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How to Access Risk from Pre-clinical to Clinical Research more Efficiently / Experiences and Suggestions

—

"The clinical Perspective"

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President AFPT-Le Club Phase 1

Former Associate Vice-President Clinical Pharmacology and Drug Safety Risk Management, Sanofi

Extent of the Problem

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- In the literature, 14 deaths in healthy participants to clinical studies have been published between 1976 and 2004 in Western countries, although probably 100,000 healthy subjects are dosed every year (i.e., about 0.5 annually).
- Three deaths could not have been avoided if accurate common rules had been strictly adhered to.
- Three of occurred because of a challenge agent or comedication (lidocaine, methionine, hexamethonium).
- None occurred in an FIH study.
- There is probably a higher risk in elderly participants, particularly in women.

Michel Sibille, Yves Donazzolo, Franck Lecoz & Emmanuel Krupka on behalf of Club Phase I members. After the London Tragedy, is it Still Possible to Consider Phase I is Safe? Br J Clin Pharmacol.2006 Oct;62(4):502-3.

Extent of the Problem

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- In 2006, a First-in-human (FIH) study with a CD28-specific monoclonal antibody (TGN1412) conducted at a clinical pharmacology unit (CPU) in London, in the UK derailed in a life-threatening "cytokine storm" in all six healthy participants receiving the starting dose.
- Ten years later, in a FIH study with a small molecule FAAH (fatty acid amid hydrolase) antagonist (BIA 10-2474) conducted at a CPU in France, a healthy participant who received a multiple dose died, and 4 others were seriously injured.
- These events have raised several questions: what is an acceptable risk for healthy participants in FIH studies? Is there a better way to assess the risk for healthy subject in FIH studies?

Mattheus (Thijs) van Iersel, Howard E. Greensberg & Mary L. Westrick. Structured Risk Assessment for First-in-human Study. Therapeutic Innovation & Regulatory Science. 2017, Vol. 51(3):288-297.

Extent of the Problem

- What is an acceptable level of risk for healthy participants to FIH studies when, except for the financial compensation, there is no possibility of benefit to a subject?
- The concept of clinical studies includes an unknown, a priori, outcome!
- Thus, there is no ”free ride” in clinical pharmacology research, and some risk needs to be accepted!
- Because the well-being of the individual research subject must take priority over all other interest for healthy participants who have nothing to gain except compensation for time spent, the risk should be at a level similar to those activities generally accepted by society.
- The death of healthy participants will often generate attention from the media and/or scientific community.

How to Better Protect Healthy Participants in FIH Studies?

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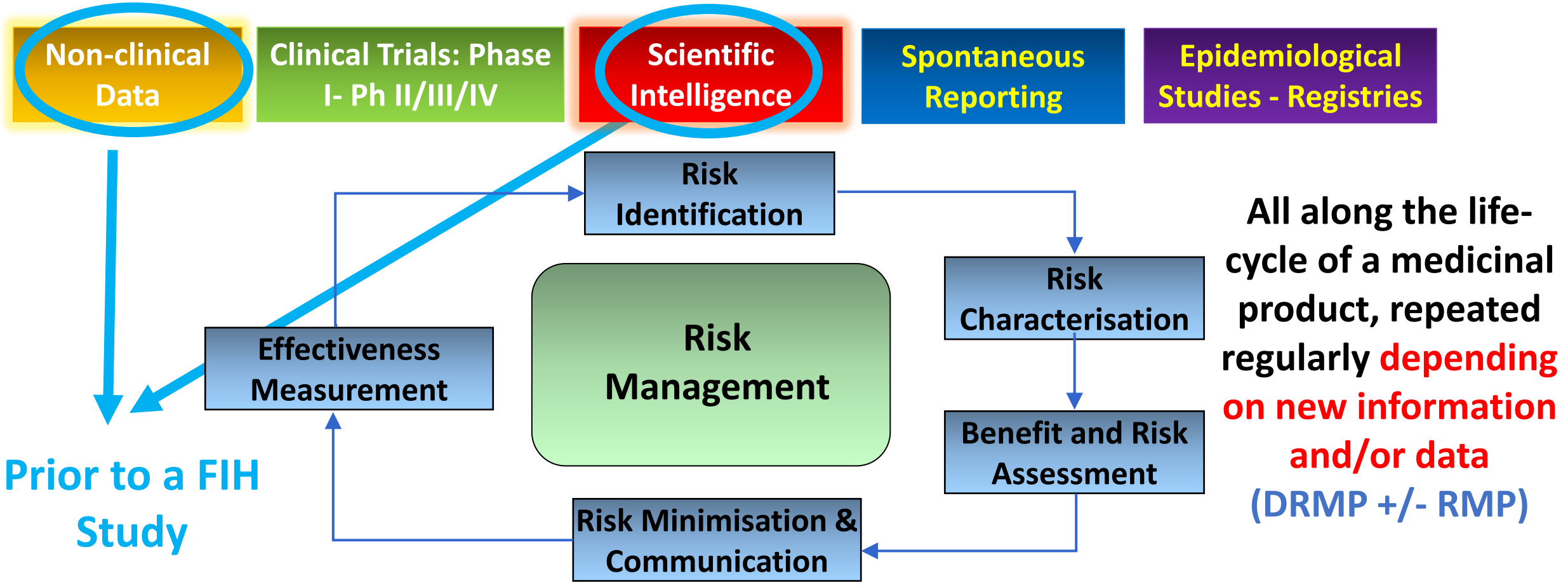
→ **Structured and Systematic Risk Assessment Approach**
= RISK MANAGEMENT APPROACH



All along the life-cycle of a medicinal product, repeated regularly depending on new information and/or data (DRMP +/- RMP)

Advantages of a Structured Risk Management

- The risk management is something everyone subconsciously performs on a daily basis, similarly, all clinical studies need to be proceeded by a careful risk management.
- The risk management for an FIH study is among the most complex, as the level of information on the Investigational product (IP) is low and the probability of safety concerns cannot be assessed from previous human exposition.
- A structured risk management process will help to:
  - Ensure that all the different elements are considered (KNOWN and UNKNOWN).
  - Avoid omissions and promotes completeness and consistency between different assessors.
  - Should be performed for IP as well as for challenge agents and study procedures.
  - Allow efficient communication between assessors.
  - Aid in the documentation of the process (well-informed decision on the acceptability of the trial and inclusion of appropriate risk mitigation in the protocol).

Careful risk management recognises gaps of knowledge and emphasizes that FIH studies are tolerability, not toxicity studies.

Cycle of Risk Management → PLAN
3 Pillars

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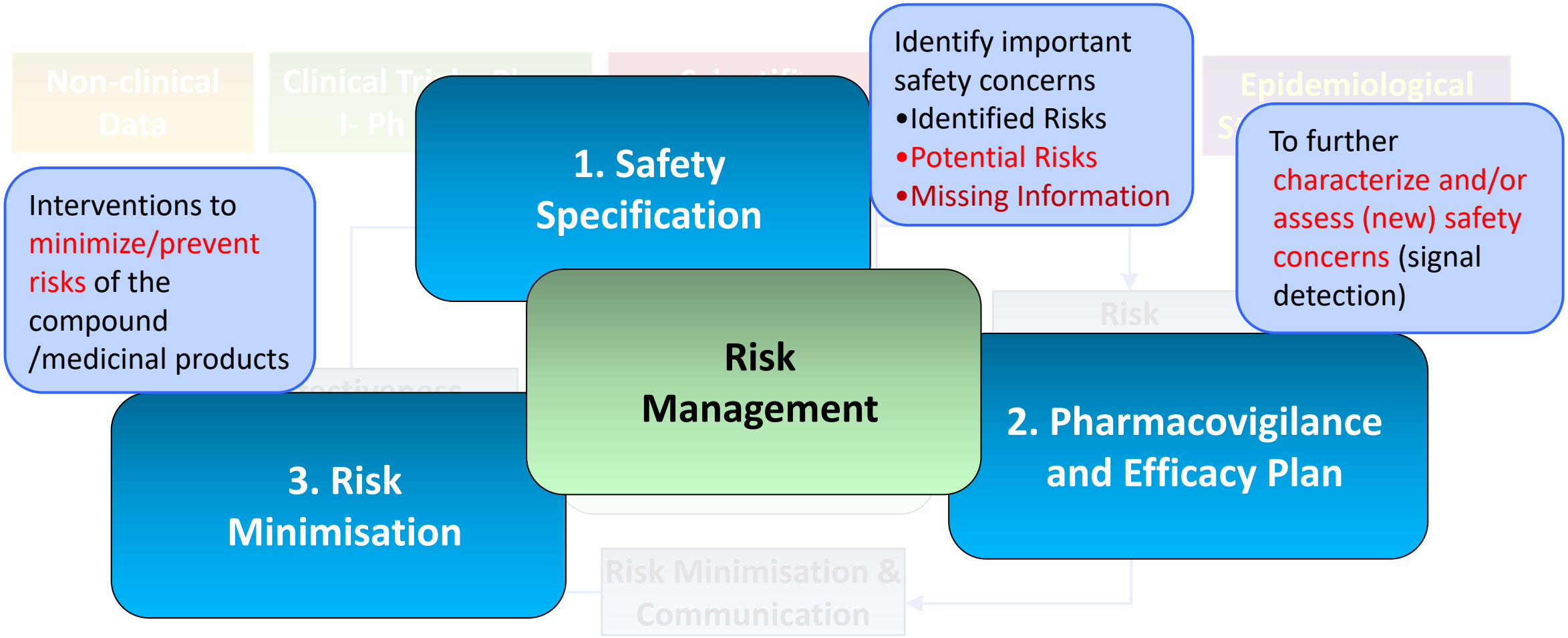

Key Players for Risk Management for FIH (1/3)

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➢ Sponsor: ICH-E6

- Responsible for the ongoing evaluation of the investigational product (IP).
- Should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) (RA) of findings that could affect adversely the safety of participants, impact the conduct of the trial, or alter IRB/IEC's approval/favourable opinion.
- Should include in the trial protocol a summary of the known and potential risks and benefits, if any, to human participants.
- Proposed structured approach: formal Development Risk Management Plan (DRMP)+++
  - Internal document.
  - Multidisciplinary (teamwork).
  - For FIH Based on:
    - ✓ non-clinical data:
      - Not only compulsory regulatory requirements,
      - Not only toxicology,
      - Pharmacology,
      - Modelling, etc..
    - ✓ Safety intelligence on external/internal compounds/products with similar properties (chemicals, mechanism of action, therapeutic class, etc…).

Key Players for Risk Management for FIH (2/3)

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- Regulator authorities (RA):
  - Responsible to ensure the protection of the rights, safety and well-being of human participants involved in a trial.
  - By, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and the methods and material to be used in obtaining and documenting informed consent of the trial participants.
- Ethics committees: responsible of the ethics considerations.
- Investigator (CRO, site, or academic centre):
  - Responsible for all trial-related medical decisions.
  - According to the Declaration of Helsinki, the health of the participants must be the first consideration of the physician, the study should be preceded after careful assessment of predictable risks and measures to minimize the risks must be implemented.
  - Physicians may not be involved in a research study involving human participants unless they are confident that the risks have been adequately assessed and can be satisfactorily managed!

