients, see CHMP/QWP/396951/2006

* 1. **Control of the investigational medicinal product (P.5)**

**Batch analyses (P.5.4)**

| **#** | **Questions** | **Yes** | **No** |
| --- | --- | --- | --- |
| 1 | Will the presented clinical batches be used in this clinical trial | [ ]  | [ ]  |
| 2 | Will other batches be used in this clinical trialIf yes, indicate the batch numbers | [ ]  | [ ]  |

**Container Closure System (P.7.)**

| **#** | **Questions** | **Yes** | **No** |
| --- | --- | --- | --- |
| 1 | For liquid critical dosage forms, are pieces of information on extractable, leachable submitted in the IMPD pages <> | [ ]  | [ ]  |
| 2 | Presence of medical device for administrationIf yes, describe the device | [ ]  | [ ]  |
| 2.1 | CE marked? | [ ]  | [ ]  |

**Stability (P.8)**

|  |  |  |
| --- | --- | --- |
| **#** | **Questions** | **Specify** |
| 1 | What is the proposed shelf life for the IMP ?  | Packaging:Months/years :Storage conditions :<without any precaution of storage> <with a precaution storage of\* >store below <25°C> <30°C>”> <store in a refrigerator> <store in a freezer> |
| 2 | What is the duration of long term stability studiesSpecify the conditio | Months : |
| 3 | What is the duration of accelerated stability studiesSpecify the conditio | Months : |
| 4 | Other conditions | Conditions studied : |

| **#** | **Questions** | **Yes** | **No** | **NA** | **Specify if necessary** |
| --- | --- | --- | --- | --- | --- |
| 5 | **Are trends or OOS results observed**  | [ ]  | [ ]  |  | For which attributes and which storage conditions: |
| 6 | Is the shelf life based on extrapolation | [ ]  | [ ]  |  | Criteria used for extrapolation: based on <accelerated stability data> < long term stability data><any other justification> |
| 7 | Is the IMP reconstituted or diluted before use | [ ]  | [ ]  | [ ]  | Specify the solvent for reconstitution/dilution or type of food: |
| 8 | Does the in-use stability study respect the concentrations and conditions described in the clinical protocol | [ ]  | [ ]  | [ ]  |  |
| 9 | Is an extension protocol of the shelf-life in accordance with the GL EMEA/CHMP/BWP/534898/2008 provided | [ ]  |  | [ ]  |  |

|  |
| --- |
| 1. **Viral safety data (If biological product is used) (A.2)**
 |

Viral Safety part is to be filled-in taking into account the Guide for Fast-Track “A.2 Adventitious Agents Safety Evaluation for biotechnology products”.

* 1. **Risk of contamination with TSE (A.2.1)**

[ ]  Yes (see Guide: this applies when materials relating to TSE-risk species are used)

[ ]  No

* 1. **Adventitious viruses (A.2.2)**

**Identification of materials of biological origin and testing (A.2.2.1)**

[ ]  Yes (see Guide: this applies when material of biological origin is used)

[ ]  No

Table: listing of raw materials /measures minimizing risk of transmission

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **List of Raw material** | **Step where used** | **Supplier** | **Source** | **Species** | **Virus testing** | **steps contributing to Viral safety (gamma-irradiation, nanofiltration,…)/results of viral validation studies** |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

**Testing of source materials: Cell bank system and cell line testing (A.2.2.2)**

* Summary of nature, origin and history of cell line :

Table: Summary of testing results performed on the cell bank system. (Add all relevant tests)

| **Adventitious virus test** | **Indicator cell lines / in vivo model used.** | **MCB****(Lot [XX])** | **WCB****(Lot [XX])** | **EOPCB****(Lot [XX])** |
| --- | --- | --- | --- | --- |
| In vitro assay for detection of adventitious viruses  |  |  |  |  |
| In vivo assay for detection of adventitious viruses  |  |   |  |  |
| Mouse antibody production (MAP) assay  |  |  |  |  |
| Hamster antibody production (HAP) assay |  |  |  |  |
| **Tests for Retroviruses and other Endogenous Viruses** |  |  |  |  |
| Infectivity (e.g. Extended S+L- focus forming assay (xenotropic retrovirus)) |  |  |  |  |
| Infectivity test (e.g extended Mus dunni assay..) |  |  |  |  |
| Extended XC plaque assay |  |  |  |  |
| Transmission electron microscopy (TEM) examination |  |  |  |  |
| Reverse transcriptase (e.g. PBRT) |  |  |  |  |
| Other virus-specific tests (as appropriate, known infectious agents) |  |  |  |  |
| **Other virus tests** |  |  |  |  |
| MVM |  |  |  |  |
| Specific adventitious virus tests (e.g. porcine, bovine, ovine, caprine ; in vitro assays, molecular assays) |  |  |  |  |

