Agence nationale de sécurité du médicament et des produits de santé

Clinical Trials of medicinal drugs under the Fast Track procedure at ANSM

Guidance to complete the additional Fast Track document

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AEC_DOC021A V01

ansm.sante.fr

Summary

This document provides guidance on how to complete the additional document required for Fast-track procedure (*additional FT document*).
For this purpose, the following is the annotated additional FT document, outlining in italic green the information that is awaited and/or how to present them.

I. GENERAL

For Fast track 1 Innovation

Eligibility criteria for a fast-track process [1]		
Early CT	☐ Yes	☐ No
Paediatric oncology and hematology	☐ Yes, specify age range : ☐ No	
Rare disease [2]	☐ Yes	☐ No

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

[2] Rare Disease *: Rare diseases are those that affect a small number of people. The threshold admitted in Europe is one in 2,000 people*

For Fast track 2 Development

Eligibility criteria for a fast-track process [3]		
Molecule or association of molecules already evaluated in France	☐ Yes	☐ No
and in the same indication [4] as for the previous trial	☐ Yes	☐ No

[3] non-eligibility criteria (for information) especially: : First CT in France**,** complex design, ATMP

[4] i.e. same disease, target population, treatment (symptomatic, curative, preventive, diagnostic); Furthermore pharmaceutical and non clinical data must have already been assessed (no new data submitted in this CT application)

Clinical trial information

Study treatments

Description of planned therapeutic schemes

IMP	Starting Dose	Maximum Daily dose	Route of administration	Schedule	Maximal treatment duration
Therapeutic scheme 1 : *[e.g. IMP1 + IMP2 association]*					
IMP1	*500 mg*	*1000 mg*	*per os*	*2/day*	*21 days*
IMP2	*1000 mg*	*2000 mg*	*per os*	*2/day*	*21 days*
Therapeutic scheme 2 : : *[e.g. IMP3]*					
IMP3	*250 mg*	*500 mg*	*per os*	*2/day*	*28 days*
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 [*]
[*] *Recommendations related to contraception and pregnancy testing in clinical trials – 15-09-2014:*
http://www.hma.eu/fileadmin/dateien/Human_Medicines/01About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

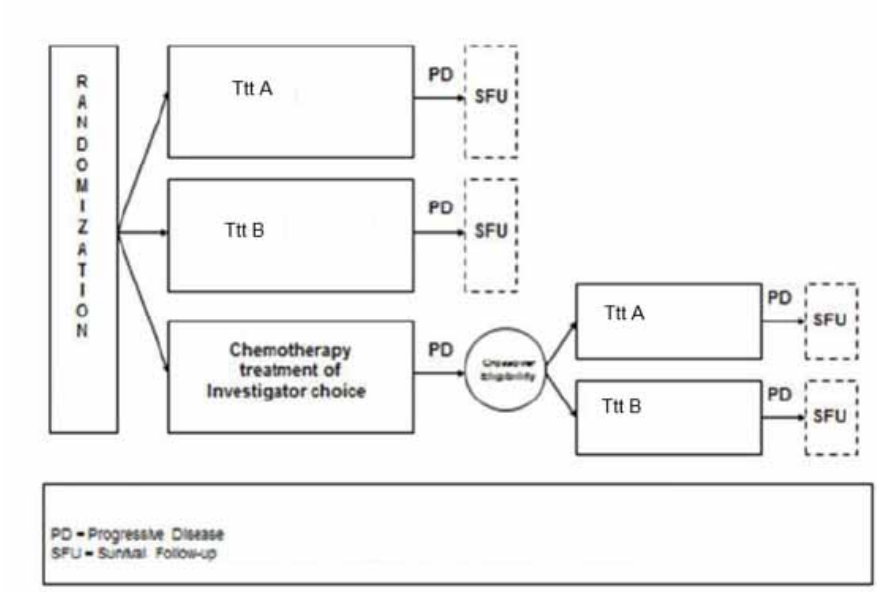
IMP	T ½ *(half-life of elimination)*	Profile *(genotoxic, teratogen)*	Type and duration of contraception *(women and men)*
IMP X (test)	*12 days*	*teratogen*	*Women :* *Highly effective method of contraception during the treatment and up to 90 days after the end of treatment* *Men :* *Condom during the treatment*
IMP Y (comparator)			

(Duplicate as necessary)

Justification in case of non-compliance with current recommendations issued by the CTFG:

Study plan

[Please insert the descriptive figure of the study plan]

Clinical trial information	
	Example: 

ICH S9	☐ Yes ☐ No If Yes, please indicate if the trial covers several indications/pathologies and if all are S9 :

ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals CHMP/ICH/646107/08

II. Quality section (Fast Track 1)

1. Active substance (Section S of IMPD)

No special recommendations for filling in this section

2. Finished product (Section P of IMPD)

No special recommendations for filling in this section

3. Viral safety data (If biological product is used) (A.2)

For tables to be completed, no special recommendations are given unless specific warnings need to be highlighted
This guide is relevant mainly to the viral safety of biotechnological medicinal products used in clinical trials.
Sections, rows and any useful item may be added when needed and relevant.
If some items or sections are not relevant, please state: NA (Not applicable)

3.1. Risk of contamination with TSE (A.2.1)

☐ Yes (see Guide: this applies when materials relating to TSE-risk species are used)
Relevant EDQM TSE-Certificate or adequate demonstration of compliance with TSE-Guideline EMEA 410/01 rev03/ Ph. Eur 5.2.8.
In the case of a bovine milk derived product, certificate stating that" the milk has been collected from healthy animals and under the same conditions as for milk fit for human consumption", is available

☐ No

3.2. 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 :
  Provide a brief description of the nature (e. g. cells, ascite..) , origin (eg. human, animal,..), history (e.g. biological products used during the production of the cells)

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

Testing performed [state the CRO or laboratory], year [Date of study completion]
If there are less than 3 batches evaluated for RVLPs, this should be indicated "no data" in the table.