ICH-E6

Assessment based on:

- IB
- Protocol
- Risk assessment made by the Sponsor

Key Players for Risk Management for FIH (3/3)

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- Sponsor:
  - Close « emotional ties » (or at least a business investment) with the Investigational product (IP).
  - Has been working on the IP for years already.
  - Is familiar with results of all preclinical studies.
  - Is familiar with other compound/product with similar properties.
- Regulatory Authorities:
  - Much less time to acquainted with the IP.
  - Could be familiar with other compound/product with similar properties.
- Ethics Committee:
  - Much less time to acquainted with the IP.
- Principal Investigator (CRO, site or academic centre):
  - Closer emotional ties with the healthy participants.
  - Much less time to get acquainted with the IP.
  - Could be familiar with other compound/product with similar properties.

Between the parties, fields of expertise differ considerably. Each parties perform the risk assessment differently.
Is for the better since risk assessments not aligned are complementary

Risk management 1st pillar:
Safety Specifications

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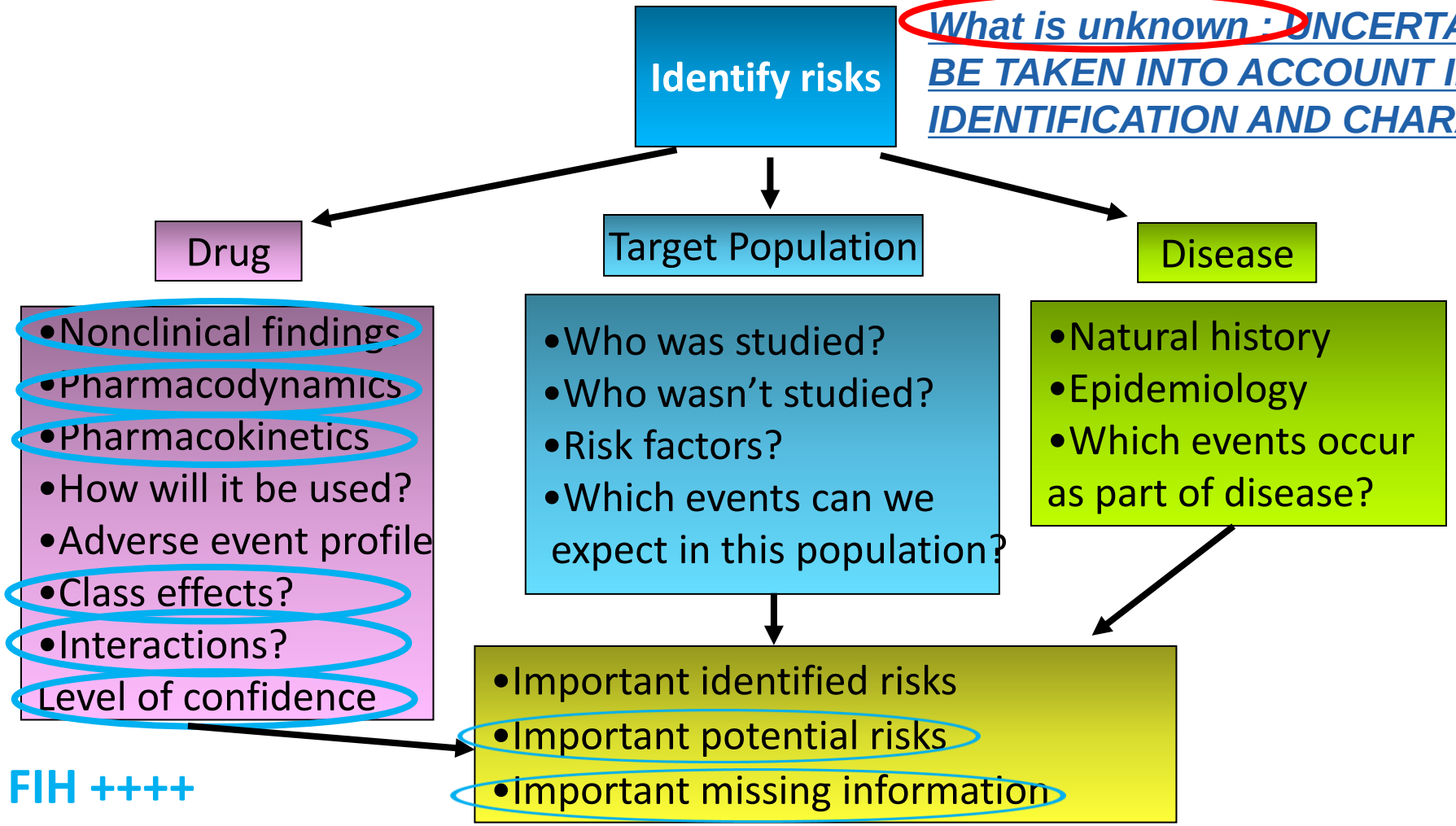
What is known: ALL INFORMATION!
What is unknown : UNCERTAINTIES SHOULD BE TAKEN INTO ACCOUNT IN THE RISK IDENTIFICATION AND CHARACTERISATION



In FIH ++++

Particularities of Safety Specifications for FIH Studies

- Based on all valuable information on drug properties at this early stage of development (limited information+++):
  - All available preclinical data (with adequate laboratory and animal experimentation).
  - Mode of Action (MOA), not only IP-specific information but also the toxicity of IPs with the same or comparable mechanism of action (MOA has to be considered). In some cases, an expert in the MOA or identified risk needs to be consulted.
  - On Target (s) – Off-target(s) activities.
  - Information on similar drugs: class effects (chemical, pharmacological, therapeutic, products related to similar regulatory history in the area).
  - Physiologically Based (PB)/Pharmacokinetic (PK)/ Pharmacodynamic (PD) modelling and simulation (M&S) support
  - Thorough knowledge of the scientific literature
  - Concomitant medication, challenge agents, and study procedures can bear an inherent risk.
  - Regulatory request

Even after a thorough risk assessment, an important conclusion can be that a lack of knowledge exists, and additional toxicology studies are needed.

Particularities of the Risk Assessment for First-in-Human Study

- All required expertise should be brought cross-functional team work to ensure safety and protection of subjects participating to FIH studies and future clinical trials

- Risk assessment:
  - Exploratory Phase with many uncertainties...
  - Predictivity of the preclinical data:
    - Lack of translational ability of preclinical models to human clinical trials in terms of efficacy and safety, leading to a large attrition rate
    - Inadequacy of animal models
  - Novelty: target(s), technology(ies), biological(s), etc.
  - PK and PD, and modelling & simulation (PB/PK/PD)
  - Tolerability and not toxicity studies
  - Quality aspects of the new IP
  - Etc.

Limitation of the Investigator's Brochure (IB)

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- IBs are a key decision support for clinical trial approvals by ethics committees, and RA.
- There are concerns that many IBs for Ph I/II trials do not allow evaluators to systematically assess the completeness and robustness of the supporting preclinical evidence.
- The summary of data and guidance for the investigator are considered as the IB section with the highest need for improvement especially with respect to readability, comprehensibility, timeliness of data, and appropriateness for risk assessment.
- Items to assess the risk of bias in the included studies were routinely missing, and little insight was provided into how the presented evidence was compiled, which raised further concerns about the reporting and design biases of the included studies.
- IB should not be a mere compilation of summaries of compulsory preclinical studies but should include a comprehensive interpretation of the data.

Relevant Personnel Undertaking the Risk Management Plan

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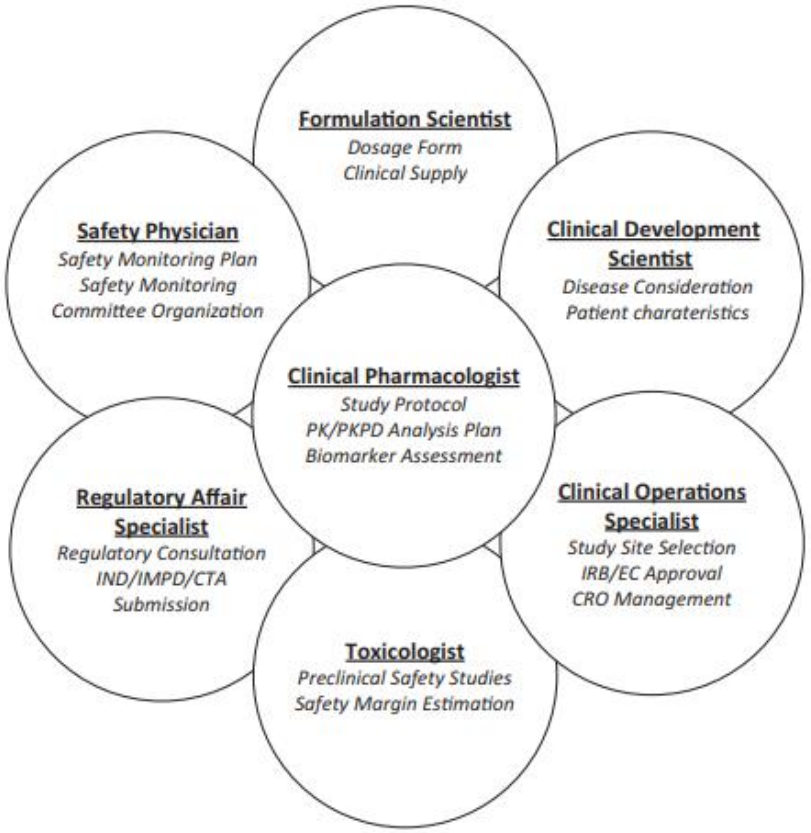

Figure 1 Key stakeholders and their main responsibilities in planning a first-in-human study. CTA, clinical trial application; CRO, contract research organization; EC, ethics committee; IMPD, Investigational Medicinal Product Dossier; IND, investigational new drug; IRB, institutional review board; PK, pharmacokinetic; PKPD, pharmacokinetic pharmacodynamic.

A Multidisciplinary Team+++

Jie Shen, Brandon Swift, Richard Mamelok, Samuel Pine, John Sinclair and Mayssa Attar. Clin Transl Sci (2019) 12, 6–19.

Limitation of the Investigator's Brochure (IB)

- Integration of preclinical toxicology, pharmacology, and PK data and the subsequent adjustment of parameters for humans is important for an accurate prediction of the anticipated efficacious human exposure, as well as the anticipated exposure in humans at which potential safety concerns can occur.
- A minimal investment in modelling can results in a better selection of the route, formulation, regimen, and dose range.
- All non-clinical pharmacology studies with negative outcomes should be reported in the IB in order to avoid assessment bias.

Limitation of the Investigator's Brochure (IB)

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Martin Haslberger, Susanne Gabriele Schorr, Daniel Strech, Tamarinde Haven. Preclinical efficacy in investigator's brochures: Stakeholders' views on measures to improve completeness and robustness.Br J Clin Pharmacol. 2023;89:340–350.

Jens Rengelshausen, Kerstin Breithaupt-Groegler, Frank Donath, Katharina Erb-Zohar, Tim Hardman, Gerd Mikus, Stephanie Plassmann, Georg Wensing and Hildegard Sourgens. How to Interpret an Investigator's Brochure for Meaningful Risk Assessment: Results of an AGAH Discussion Forum. Therapeutic Innovation & Regulatory Science (2021) 55:612–618.