**Testing of unprocessed bulk (A.2.2.3)**

|  |  |
| --- | --- |
| **Adventitious virus test** | **Indicator cell lines / in vivo model used** |
| In vitro assay for detection of adventitious viruses |  |
| Other virus testing |  |

|  |  |
| --- | --- |
| **Batch n°** | **RVLP concentration (RVLPs/ml)** |
| Lot [XX] |  |
| Lot [XX] |  |
| Lot [XX] |  |

RVLPs: retrovirus like-particles

**Viral clearance studies (Industrial production scale should be indicated) (A.2.2.4.)**

Specific / dedicated viral validation studies were undertaken: [ ]  Yes [ ]  No

|  |  |  |
| --- | --- | --- |
| **Steps** | **Describe the mechanism of action** | **Specify for each step if specific or modular studies were considered** |
| 1) |  |  |
| 2) |  |  |
| 3) |  |  |

Table: summary of Log10 reduction factors (LRF) from validation studies

|  |  |  |
| --- | --- | --- |
|  | **Model virus X** | **Model virus Y** |
| **Steps** | **Run A** | **Run B** | **Run A** | **Run B** |
|  |  |  |  |  |
|  |  |  |  |  |
| **Total LRF** |  |  |  |  |

Are process parameters between manufacturing process scale and scale-down viral clearance study comparable?

[ ]  Yes

[ ]  No, justify:

Table: comparison of process parameters between manufacturing and scale-down viral clearance study

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Steps** | **Process parameter (lists of critical parameters for viral safety)** | **Manufacturing process scale** | **scale-down viral clearance study** | **Justification of scale-down parameters** |
|  |  |  |  |  |
|  |  |  |  |  |

**Retroviral Risk assessment (A.2.2.5.)**

* Highest possible retroviral load in bulk harvest: [XX] RVLPs/m
* [Volume] in mL of cell culture harvest fluid needed to produce a [X] mg dose :
* RVLP input per dose:
* Cumulative log reduction factor: >[X] log10
* Result: Estimated particles / Dose (after viral clearance ):

**Function and regeneration of columns (A.2.2.6.)**

Are column re-used?

[ ]  Yes, short description of sanitisation should be included:

[ ]  No

|  |
| --- |
| **NON CLINICAL SECTION** |

|  |
| --- |
| 1. **Regulatory context**
 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Which guidelines have been used?** | **S9** | **M3** | **S6** | **FIM** |
| *Thick the related guideline(s)* | [ ]  | [ ]  | [ ]  | [ ]  |

|  |
| --- |
| 1. **Pharmacology**
 |

**Primary Pharmacodynamics**

What are the In vivo / in vitro studies performed? (Mechanism of action, proof of concept, justification of animal models…) :

**Secondary pharmacodynamics**

Screening of other targets binding (« off-target »):

**Safety pharmacology**

Table 1: Safety pharmacology studies

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Study type** | **Doses** | **Major findings** |
| **Cardiovascular** |
| *in vitro* [1] |  |  |  |
| *in vivo* |  |  |  |
|  |  |  |  |
| **Central nervous system** |
|  |  |  |  |
|  |  |  |  |
| **Respiratory** |
|  |  |  |  |
|  |  |  |  |
| **Others (e.g. renal, GI system..)** |
|  |  |  |  |
|  |  |  |  |

[1] Alert if safety margin Cmax (Human) (free fraction) / IC50 hERG < 30 (An evaluation of hERG current assay performance: Translating preclinical safety studies to clinical QT prolongation; [*Pharmacol Ther.*](https://www.ncbi.nlm.nih.gov/pubmed/20807552) 2011 Feb;129(2):109-19. doi: 10.1016/j.pharmthera.2010.08.008. Epub 2010 Aug 31.)

|  |
| --- |
| 1. **Pharmacokinetics**
 |

Table 2: Pharmaco/toxicokinetics data

| **Species** |  **X** | **Y** | **Z** |  |
| --- | --- | --- | --- | --- |
| **Dose**  |  |  |  |  |
| **Route of administration** |  |  |  |  |  |
| **AUC****(ng.h/ml)** | M |  |  |  |  |
| F |  |  |  |  |
| **Cmax****(ng/ml)** | M |  |  |  |  |
| F |  |  |  |  |
| **Tmax****(h)** | M |  |  |  |  |
| F |  |  |  |  |
| **T1/2** | M |  |  |  |  |
| F |  |  |  |  |
| **Vd** | M |  |  |  |  |
| F |  |  |  |  |
| **CLT** | M |  |  |  |  |
| F |  |  |  |  |
| **F (%)** |  |  |  |  |  |