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):

Please follow the ICHQ5A guideline: APPENDIX 5.

Function and regeneration of columns (A.2.2.6.)

Are column re-used?

☐ Yes, short description of sanitisation should be included:
☐ No

III. NON CLINICAL SECTION (Fast Track 1)

For tables to be completed, no special recommendations are given unless specific warnings need to be highlighted

1. Regulatory context

Which guidelines have been used?	S9	M3	S6	FIM
Thick the related guideline(s)	☐	☐	☐	☐

ICH S9: Nonclinical Evaluation for Anticancer Pharmaceuticals CHMP/ICH/646107/08
ICH M3 (R2): Note for guidance on non-clinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals" [CPMP/ICH/286/95]
ICH S6 (R1): Preclinical safety evaluation of biotechnology-derived pharmaceuticals" [CPMP/ICH/302/95]
FIM: Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational medicinal products" (EMEA/CHMP/SWP/28367/07 Rev1).

2. Pharmacology

Primary Pharmacodynamics

What are the *In vivo* / *in vitro* studies performed? (Mechanism of action, proof of concept, justification of animal models…):
Provide a brief summary of only relevant in vivo and in vitro studies

Secondary pharmacodynamics

Screening of other targets binding (« off-target »):
Outline of target organs different other than primary pharmacodynamics effects

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) / IC_{50} hERG < 30 (An evaluation of hERG current assay performance: Translating preclinical safety studies to clinical QT prolongation; *Pharmacol Ther.* 2011 Feb;129(2):109-19. doi: 10.1016/j.pharmthera.2010.08.008. Epub 2010 Aug 31.)

3. Pharmacokinetics

Complete the table for each specie studied

Table 2: Pharmaco/toxicokinetics data

Species		*Name the specie* **1**	*Name the specie* **2**	*Name the specie* **3**	*Name the specie* **n**
Dose (mg/kg)					
Route of administration *(gavage, IM, IV, IP, IT….)*					
AUC (ng.h/ml)	M				
	F				
C_{max} (ng/ml)	M				
	F				
T_{max} (h)	M				
	F				
$T_{1/2}$ (h)	M				
	F				
Vd (L/kg)	M				
	F				
CL_T (L/hxkg)	M				
	F				
F (%)					

M = male F = female $T_{1/2}$ = half-life of elimination
Vd = volume of distribution CLT = clearance F (%) = bioavailability

4. 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			F0 F1		
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

5. 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	☐	☐	

#	Questions	Yes	No	Specify
	for stop-dose?			

Safety margin

Table 10: Summary of safety margin

Species	Dose (/)	Route of administration	NOAEL (mg/kg/day)	C_{max} (ng/ml)	Safety margin (C_{max})	AUC_{0-24} (ng.h/ml)	Safety margin (AUC)

IV.CLINICAL SECTION (Fast Track 1 + Fast Track 2)

For tables to be completed, no special recommendations are given unless specific warnings need to be highlighted

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

[Please provide a summary of available data that support the use of the product(s) in the target population of the trial]

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

[Please take into account current national and international recommendations and availability of treatment(s) in France]

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

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

2. Study treatments

Justification of planned therapeutic schemes and doses

[Please provide a summary of available data that support the use of the product(s) in the planned therapeutic schemes and doses, including data in case of products association]

Identification of each expected adverse effect and planned risk minimization measures

(for each treatment arm, including the comparator arm) *[Please fill-in the table below]*

[Risk minimization measures include for instance: subject monitoring, eligibility/non-eligibility criteria, premedication]

	Expected adverse effect	Planned risk minimization measures
Therapeutic scheme 1 : *[e.g. IMP1 + IMP2 association]*		
	Increase of serum creatinine	- *Non-inclusion of patients with severe renal insufficiency (CrCl <30mL/min/1.73m²)* - *Monthly renal follow-up* - *Hydration measures*
Therapeutic scheme 2 : *[e.g. IMP3]*		

Identification of potential toxicities and planned risk minimization measures
(for each treatment arm, including the comparator arm) *[Please fill-in the table below]*
[Risk minimization measures include for instance: subject monitoring, eligibility/non-eligibility criteria, premedication]

	Potential toxicities	Planned risk minimization measures
Therapeutic scheme 1 : *[e.g. IMP1 + IMP2 association]*		
	Hypersensitivity reaction to ABC	- *Patient card*
	QT increase	- *ECG at each visit*
Therapeutic scheme 2 : *[e.g. IMP3]*		

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:

3. Associated medications

Description of planned auxiliary medicinal products

[Please fill-in the table below with the products to be used in the trial according to the protocol, but not as investigational medicinal products.
Examples of auxiliary medicinal products are provided in the « Guidance on Investigational Medicinal Products (IMPs) and Non Investigational Medicinal Products (NIMPs) » available on the European Commission website (Eudralex-– Volume 10 Clinical trials guidelines)]

Auxiliary medicinal product	Indication
Morphine	*Pain treatment (rescue medication)*
Skin prick test	*Identification of allergic responses (challenge agent)*
Contrast agent	*Primary endpoint assessment (medicinal product used to assess endpoint(s) in the trial)*
Treatment X	*Treatment prescribed to all subjects (background treatment)*

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:

4. 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:

* *
*