Joop van Gerven and Adam Cohen. Integrating data from the Investigational Medicinal Product Dossier/investigator's brochure. A new tool for translational integration of preclinical effects. Br J Clin Pharmacol (2018) 84 1457–1466.

Elements of Risks Related to the Intended Mode of Action

- A lack of understanding of the mechanism of action
- Acting on a self-amplifying mechanism, cascade (e.g., an immunologic or coagulation target)
- Steep dose-response (e.g., CNS compounds)
- A species difference in target distribution, binding affinity, or downstream pharmacology
- Lack of animal model with expression and function of the target
- Irreversible or prolonged binding of the investigational product (IP) to the target
- No previous exposure in humans of an IP directed to the same target (first in class
- Potential class-related toxicities
- Significant effects in animals or humans with loss of unction, or gain in function due to absence of the target or a mutated target
- Absence of in vitro human pharmacodynamic data
- Insufficient insight in the anticipated exposure levels needed for human efficacy

Elements of Risk Relating to Off-Target Effects

- None or insufficient in vitro selectivity studies performed vs. Structurally closely related targets
- Irreversibility or severe toxicity without a sentinel biomarker
- Irreversible or severe toxicity with a steep dose response
- Irreversibility or severe toxicity with a delayed time of onset; these may result in adverse events in humans occurring after the follow-up period used for the evaluation of a dose escalation

Elements of Risk Relating to the Study Design

- Vulnerable population in an FIH study with healthy subjects, e.g., women of childbearing potential (WOCBP) or elderly
- Challenge agents or concomitant medication with potential significant toxicity
- Invasive study procedure with a risk of, e.g., infraction or trauma notably higher as compared to venous puncture

Elements Relating to the Exposure

- Significant species difference in free fraction in plasma
- Clearance relying on pathways susceptible to genetic variability
- Very low bioavailability with a potential for a much higher bioavailability in humans, for instance, when using a different formulation in humans or when administered after food
- Long half-life causing (1) significant accumulation after multiple doses and (2) extended exposure in case administration is discontinued because tolerability issues
- Non-dose linearity of pharmacokinetics
- Maximum tolerated doses at a study objective; this objective may cause unnecessary high exposures in healthy subjects
- Escalation based on tolerability only, without considering plasma concentrations and available pharmacodynamic markers
- An insufficient margin between the anticipated maximum exposure levels in the study versus exposures in animals resulting in irreversible or severe toxicity, especially when no sentinel safety biomarkers to monitor the specific toxicity is available

All substances are poisons; it is the dose that makes the poison »
Paracelsus

Translation to Humans

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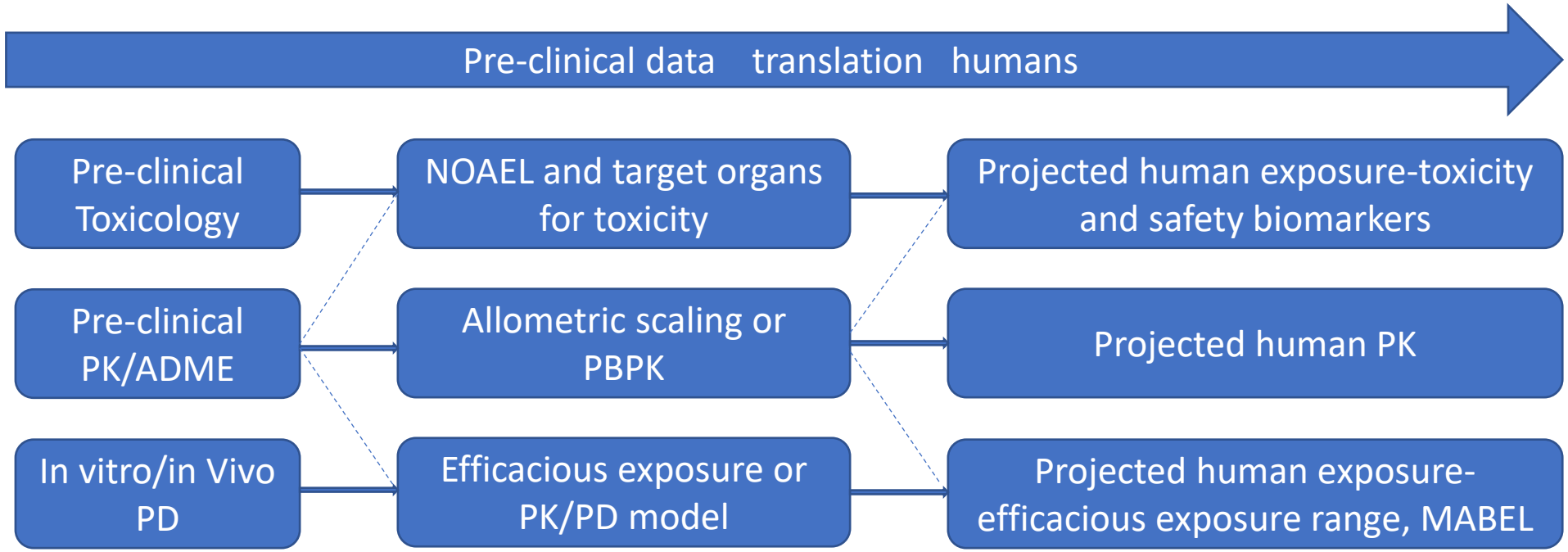
Vulnerability of humans versus animals can be estimated on the basis of comparative data. Some elements to consider are comparative pharmacodynamic (PD) data on binding affinity, potency and expression of the target, and comparative pharmacokinetics (PK data on free fraction, metabolism, formulation and dose regimen

Integration of pre-clinical toxicology, pharmacology and pharmacokinetic data and translation to human exposure



ADME: absorption, distribution, metabolism and excretion
MABEL: minimum anticipated biological effect level
NOAEL: no observed adverse effects level
PBPK: physiologically based pharmacokinetics

Safety Specifications & Risk Management Activities (DSUR/PSUR/PBRER/DRMP/RMP)

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Important identified, potential, or theoretical risk (select appropriate)	**Specify reason(s) for considering and provide details:** •Literature findings •Pharmacological activity(ies) (including off-taget(s)) •Class effect(s) (based on knowledge from related compounds which share chemical/pharmacological/therapeutic properties) •Non-clinical/toxicology safety findings •Systematically considered (e.g., hepatic effects, effect on QT, drug-drug and food-drug interactions, immunogenicity [for biologics], hypersensitivity, potential for reactive metabolites, bone marrow toxicity) •Regulatory request(s)
Reason for considering	
Actions and/or plans for evaluating and mitigating risk	
Nature of risk, and severity	
Seriousness/outcomes	
Frequency	
Background incidence/prevalence	
Risk groups or risk factors	
Potential mechanism(s)	
Preventability	
Evidence source	
Regulatory action taken	
Comments	

Key Safety Findings from Non-Clinical Studies

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Key Safety Findings	Relevance to human usage +++
Toxicity **EMA guidance: Including** • **Single and repeat-dose toxicity,** • **Reproductive (must be discussed if medicine might be used in women of child-bearing potential)** • **Developmental toxicity** • **Nephrotoxicity** • **Hepatotoxicity** • **Genotoxicity** • Carcinogenicity, etc. Enter text	Enter text

Multidisciplinary Teamwork

Key Safety Findings from Non-Clinical Studies

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Key Safety Findings	Relevance to human usage +++
General safety pharmacology **Includes:** • **Cardiovascular (including potential for QT interval prolongation)** • **Nervous system** • **etc.** Enter text	Enter text
Mechanism for drug interactions Nonclinical data only; i.e., drug interactions that were assessed in animal species Enter text	Enter text
Other toxicity-related information or data Enter text	Enter text

Multidisciplinary Teamwork

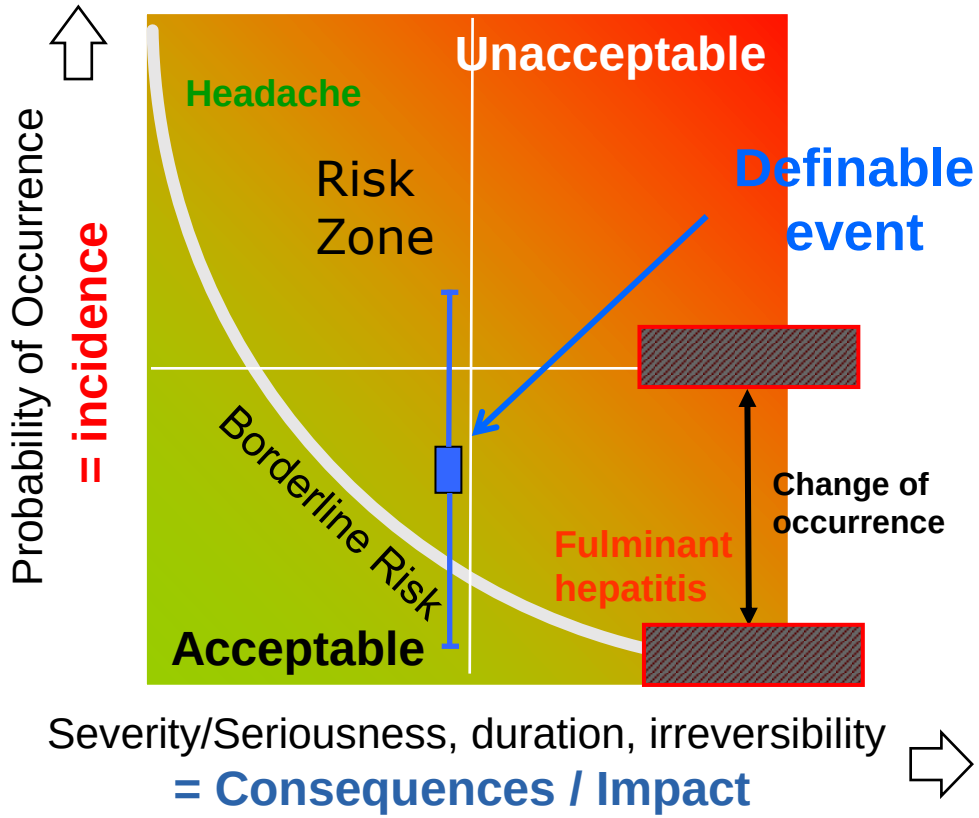
Weighing Risks

- Identification of the safety concerns
- Consideration of the exposure
- Translation to humans

Will results in a list of potential safety concerns with different impact and probabilities.

Weighing risks consist of prioritizing safety concerns on basis of the impact on participants and their probability of occurrence.

Risks that matter may be safety concern of mild or moderate severity but of high probability, irreversibility or long duration just as well as risks of severe severity with a low probability.



Safety Specifications
Summary of the Safety Concerns

- **Tabulated/organized/« prioritized » - safety concerns requiring more assessment or being able to impact the risk-benefit balance:**
  - **Important identified risks;**
  - **Important potential risks;**
  - **Missing information;**

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	<List>
Important potential risks	<List>
Missing information	<List>

- **This list is the backbone of the two other RMP "pillars" (PV plan, minimisation plan);**
- **Safety concerns should be prioritized in terms of frequency, seriousness, severity, impact on individuals/**public health **and preventability.**

Risk Management 2nd Pillar:
Risk Assessment

➢It is a Risk Assessment activity:

- Risk assessment occurs throughout a product's lifecycle, from the earliest identification of a potential product, through the pre-marketing development process, and after approval during marketing.
- In FIH: signal detection during the clinical trial, keeping in mind than small signal could be the start of a deleterious safety signal!