M = male F = female T1/2 = half-life of elimination

Vd = volume of distribution CLT = clearance F (%) = bioavailability

|  |
| --- |
| 1. **Toxicology**
 |

**Single dose toxicity**

Table 3: Summary of single dose toxicity studies.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Species** | **Sex** | **Number/****Group** | **Dose/Route of administration** | **Approx. Lethal dose/ MTD/LD50** | **Major findings** |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

**Repeat-dose toxicity**

Table 4: Summary of repeated administration studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Species/ Number of****animals** | **Doses****(mg/kg/day)** | **Route and duration** | **NOEL/ NOAEL****(mg/kg/joday)** | **AUC****(ng.h/ml)****For Antibodies = (µg.day/ml)** | **Major findings** |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

**Genotoxicity**

Table 5: Summary of genotoxicity studies

|  |  |  |  |
| --- | --- | --- | --- |
| **Type of test/GLP** | **Test System** | **Concentrations / Concentration range / Metabolising system** | **Results** |
| Gene mutations in bacteria | *Salmonella typhimurium* / E.coli | +/- S9 |  |
| Gene mutations in mammalian cells | CHO-cells, HGPRT-locus | +/- S9 |  |
| Chromosomal aberrations *in-vivo* | Mouse, micronuclei in bone marrow | mg/kg |  |
| Others |  |  |  |

**Carcinogenicity**

Table 6: Summary of carcinogenicity studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Species/Number of animals** | **Dose/route of administration** | **Duration** | **NOEL/ NOAEL****(mg/kg/day)** | **AUC****(ng.h/ml)** | **Major findings** |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

**Reproductive and developmental toxicity**

Table 7: Summary of reproductive and developmental toxicity studies:

| **Species****Study / GLP****Number of animals** | **Dose (mg/kg)/ Route** | **Dosing period** | **NOAEL (mg/kg)** | **AUC****(ng.h/ml)** | **Major findings** |
| --- | --- | --- | --- | --- | --- |
| **Fertility (M)** |  |  |  |  |  |
| **Fertility (F)** |  |  |  |  |  |
| **Embryo-foetal development** |  |  | F0F1 |  |  |
| **Peri&postnatal** |  |  |  |  |  |

Table 8: Points to be taken into account for the calculation of the post-treatment contraception period

|  |  |
| --- | --- |
| **PRODUCT** |  |
|  **Half-life (t½) in human** |  |
| **Genotoxicity**  |  |
| **Carcinogenicity**  |  |
| **Calculation based on 5 half-lives**  |  |
| **Woman post-treatment contraception period**  |  |
| **Man post-treatment contraception period** |  |

**Juvenile toxicity**

Table 9: Summary of juvenile animal studies

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Species****(age)** | **Dose** | **Duration****and route** | **NOEL/ NOAEL****(mg/kg/jday)** | **AUC****(ng.h/ml)** | **Major findings** |
|  |  |  |  |  |  |
|  |  |  |  |  |  |

**Local tolerance**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **#** | **Questions** | **Yes** | **No** | **If no, justify** |
| 1 | Is local toxicity (skin, eye…) studied : signs of irritation, inflammation, histology…? | [ ]  | [ ]  |  |

**Phototoxicity**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **#** | **Questions** | **Yes** | **No** | **If no, justify** |
| 1 | Is photosafety studied ? | [ ]  | [ ]  |  |

**Other studies**

Provide other non-clinical studies

|  |
| --- |
| 1. **Grounds for doses selection for clinical trials**
 |

**Starting dose**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Indicate the non-clinical endpoints used for the selection of the starting dose:** | **HED (NOAEL)** | **MRSD** | **MABEL** | **PAD** | **STD** | **HNSTD and other** |
| *Thick the related endpoints* | [ ]  | [ ]  | [ ]  | [ ]  | [ ]  | [ ]  |

| **#** | **Indicate the scaling approach used?** | **Yes** | **No** | **Specify** |
| --- | --- | --- | --- | --- |
| 1 | Allometric (HED) | [ ]  | [ ]  |  |
| 2 | Modelling approach | [ ]  | [ ]  |  |
| 2.1 | PB/PK | [ ]  | [ ]  |  |
| 2.2 | PK/PD | [ ]  | [ ]  |  |
| 2.3 | Other | [ ]  | [ ]  |  |