Risk management 2nd pillar:
Risk Assessment

Identify & characterize risks

Pharmacovigilance Plan (PV Plan)

* "routine" in EU guidance

Standard PV*:
- Collection of ADRs
- Case report follow-up (questionnaire)
- Signal detection /analysis
- Expedited reporting
- Annual reports – DSURs/ PSURs/PBRERS
- Literature review

Additional PV activities:
- Active surveillance (sentinel sites, etc.)
- Observational studies:
  - Registry/Cohort studies
  - Case control studies
  - Cross-sectional studies
  - Record linkage
- Large simple (pragmatic) trials
- Drug utilization studies
- Randomised clinical trials
- PK, PD, PK/PD studies
- Nonclinical studies
- Others…

Additional activities:
- Assessment of the effectiveness of risk minimization measures (e.g., DUS)

In early Clinical Development

Monitoring

➢ Monitoring:

- Frequent/continuous and adapted (clinical, Lab tests and other explorations):
  - Anticipated adverse reactions: safety profile done with nonclinical data, mode of action(s), information on similar drugs (class effects), modelling and simulation, literature.
  - Unanticipated: on a systematic approach (QT prolongation, ALT increase).
- Translational biomarkers.
- Alerting values (below stopping criteria for minimisation).
- FIH emerging safety data (medical/clinical aspects/Lab tests): not necessarily serious… a series of moderate or even non-serious severe AEs in a FIH may indicate a safety signal emerging.

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Alerting Procedure for ALT Increase

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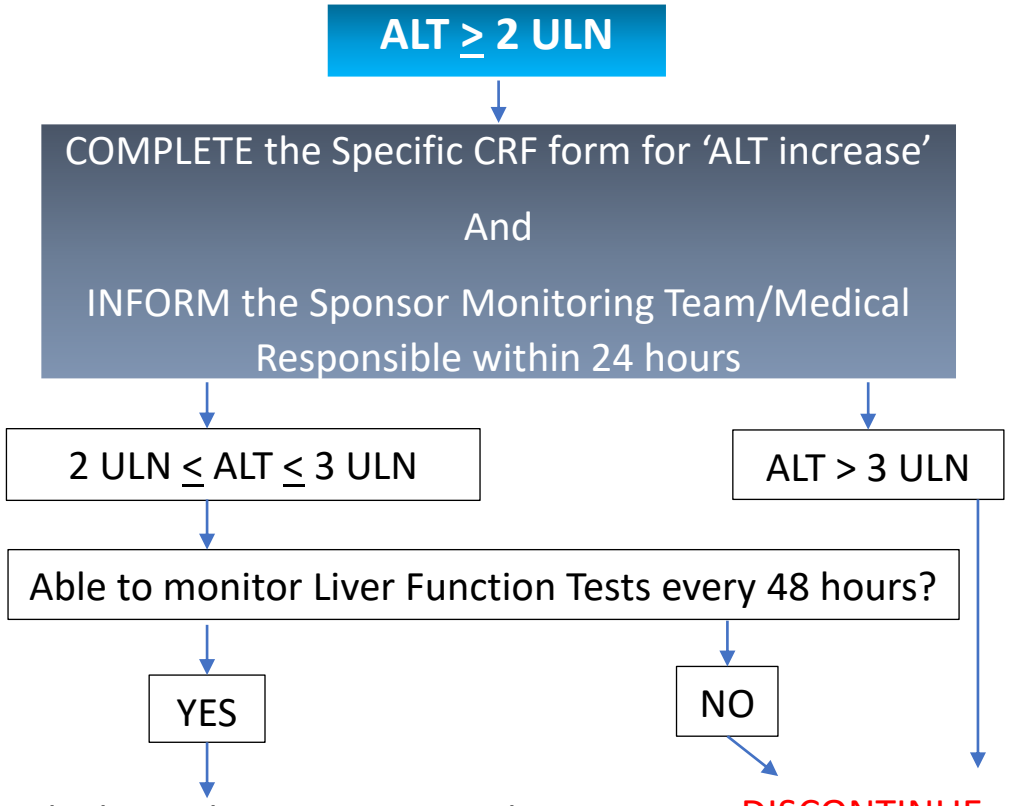

Monitor Liver Function Tests (LFT) every 48 hours until return to < 2ULN.

If ALT elevation (2 ULN ≤ ALT ≤ 3 ULN) persist beyond 2 weeks: perform LFT every 2 weeks and 15 to 30 days after the last dose, or until return to < 2 ULN, whichever comes first.

Date: 25 May 2023

PROCEDURE TO BE SYSTEMATICALLY FOLLOWED:

1) **CONSIDER** reporting as Adverse Event (AE) or Serious Adverse Event (SAE):
   - Acute liver injury (ALI): is defined by INR higher than 1.5 without associated hepatic encephalopathy.
   - Fulminant hepatitis (FH) or acute liver failure (ALF): is defined by an INR > 1.5 and the presence of hepatic encephalopathy but the absence of chronic, underlying (or prior) disease.
   - Hy's law: composite algorithm to **predict** ALI in subjects with drug-induced liver injury (DILI) = ALT or AST ≥ 3 ULN and Total Bilirubin (BT) > 2 ULN in the absence of alkaline phosphatase (ALP) elevation < 2 ULN.
2) **INVESTIGATE** THE CLINICAL PICTURE:
   - Detailed anamnesis: age, race and/or ethnicity, gender, individual and family past-history, and particularly history of recent travels, alcohol consumption, any prescribed (including vaccination) or over-the-counter drug (including acetaminophen/paracetamol, non-steroidal anti-inflammatory drugs), or vitamins/herbal/dietary supplements or recreation drugs intake, strong physical activities (documented), physical injury, infection.
   - Clinical context in the previous 72 hours: signs of hepatitis (fever, jaundice, icteric sclera, abdominal tenderness, dark-coloured urines, light-coloured stools, extrahepatic manifestations (e.g., neurological signs, infectious signs, cutaneous rashes) and specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia; rule out muscular injury.
   - Detailed physical examination: particularly body temperature, abdominal examination (pain, hepatomegaly), skin and eyes examination (urticaria, rash, icteric sclera), nodes examination (lymphadenopathy), neurological examination, ENT and pulmonary examination.
3) **PERFORM** the following tests:
   - LFT: ALT, AST, ALP, Total and Conjugated Bilirubin, and Prothrombin Time/INR.
   - CPK, serum creatinine, complete blood count (with differential white blood cell count), lipase.
   - Anti-Covid-19 IgM, anti-HAV IgM, anti-HBc IgM, anti-HCV and HCV RNA, anti-HEV IgM, anti-CMV IgM antibodies, and depending on the clinical context, other infections (e.g., EBV, Herpes viruses, toxoplasma).
   - Hepatobiliary ultrasonography (can be completed by other imaging investigations if needed).
4) **CONSIDER** auto-antibodies: anti-nuclear, anti-DNA, anti-smooth muscle, anti-LKM (anti liver and kidney microsome).
5) **CONSIDER** consultation with hepatologist.
6) **CONSIDER** subject hospitalisation if INR > 2 (or PT < 50%) and/or central nervous system disturbances suggesting hepatic encephalopathy.
7) **MONITOR** LFT as closely as possible to every 48 hours until stabilization then every 2 weeks until return to < 2 ULN or to a maximum of 3 months, after the last dose, whichever comes first.
8) **COLLECT/STORE** 1 sample following procedures described in blood samples collection section of the protocol and freeze one serum sample at minus 20°C (5 mL).

Standardised forms

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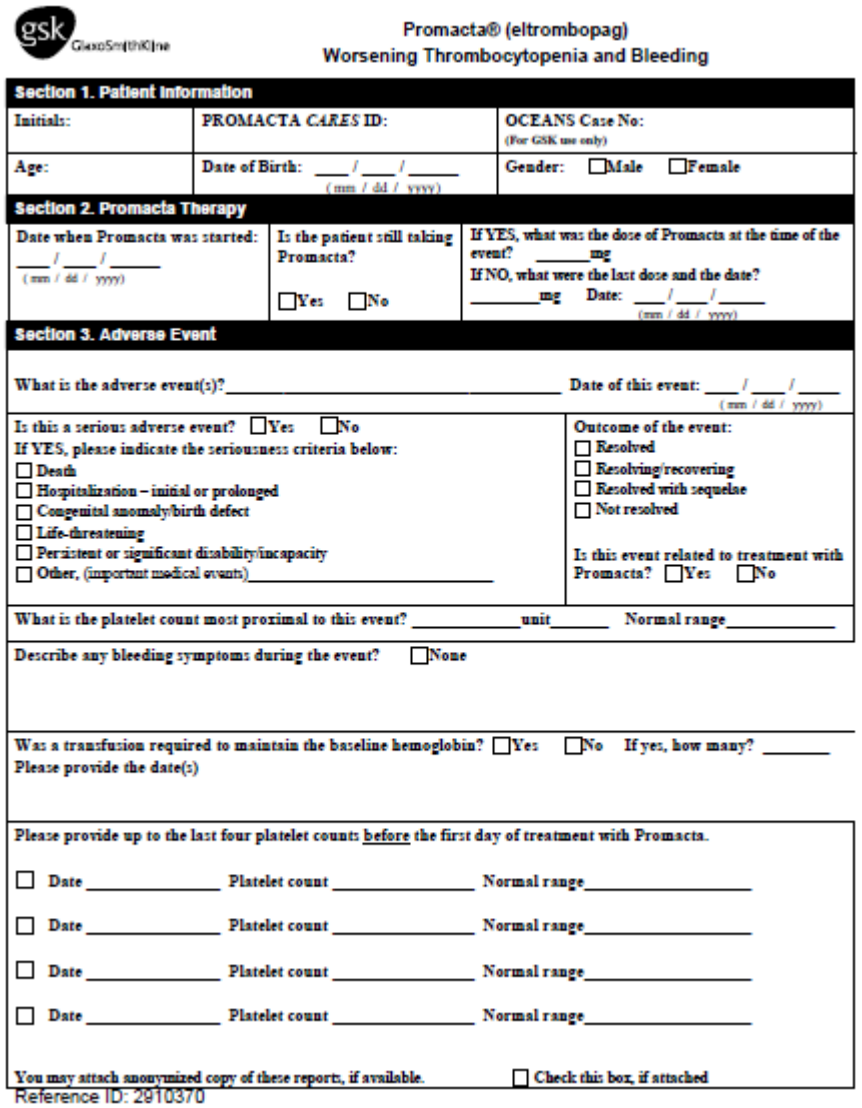

Promacta® (eltrombopag)
Worsening Thrombocytopenia and Bleeding

Section 1. Patient Information

Initials:	PROMACTA *CARES* ID:	OCEANS Case No: (For GSK use only)
Age:	Date of Birth: ___/___/_____ (mm / dd / yyyy)	Gender: ☐Male ☐Female

Section 2. Promacta Therapy

Date when Promacta was started: ___/___/_____ (mm / dd / yyyy)	Is the patient still taking Promacta? ☐Yes ☐No	If YES, what was the dose of Promacta at the time of the event? _____mg If NO, what were the last dose and the date? _____mg Date: ___/___/_____ (mm / dd / yyyy)

Section 3. Adverse Event

What is the adverse event(s)?_____ Date of this event: ___/___/_____ (mm / dd / yyyy)

Is this a serious adverse event? ☐Yes ☐No
If YES, please indicate the seriousness criteria below:
☐ Death
☐ Hospitalization – initial or prolonged
☐ Congenital anomaly/birth defect
☐ Life-threatening
☐ Persistent or significant disability/incapacity
☐ Other, (important medical events)_____

Outcome of the event:
☐ Resolved
☐ Resolving/recovering
☐ Resolved with sequelae
☐ Not resolved

Is this event related to treatment with Promacta? ☐Yes ☐No

What is the platelet count most proximal to this event? _____unit_____ Normal range_____

Describe any bleeding symptoms during the event? ☐None

Was a transfusion required to maintain the baseline hemoglobin? ☐Yes ☐No If yes, how many? _____
Please provide the date(s)

Please provide up to the last four platelet counts before the first day of treatment with Promacta.