**Dose-escalation**

| **#** | **Questions** | **Yes** | **No** |
| --- | --- | --- | --- |
| 1 | Is the Dose/exposure relationship established from former clinical steps studies (lower doses) is taken into account to refine the dose increment if needed? | [ ]  | [ ]  |
| 2 | Is exposure to major metabolites (if any) is taken into account in these estimations? | [ ]  | [ ]  |

**Maximum dose / Stop dose**

| **#** | **Questions** | **Yes** | **No** | **Specify** |
| --- | --- | --- | --- | --- |
| 1 | What is the planned maximum dose? |  |  | Specify : |
| 2 | Grounds for maximum dose selection |  |  |  |
| 2.1 | MTD | [ ]  | [ ]  | Specify if not determined |
| 2.2 | Other | [ ]  | [ ]  | Specify :  |
| 3 | What the target exposure (AUC and Cmax) for the maximum dose is? |  |  | Specify |
| 4 | Is attainment of the above mentioned target exposure integrated as an additional criteria for stop-dose? | [ ]  | [ ]  |  |

**Safety margin**

Table 10: Summary of safety margin

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Species** | **Dose****(/)** | **NOAEL (mg/kg/day)** | **Cmax (ng/ml)** | **Safety margin****(Cmax)** | **AUC0-24 (ng.h/ml)** | **Safety margin****(AUC)** |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

|  |
| --- |
| **CLINICAL SECTION** |

|  |
| --- |
| 1. **Justification of the study population and line of treatment**
 |

[Possible references: SmPC, national and international recommendations, relevant bibliographical articles…]

**Justification of the study population in relation to the presumption of clinical efficacy of the IMP**

**Description of the therapeutic alternatives available in France in the proposed indication**

**Justification of the proposed line of treatment in regard to the existing therapeutic alternatives**

**Justification of the choice of the control arm (if applicable)**

|  |
| --- |
| 1. **Study treatments**
 |

**Justification of planned therapeutic schemes and doses**

**Identification of each expected adverse effect and planned risk minimization measures**

(for each treatment arm, including the comparator arm)

|  |  |  |
| --- | --- | --- |
|  | **Expected adverse effect** | **Planned risk minimization measures** |
| Therapeutic scheme 1 : |
| A |  |  |
| B |  |  |
| Therapeutic scheme 2 : |
| C |  |  |
| D |  |  |
|  |  |  |

**Identification of potential toxicities and planned risk minimization measures**

(for each treatment arm, including the comparator arm)

|  |  |  |
| --- | --- | --- |
|  | Potential toxicities | Planned risk minimization measures |
| Therapeutic scheme 1 : |
|  |  |  |
|  |  |  |
|  |  |  |
| Therapeutic scheme 2 : |
|  |  |  |
|  |  |  |
|  |  |  |

**The eligibility and non-eligibility criteria planned in the protocol are in accordance with the recommendations detailed in the documents provided in support of the clinical trial request for authorization (IB / SmPC):** [ ]  Yes [ ]  No

Any discrepancy is to be justified below:

**The safety monitoring scheduled in the protocol (including type and frequency of examination) is in accordance with the recommendations detailed in the documents provided in support of the clinical trial request for authorization (IB / SmPC):**

 [ ]  Yes [ ]  No

Any discrepancy (in terms of type and/or frequency of examination) is to be justified below:

**Sampling volume**

Indicate the volume of sampling at each visit:

|  |
| --- |
| 1. **Associated medications**
 |

**Description of planned auxiliary medicinal products**

|  |  |
| --- | --- |
| **Auxiliary medicinal product**  | **Indication**  |
| Treatment X |  |
| Treatment Y |  |
|  |  |
|  |  |

**Concomitant therapies**

The planned concomitant therapies (permitted and prohibited) are in accordance with the recommendations detailed in the documents provided in support of the clinical trial request for authorization (IB / SmPC): [ ]  Yes [ ]  No

Any discrepancy is to be justified below:

|  |
| --- |
| 1. **Conditions of use**
 |

The patient management planned in the protocol in case of toxicity (toxicities management, guidelines for dose modifications, including reductions, delays, interruptions, and discontinuation) is in accordance with the recommendations detailed in the documents provided in support of the clinical trial request for authorization (IB / SmPC): [ ]  Yes [ ]  No

Any discrepancy is to be justified below:

|  |
| --- |
| I hereby certify that the information provided in this document is accurate and consistent with the constituent elements of the CT application and attached to this document |
| **Do it :** | **Name and surname of the signatory** |  |
| **Signature** |

**\* \***

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