☐ Date _____ Platelet count _____ Normal range_____
☐ Date _____ Platelet count _____ Normal range_____
☐ Date _____ Platelet count _____ Normal range_____
☐ Date _____ Platelet count _____ Normal range_____

You may attach anonymized copy of these reports, if available. ☐ Check this box, if attached

Reference ID: 2910370

Section 4. Medical Information

Were there any similar bleeding events prior to therapy with Promacta? ☐Yes ☐No
If YES, please describe:

Has the patient experienced bleeding symptoms on discontinuation of other treatments for ITP? ☐Yes ☐No
If YES, please describe:

Please list concurrent disease(s) ☐None

Were there any changes to the concomitant therapy(ies) for ITP prior to this event? ☐Yes ☐No
If YES, please specify:

Please list concurrent medication(s) (e.g. anti-platelet medications, NSAIDs) ☐None

Section 5. Reporter

☐ PROMACTA *CARES* specialist Name and Title _____
☐ Healthcare Provider Name and Title _____
☐ Institution Name and Title _____
☐ Other (specify) _____ Name and Title _____

Date of this report ___/___/_____ (mm / dd / yyyy) Signature_____

Eltrombopag (REVOLADE®) = thrombopoietin analogue and used for thrombocytopenia

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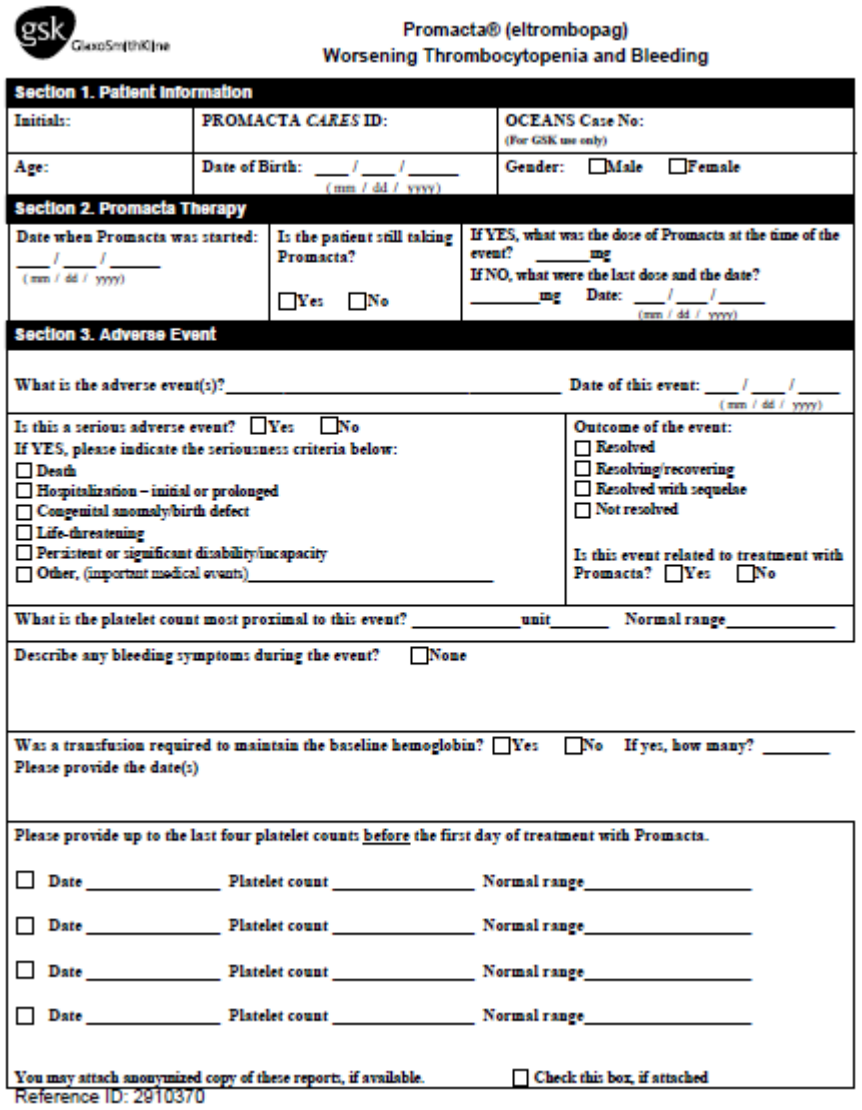

Promacta® (eltrombopag)
Worsening Thrombocytopenia and Bleeding

Section 1. Patient Information

Initials:	PROMACTA *CARES* ID:	OCEANS Case No: (For GSK use only)
Age:	Date of Birth: ___/___/_____ (mm / dd / yyyy)	Gender: ☐Male ☐Female

Section 2. Promacta Therapy

Date when Promacta was started: ___/___/_____ (mm / dd / yyyy)	Is the patient still taking Promacta? ☐Yes ☐No	If YES, what was the dose of Promacta at the time of the event? _____mg If NO, what were the last dose and the date? _____mg Date: ___/___/_____ (mm / dd / yyyy)

Section 3. Adverse Event

What is the adverse event(s)?_____ Date of this event: ___/___/_____ (mm / dd / yyyy)

Is this a serious adverse event? ☐Yes ☐No
If YES, please indicate the seriousness criteria below:
☐ Death
☐ Hospitalization – initial or prolonged
☐ Congenital anomaly/birth defect
☐ Life-threatening
☐ Persistent or significant disability/incapacity
☐ Other, (important medical events)_____

Outcome of the event:
☐ Resolved
☐ Resolving/recovering
☐ Resolved with sequelae
☐ Not resolved

Is this event related to treatment with Promacta? ☐Yes ☐No

What is the platelet count most proximal to this event? _____unit_____ Normal range_____

Describe any bleeding symptoms during the event? ☐None

Was a transfusion required to maintain the baseline hemoglobin? ☐Yes ☐No If yes, how many? _____
Please provide the date(s)

Please provide up to the last four platelet counts before the first day of treatment with Promacta.

☐ Date _____ Platelet count _____ Normal range_____
☐ Date _____ Platelet count _____ Normal range_____
☐ Date _____ Platelet count _____ Normal range_____
☐ Date _____ Platelet count _____ Normal range_____

You may attach anonymized copy of these reports, if available. ☐ Check this box, if attached

Reference ID: 2910370

Section 4. Medical Information

Were there any similar bleeding events prior to therapy with Promacta? ☐Yes ☐No
If YES, please describe:

Has the patient experienced bleeding symptoms on discontinuation of other treatments for ITP? ☐Yes ☐No
If YES, please describe:

Please list concurrent disease(s) ☐None

Were there any changes to the concomitant therapy(ies) for ITP prior to this event? ☐Yes ☐No
If YES, please specify:

Please list concurrent medication(s) (e.g. anti-platelet medications, NSAIDs) ☐None

Section 5. Reporter

☐ PROMACTA *CARES* specialist Name and Title _____
☐ Healthcare Provider Name and Title _____
☐ Institution Name and Title _____
☐ Other (specify) _____ Name and Title _____

Date of this report ___/___/_____ (mm / dd / yyyy) Signature_____

Eltrombopag (REVOLADE®) = thrombopoietin analogue and used for thrombocytopenia

Adverse Events of Special Interests (AESIs)

Question: AESI

What does AESI stand for?

a) Adverse Event of Severe Intensity

b) Adverse Event of Strong Intensity

c) Adverse Event of Special Interest

d) Adverse Event without Slightest Interest

Solicited AESI

An adverse event (serious or non-serious) of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor may be appropriate. Such events may require further investigation in order to characterize and understand them.

Such events should be described in protocols or protocol amendments, and instructions provided for investigators as to how and when they should be reported to the sponsor.

Unsolicited AESI:
An adverse event (serious or non-serious) of scientific and medical concern specific to the Marketing Authorization Holder's (MAH) product or program, for which ongoing monitoring by the MAH may be appropriate.
Such events may require further investigation/follow-up in order to characterize and understand them.

Risk Management 3rd Pillar: Risk Minimization

FOR POST-MARKETING PRODUCTS!!!!

Prevent or minimize risks

↓

Evaluation of the need for risk minimization

↙ ↘

Routine risk minimization such as:
- Labeling (SPC, USPI,…)
- Package leaflet (PIL)
- Pack size and design
- Legal status of the product*

(e.g., administration in hospital/clinic or prescription by a specialist)

Additional minimisation measures may differ widely in purpose, design, target audience and complexity.

These measures might be used to guide appropriate patient selection, to support on-treatment monitoring relevant to important risks and/or management of adverse reactions once detected.

- Communication/Educational programme (including reminder tools/patient cards, etc…)
- Controlled access programme
- Other risk minimisation measures
  - Controlled access/distribution systems
  - Pregnancy prevention programme (PPP)
  - Direct HCP communication

Routine minimisation is sufficient for the majority of products+++

**** Routine minimization activity as per EU-GVP Module V (RMP) and XVI (Risk minimisation)***

Risk Acceptance

- Does not reduce the risk, but when the risk level is expected to balance with the possible therapeutic benefit, they can be an acceptable strategy in first-in-human (FIH) studies:

  - The risk for healthy subjects can be accepted if the risk is not higher than the risk resulting from activities deemed acceptable to the general public.
  - Performing studies in patients with a high therapeutic need can result in risk acceptance even when the risk is not acceptable for healthy participants.

Conditions for Minimization Interventions

➢ Only preventable (+++) risks can be minimized:

- To be assessed using clinical trial data, literature…

➢ Risk minimization strategies:

- Avoiding exposure levels possibly resulting in significant safety concerns.
- Decreasing the vulnerability of subjects.
- Risk Limitation: this requires evidence of:
  - Reversibility of the effect.
  - A time course of the effect allowing window for intervention.
    - ✓ Need to identify prognostic factors.
  - Availability of biological markers for early detection of effect.
  - Availability of a rescue treatment or an antidote.

Particularities of the Risk Minimization Activities for First-in-Human Study

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➢ Starting dose:

- The dose needs to be enough to avoid toxicity at the initial dose and high enough to allow reasonably rapid attainment of Phase 1 trial objectives
- Different method to estimate the maximum recommended starting does (MRSD)
- Not easy, and a case-by-case approach may be more appropriate
- In any case, a conservative and consistent approach is required because safety is the most important factor

➢ Dose escalation/increase:

- Apply a safe multiplying factor, i.e., factor 3 for the first 2 or 3 steps, then factor 2 for subsequent 2 steps and factor 1.5 at the end
- A review of the safety, PK and PD data should be done throughout the trial, and the decision escalate to a next dose or to stop escalation should be made according to predefined criteria

Particularities for the Risk Minimisation Activities of First-in-Human Study

- Based on experimental and scientific rationale:
  - FIH dose escalation trials are still conservative and seem to be based more on habit and preferences than experimental and scientific rationale
  - For example, the Bayesian adaptative method combines a flexible number of cohorts and a flexible number of subjects per cohort with simple empirical rules to increase performance and facilitate implementation
- Monitoring:
  - Frequent/continuous and adapted (clinical, Lab tests and other explorations)
    - Anticipated adverse reactions: safety profile done with nonclinical data, mode of action(s), information on similar drugs (class effects), modelling and simulation, literature
    - Unanticipated: on a systematic approach (QT prolongation, ALT increase)
  - Translational biomarkers+++

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Avoiding Exposure Levels Possibly Resulting in Significant Safety Concerns

- Avoiding exposure levels that are likely to results in significant toxicity by using a safe starting dose as well the maximum dose level planned in the FIH study.
- An exposure cap (stop criteria based upon Cmax and/or area under the curve [AUC])should be included in case of either:
  - Irreversible or severe toxicity, especially in absence of a sentinel safety biomarker, or
  - Chance of exceeding exposures reached in the general toxicity studies.
- Avoiding significant safety concern by including sentinel safety biomarkers; use specific and sensitive safety biomarkers indicating in-target or off-target toxicity is imminent so dosing and/or escalation can be stopped before significant safety concerns occurs.
- Avoiding unnecessarily high exposure levels by **monitoring relevant pharmacodynamic (PD)** or toxic effects; in general, dose escalation steps should be using a decreasing or fixed factor, but not an increasing factor when escalating from low to high-dose cohorts.
- If a considerable food effect is expected (low bioavailability, high lipophilicity), a food effect cohort should have a sufficient margin with previously well-tolerated dose levels in fasting conditions. The same considerations are valid for DDI studies. Usually, the difference in exposure is limited to about 2-fold. But, for instance, the maximum food effect on exposure can be up to 30-fold.

Safe Starting Dose

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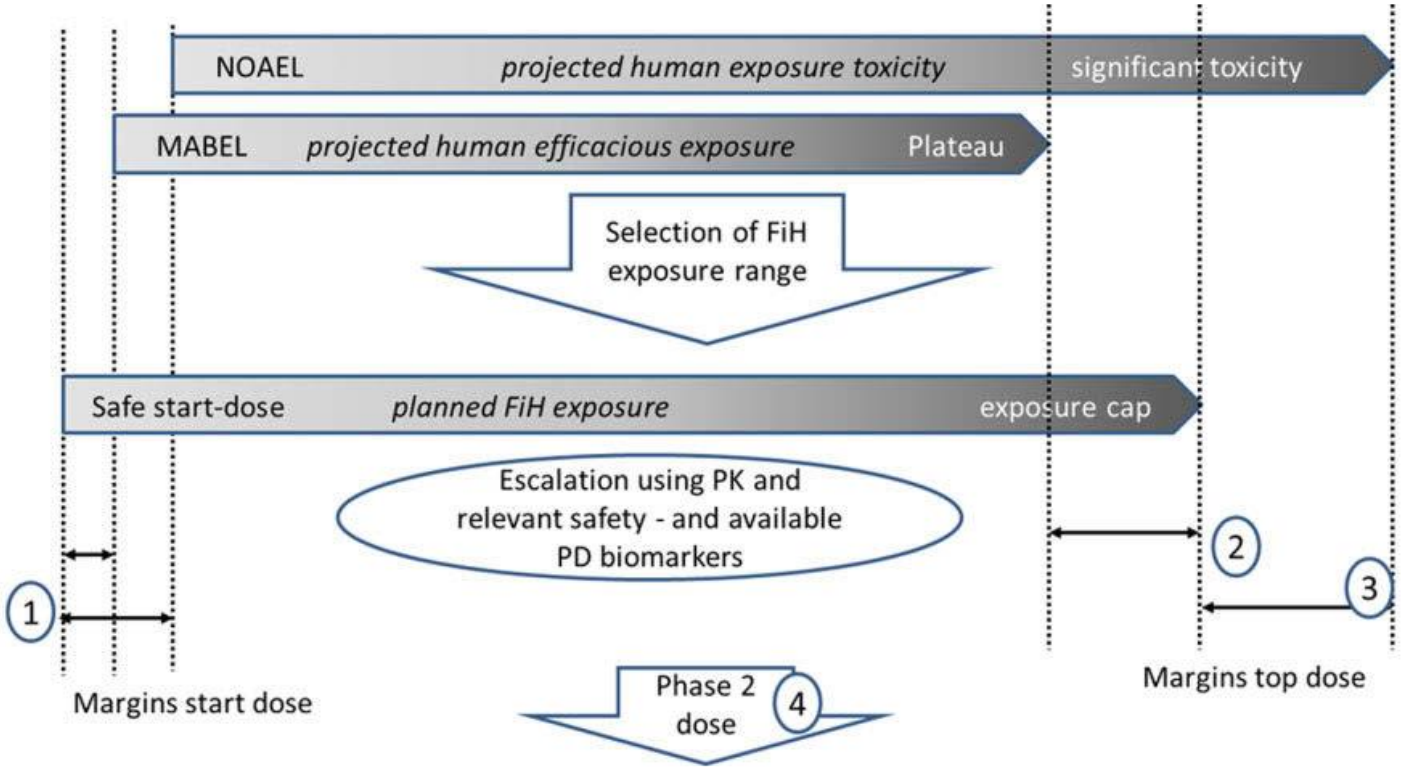
CASE BY CASE APPROACH WITH A STRUCTURED FRAMEWORK



Selection of FIH exposure based on projected exposures.

Note:

(1) Whichever is lowest of NOAEL (including a necessary margin) and PAD/MABEL (including a necessary margin) should be the starting dose.

(2) Aiming for an exposure after the highest dose of, e.g., 5 times the therapeutic exposure.

(3) A margin is needed between the highest exposure in humans and the maximum exposure reached in animals or exposure in animals with significant toxicity without safety biomarker.

(4) Selection of the phase 2 dose range, based on the projected human exposure-efficacy relationship and tolerability in the FIH study.

FIH, first-in-human; MABEL, minimum anticipated biological effect level; NOAEL, no observed adverse effect level.

Aspects to Take into Account for Dose Escalation (1/2)

- Calculated pharmacologically active dose (PAD) and the anticipated therapeutic dose range (ATD):
  - Dose/exposure-toxicity and/or dose/exposure-effect relationship.
  - Derived from non-clinical studies and adapted according to PK/clinical data from previous cohorts.
  - Steepness of the dose/exposure-toxicity or dose/exposure-effect curves
  - Reliability with which potential AEs can be monitored before potential serious/irreversible effects may develop.
  - Chance of non-linear PK resulting in a supra-proportional increases in exposure.

Aspects to Take into Account for Dose Escalation (2/2)

- Check if available clinical data reveal substantial differences from non-clinical.
- or modelling/simulation data.
  - Consider potential saturation effects (target, PK).
  - Check for plateauing of exposure.
  - All changes in dose levels require a substantial amendment unless such changes are covered by predefined decision criteria in the protocol and no predefined dose/exposure limits are exceeded.

Highest Acceptable Exposure in FIH Studies

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- No guidelines exist for the highest acceptable exposure to be studied in an FIH study.
- Margins for highest exposure levels between animal toxicity studies and the clinical exposures for phase 3 trials are mentioned in ICH-M3-R2,26 but guidance on maximum acceptable exposure during early clinical development is not included.
- Instead, often the maximum tolerated dose (MTD) has been used as a study objective for FIH studies. The question is whether this tradition must change.
- With an accurate prediction of exposure at which significant toxicity may occur and an accurate prediction of an efficacious exposure range, the exposure range in the FIH study can be chosen to cover the exposure at the MABEL or fraction of the NOAEL (whichever is lowest), up to a sufficient supratherapeutic dose.
- The supratherapeutic exposure needs to represent exposures that can occur in subjects experiencing for instance drug-drug interactions (DDIs) while suffering from kidney or hepatic failure: a so-called perfect storm, increasing the exposure during clinical use.
- Other than defining a safety margin, this exposure range will also potentially, for small molecules, enable a definite QTc evaluation already in the FIH study.
- Even for many IPs currently developed for oncology, the identification of the MTD is obsolete because many of these IPs are reasonably well tolerated at maximum efficacious exposures.

Decreasing the Vulnerability of Subjects

- If necessary, the vulnerability of subjects can be decreased by using appropriate inclusion and exclusion criteria.
- Safety concerns can be avoided by the use of, e.g., premedication or sufficient hydration.
- Study restrictions can be imposed, such as a period during which driving is prohibited.

Risk Limitation

- Elements of Risk Limitation: in case some level of risk is accepted, and risk cannot be avoided, the risk can still be limited:
  - Reversibility of the adverse reaction.
  - Existence of a time course of the adverse reaction allowing window for intervention (Need to identify prognostic factors).
  - Availability of biological markers for early detection of adverse effects (sentinel biomarker).
  - The available treatment of possible safety concerns should be identified, and these treatments should be available.
  - Sentinel dosing, starting with only one subject on active and one subject on placebo, after a sufficient time followed by the rest of a dosing cohort. The concept of sentinel dosing was introduced after the Tegenero tragedy in which translation from animals to humans resulted in a grossly overestimated safe starting dose for the first dose cohort. This approach can be a sensible approach in case of severe safety concerns with a steep dose response or without safety biomarkers.
  - Risk is to be limited (and can sometimes be avoided) by performing the study in a Clinical Pharmacology Unit with staff well trained in Life Support and with the proper equipment available. (Caution: ROUTINE!, low cases of serious safety events!, 24 upon 24 hours!)

Stopping rules in First-in-Human Study

- Adverse reactions stopping rules in early clinical trials are a regulatory requirements and necessary for subject safety.

- Designing stopping rules can present challenges:
  - Firstly, they need to ensure that trials do not get terminated prematurely without clinical justification.
  - Secondly, they may need to accommodate multiple concurrent trial arms and parts (integrated protocols).
  - Thirdly, where IMP have anticipated ARs based on class effects, mode of action or preclinical data, the boundary between acceptable and unacceptable ARs need to be determined.

- To be considered:
  - Final stop to dosing and termination of the trial.
  - Stopping of an individual subject, at any time in the trial.
  - Stopping within a cohort:
    - When subjects in a cohort are dose staggered.
    - During multiple dose.
  - Progression to the next part(s) of the trial (integrated designs).
  - Any dose escalation parts of the trial.

Stopping rules in First-in-Human Study

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  - Any **dose escalation parts** of the trial

Template Adverse Reactions Stopping rules

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Practical risk management in early phase clinical trials. Simon Coates, Jörg Taubel, Ulrike Lorch. Eur J Clin Pharmacol. 2019 Apr;75(4):483-496.

Grade (Severity)	Serious -ness	Individuals	Within-cohort decision				Study progression
			N° subject		Reversi -bility	Continuation within a dosing regimen	Escalation to cohorts with a higher dose (1) Progression to successive parts of the study with an equal of higher dose (2) Continuation or suspension of the overall study (3)
			In one SOC	In total			
I (Mild)	N/A	N/A	Any	Any	N/A	No action required	No action required
II (Moderate)	Not serious	IMP continued, amended, temporarily suspended or discontinued	≤ 2	≤3	Yes	Yes +/- Dosing regimen extended	No action required or (1) and (2). On hold until results of extended regimen if applicable
			≥ 3	≥ 4	Yes	Suspended	
			N/A	1	No	Yes +/- Dosing regimen extended	No action required or (1) and (2). On hold until results of extended regimen if applicable
				≥ 2	No	Suspended	(1) and (2) with substantial amendment. (3) Lower dose levels (cohort and parts) can continue
	Serious	IMP discontinued	N/A	≥ 1	N/A	Suspended	(1) and (2) with substantial amendment. (3) Lower dose levels (cohort and parts) can continue

Template Adverse Reactions Stopping rules

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Grade (Severity)	Serious - ness	Individuals	Within-cohort decision				Study progression
			N° subject		Reversi -bility	Continuation within a dosing regimen	Escalation to cohorts with a higher dose (1) Progression to successive parts of the study with an equal of higher dose (2) Continuation or suspension of the overall study (3)
			In one SOC	In total			
III (Severe)	Not serious	IMP discontinued	N/A	1	Yes	Yes +/- Dosing regimen extended	No action required or (1) and (2). On hold until results of extended regimen if applicable
				≥ 2	Yes	Suspended	(1) and (2) with substantial amendment. (3) Lower dose levels (cohort and parts) can continue
				≥ 1	No	Suspended	(1) and (2) with substantial amendment. (3) Lower dose levels (cohort and parts) can continue
	Serious (except LT and fatal)	IMP discontinued	N/A	≥ 1	N/A	Suspended	Suspended
IV (life-threatening-LT)	Serious (LT non-fatal)	IMP discontinued	N/A	≥ 1	N/A	Suspended	Suspended
V (fatal)	Serious (fatal only)	N/A	N/A	≥ 1	N/A	Suspended	Suspended

Alerting Procedure for ALT Increase

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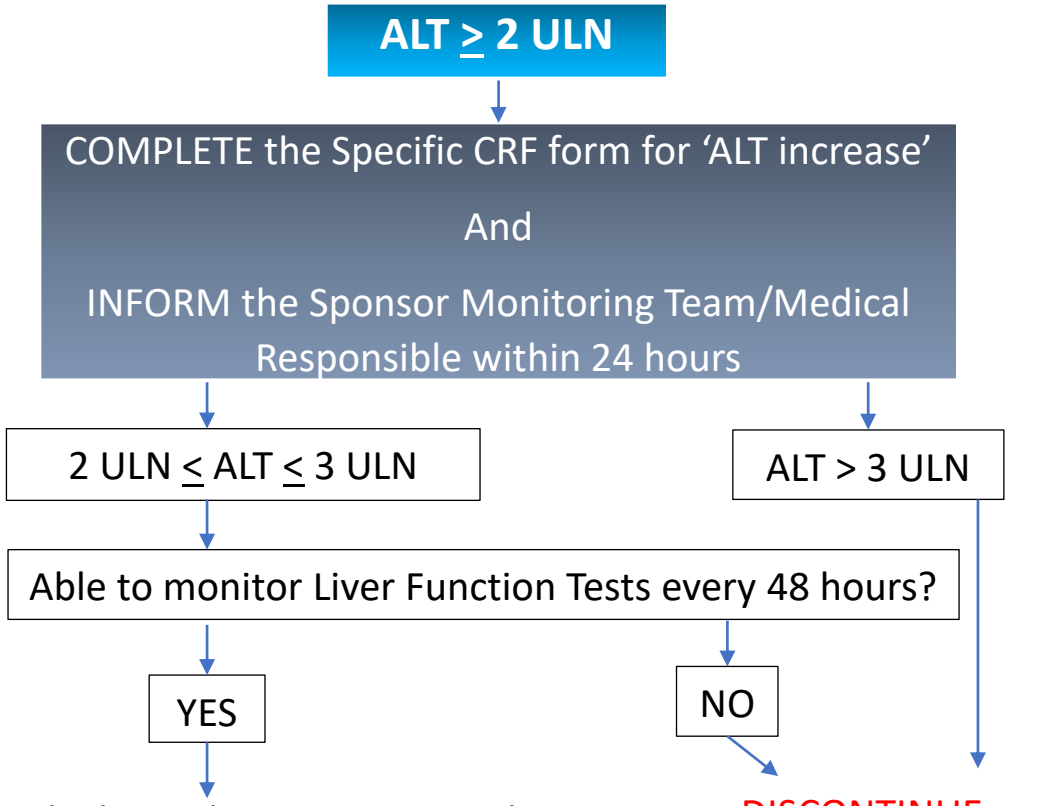

Monitor Liver Function Tests (LFT) every 48 hours until return to < 2ULN.

If ALT elevation (2 ULN ≤ ALT ≤ 3 ULN) persist beyond 2 weeks: perform LFT every 2 weeks and 15 to 30 days after the last dose, or until return to < 2 ULN, whichever comes first.

Date: 25 May 2023

EUFEMED

PROCEDURE TO BE SYSTEMATICALLY FOLLOWED:

1) **CONSIDER** reporting as Adverse Event (AE) or Serious Adverse Event (SAE):
   - Acute liver injury (ALI): is defined by INR higher than 1.5 without associated hepatic encephalopathy.
   - Fulminant hepatitis (FH) or acute liver failure (ALF): is defined by an INR > 1.5 and the presence of hepatic encephalopathy but the absence of chronic, underlying (or prior) disease.
   - Hy's law: composite algorithm to **predict** ALI in subjects with drug-induced liver injury (DILI) = ALT or AST ≥ 3 ULN and Total Bilirubin (BT) > 2 ULN in the absence of alkaline phosphatase (ALP) elevation < 2 ULN.
2) **INVESTIGATE** THE CLINICAL PICTURE:
   - Detailed anamnesis: age, race and/or ethnicity, gender, individual and family past-history, and particularly history of recent travels, alcohol consumption, any prescribed (including vaccination) or over-the-counter drug (including acetaminophen/paracetamol, non-steroidal anti-inflammatory drugs), or vitamins/herbal/dietary supplements or recreation drugs intake, strong physical activities (documented), physical injury, infection.
   - Clinical context in the previous 72 hours: signs of hepatitis (fever, jaundice, icteric sclera, abdominal tenderness, dark-coloured urines, light-coloured stools, extrahepatic manifestations (e.g., neurological signs, infectious signs, cutaneous rashes) and specifically for malaise with or without loss of consciousness, dizziness, and/or hypotension and/or episode of arrhythmia; rule out muscular injury.
   - Detailed physical examination: particularly body temperature, abdominal examination (pain, hepatomegaly), skin and eyes examination (urticaria, rash, icteric sclera), nodes examination (lymphadenopathy), neurological examination, ENT and pulmonary examination.
3) **PERFORM** the following tests:
   - LFT: ALT, AST, ALP, Total and Conjugated Bilirubin, and Prothrombin Time/INR.
   - CPK, serum creatinine, complete blood count (with differential white blood cell count), lipase.
   - Anti-Covid-19 IgM, anti-HAV IgM, anti-HBc IgM, anti-HCV and HCV RNA, anti-HEV IgM, anti-CMV IgM antibodies, and depending on the clinical context, other infections (e.g., EBV, Herpes viruses, toxoplasma).
   - Hepatobiliary ultrasonography (can be completed by other imaging investigations if needed).
4) **CONSIDER** auto-antibodies: anti-nuclear, anti-DNA, anti-smooth muscle, anti-LKM (anti liver and kidney microsome).
5) **CONSIDER** consultation with hepatologist.
6) **CONSIDER** subject hospitalisation if INR > 2 (or PT < 50%) and/or central nervous system disturbances suggesting hepatic encephalopathy.
7) **MONITOR** LFT as closely as possible to every 48 hours until stabilization then every 2 weeks until return to < 2 ULN or to a maximum of 3 months, after the last dose, whichever comes first.
8) **COLLECT/STORE** 1 sample following procedures described in blood samples collection section of the protocol and freeze one serum sample at minus 20°C (5 mL).

Risk Communication Plan

- Between:
  - Staff involved in the study.
  - Health care facilities that might come into play in case of emergency (prior to and during the study).
  - Different study sites (if applicable).
  - Sponsor.
  - Regulatory authorities (RA).

- This should mitigate the possibility that faults in communication – as the chronicles of events from the BIAL trial and the subsequent report from the Inspection Générale des Affaires Sociales (IGAS) have shown – should lead to dosing further subjects after a serious adverse event occurred.

Development Risk Management Plan Planning

How to Fill a Risk Management Plan prior to the CTA/IND: Simple Version with Table Log

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Risk / Missing Information	Data Summary (Clinical and pre-clinical; including class effects)	Mitigation / Management Actions (including Routine and additional PV & Risk Minimisation Plan)
Risk Example : Infertility in men; Sexual dysfunction *Missing Information Example : Use in special populations (paediatric, elderly, pregnancy, breast feeding, liver or renal impairment, others as applicable...).* *Note: this may be not applicable depending on target population and/or stage of development*	Clinical data: *Example : Reductions on mating and fertility indices in rats (transient in nature and in doses exceeding the human exposure)* Pre-clinical data: *Example : Some anti-testosterone agents causes infertility (eg LHRH agonists) has been reported with erectile dysfunction although this is not a listed event for comparator*	Summary: *Example : Routine collection of AEs, vital signs, laboratory parameters monitoring* PV Plan (optional): *Example :* - *Secondary safety objective to measure biomarkers for infertility (size of testes, sperm analysies, hormone measures)* - *Safety questionnaire* Risk Minimisation Plan (optional): *Example :* - *Exclusion criteria : history of erectile dysfunction / infertility* - *Treatment guidelines*

Safety signals/Risks considered	Reason for considering	Relevance in humans / Potential impact	Risk assessment	Risk minimization
Specific findings potentially linked to the compound (non-clinical)				
Liver effect	**Nonclinical signal** • Covalent binding in most of species including human and potential for mechanism-based inhibition (MBI) for CYP s 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. • Increases in transaminases and ALPs: rats at 80 mg/kg/day PO + 30 mg/kg/day IV and dogs at 60 mg/kg/day PO. Reversible • In all rats, centrilobular hepatocellular hypertrophy: 80 mg/kg/day PO and 30 mg/kg/day IV. In dogs, ≥ 30 mg/kg/day PO: vacuolation and/or epithelial single cell necrosis in large bile ducts, and centrilobular mixed inflammatory cell infiltrates at 300 mg/kg/day PO • Distribution/retention of the drug: residual radioactivity in the liver observed 3 months post-dose in rats	Relevance in human unknown	**Clinical:** Objectives: Standard Signal detection Methods: Monitoring of LFTs (+ DILI form) at pre-dose (baseline), during treatment period, at the FU visits up to the EOS visit (*longer follow-up than usual i.e., 28 days based on potential long half-life of 105h in human up to 5 effective half-lives in the SAD)* Further nonclinical investigations to be performed if signal observed in human.	**Clinical** *None beyond routine* (Stopping rules: ALT>3ULN; Exclusion criteria: LFT not exceeding ULN). Communication to participants, investigators and Heath authorities (HA) through Written Subject Information (WSI)/Investigator Brochure (IB)/DSUR/IMPD will summarize the preclinical data ALT/AST and bilirubin will be part of the parameters systematically reviewed with the PI at the dose progression meetings DILI consultation if needed after results of phase 1.

Safety signals/Risks considered	Reason for considering	Relevance in humans / Potential impact	Risk assessment	Risk minimization
Potential risks systematically considered due to class effect or type of molecule (e.g., small molecule, monoclonal antibody)				
Phototoxicity	Light absorbance of Product X at 331 nm (molar extinction coefficient = 1913 l/mol/cm) Product X is distributed in the uveal tract and pigmented part of the fur of rats after a single dose	The risk of phototoxicity is considered low, based on the value of the molar extinction coefficient	Phototoxicity study to be done to confirm or rule out this potential risk before TDR.	Depends on the results from the phototoxicity study. The phototoxicity study should be performed before start of the MAD. Communication to patients through WSI
Potential risks systematically considered				
Effect on QT	**Nonclinical** • *In vitro*: Inhibition of hERG currents from concentrations of Product X # 0.14 µM. Decrease in Action Potential Duration (APD50 and APD90) at concentrations # 0.1 µM Due to the instability of in vitro formulations, these alerts were attributed to Product X and/or its degradation products • *In vivo*, no effect on QTc duration in dog up to 500 mg/kg	Unknown *In vitro* results are not conclusive as adequate formulation to conduct such assay (i.e., pH around 7.4) cannot be used with Product X (compound stable at pH 2.8)	Objectives: Standard Signal detection Methods: 12-lead ECG at selected timepoints + 24h-holter ECG at Day-1 and Day 14 in MAD. Thorough ECG study planned before start of phase 3	Preventability/Predictability unknown Standard stopping rule on QT≥500 msec

Safety signals/Risks considered	Reason for considering	Relevance in humans / Potential impact	Risk assessment	Risk minimization
Potential risks systematically considered				
Drug-drug and food-drug Interactions	• Drug-Drug Interaction: *in vitro* data: Product X is a time dependent inhibitor of Cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4. Concomitant use of Product X could result in increasing the exposure of CYPs substrates with potential for toxicity. *In vitro* data indicate a contribution of CYP3A to Product X metabolism (65 to 87%) => Potential risk of Product X toxicity or lack of efficacy in presence of potent CYP3A inhibitors or inducers respectively • Food-Drug interaction (in case oral development required): Product X exhibited a low solubility (< 21 µg/mL) in simplified media affected by pH (pH 3 vs pH 6.5) and the solubility was 9-fold higher in Fed State Simulated Intestinal Fluid (FeSSIF) than in Fasted State Simulated Intestinal Fluid (FaSSIF) suggesting some potential food effect	Will depend on the extent of interaction (results of planned FE and Interaction studies)	**Clinical** Objectives: Risk characterization Interaction study to document the effect of repeated administration of Product X on selected probe substrates: • Interaction cocktail study (Several CYP substrates) (after the POC) • Interaction study with ketoconazole (potent CYP3A4 inhibitor) (after the POC study) • Interaction study with rifampicin (potent CYP3A4 inducer) (after POC) • Relative biodisponibility study to document the food effect *in vivo*	Duration of hospitalization based on time of CYP renewal Prohibit concomitant medications before entry in study (5 half-lives) and during study Warning about the risk of interaction and guidance about medications with narrow therapeutic index that are substrates of the Cyp3A Depending on exposure results an online PK review may be necessary, in particular for high dose levels of TDR Ensure with investigator proper access to decoding material.

Safety signals/Risks considered	Reason for considering	Relevance in humans / Potential impact	Risk assessment	Risk minimization
Potential risks systematically considered				
Potential for reactive metabolite and Hypersensitivity	*In vitro*, low level of covalent binding	Unknown	None beyond routine assessment (see above liver)	No
Mandatory EU-RMP considerations (e.g., potential risks related to post-marketing use)				
Potential for transmission of infectious agents and/or contaminants	Potential risk related to post-marketing use. Not a biologic	None	None	None (apart of aseptic preparation of the solution for infusion by Health Care Professional)
Potential for misuse for illegal purposes	Potential risk related to post-marketing use.	Unknown, however Product X crosses the Blood Brain Barrier	Routine PV	None
Drug Abuse and Dependence	Potential risk related to post-marketing use.	Unknown, however Product X crosses the Blood Brain Barrier	Routine PV	None
Medication errors	Potential risk related to post-marketing use.	Unknown, however IV product	Routine PV	None
Off-label use	Potential risk related to post-marketing use.	Unknown	Routine PV	None

DRMP/DSUR Progression during Drug Development

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DRMP before first-in-human trial:

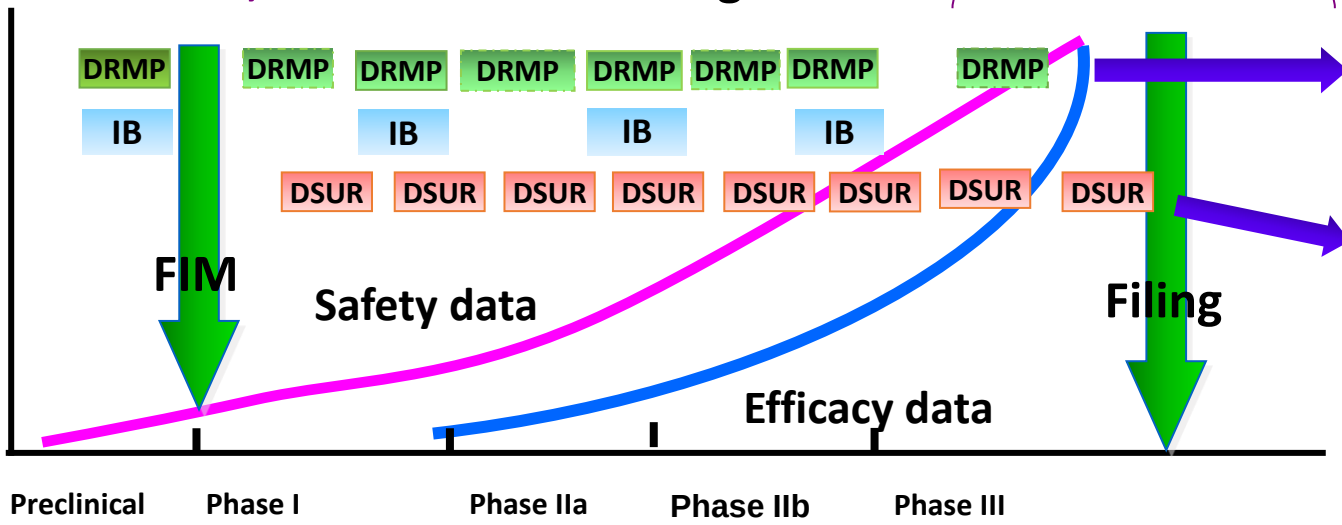
- Non-clinical findings that are relevant and important in humans
- Safety intelligence: history of previous compounds (external/internal) and literature findings

DSUR:

- Regulatory document to be submitted to HA
- One year after the first human exposure
- Every year

Regulatory Submission kick-off, start transitioning into RMP

Continuously updated with nonclinical findings, clinical observations, and literature findings



RMP/REMS* Document for Regulatory Submission

PSUR/PBRER* in post-marketing

RMP = Risk Management Plan (EU/Japan/Rest of the world)/REMS = Risk Evaluation and Mitigation Strategy (US)
PSUR = Periodic Safety Update Report (EU)/PBRER = Periodic Benefit Risk Evaluation Report (US/Japan/Rest of the world) – ICH E2C

In general, following points and future steps should considered

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- Careful screening and evaluation of investigational compounds for their on- and off-target effects is important to know the potential and expected AEs.
- This will help in better management of anticipated safety concerns.
- Careful selection of preclinical models including relevant species and correct interpretation of preclinical toxicity data is needed.
- Careful selection of starting dose is important as minor errors in calculation of starting dose based on predicted NOAEL may prove dangerously wrong.
- Execution of dosing intervals between the dosing of one subject and the other is a key step as this helps researchers to watch for possible toxicity in one subject before other subjects being exposed to the drug, therefore protecting next subjects.
- Implementation of stringent stopping rules is important. The EMA recommendations on risk management include a risk minimization strategy based on clearly defined stopping rules. Club Phase I working group also proposed a safety grading system that might help in rationalizing dose escalation and stopping decisions.

A safety grading scale to support dose escalation and define stopping rules for healthy subject first-entry-into-man studies
Some points to consider from the French Club Phase I working group.
Michel Sibille, Alain Patat, Henri Caplain, Yves Donazzolo.
Br J Clin Pharmacol. 2010 Nov;70(5):736-48.

In general, following points and future steps should considered

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- More transparency in NCE/BLE structure, preclinical data, publication and accountability regarding the ethical conduct of the trial is crucial. Timely information of any AE to other study subjects and consideration of revised consent before giving them further doses could avoid toxicity in other subjects. Adequate plan, for tackling AEs where there is a known theoretical risk, is needed. Any anticipated safety concerns toxicity should not be ignored, and all measures should be kept ready to deal with them.
- During the conduct of Phase I trials, stringent monitoring and inspection should be mandatory by clinical trial monitors, Ethics Committees and Regulators.
- Microdosing or Phase 0 studies can be employed before Phase I to explore certain aspects of the drug effects. The role of microdosing is now expanding (initially designed for purely pharmacokinetic prediction), for example, to predict the levels of a drug in cell or tissue types (could be helpful in predicting tissues/organs likely to be affected by the drug toxicity), drug-drug interactions before and after the administration of a drug known to inhibit or induce cytochrome P450 system and obtaining information regarding the metabolism of a drug candidate by administering a carbon-14 labelled and comparing the plasma concentration-time curves to the parent compound.

Conclusion (1/2)

- The DRMP/RMP summarizes what is known and non-known concerning the safety profile of the compound/product.
- It is a powerful tool for risk assessment and risk minimisation.
- Companies should start early in R&D with the nonclinical data and “safety intelligence”.
- It is opportunity of developing an “IMPaCtS” approach:
  - Iteratively and interactively (internally and externally with Authorities).
  - Multidisciplinary.
  - Pro-actively.
  - Early.
  - Continuous benefit-risk evaluation.
  - Anticipation.
  - Systematic.

Conclusion (2/2)

- Risk management offers:
  - Better management of issues.
  - Anticipation of crises and thus to avoid them.
- Should give a reinsurance to the regulators:
  - With a reasonable level of knowledge.
  - With consideration of the differences between targeted population and trials population.
  - That appropriate measures are planned to investigate potential risks and missing information, and to better quantified identified risks.
  - That risks can be appropriately managed (minimised) outside the clinical situation.

First in Human of a new compound is only at the beginning of the research!