First-in-human studies: Recent experiences in Europe

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First-in-human trials

- 11 January 2016, Rennes, FR
  - BIOTRIAL
  - FAAH-inhibitor

- 13 March 2006, Northwick Park Hospital, London, UK
  - Tegenero
  - TGN1412
What we know: Biotrial clinical trial tragedy

By Melissa Fassbender, 18-Jan-2016

Related topics: Clinical Development

On Friday, the French Minister of Health addressed the public pledging to provide answers after one man was declared clinically dead as the result of a clinical trial gone wrong.

In the press release, translated from French, Marisol Touraine, Minister of Social Affairs, Health and Women's Rights, expressed the seriousness of the event, adding that no such comparable event has ever been documented,

As Outsourcing-Pharma.com previously reported, six people have been hospitalized and one declared clinically dead.
• Fatty Acid Amide hydrolase (FAAH) – inhibitor (not the first one)

• Endocannabinoid system
  – Endogenous cannabinoids:
    • Anandamide (AEA)
    • 2-archidonoylglycerol (2-AG)

  FAAH-inhibitors are intended to enhance AEA.

• BIA 10-2474 is intended to be a long-acting inhibitor in brain and periphery. In fact: irreversible inhibitor

• Misunderstanding of pharmacology and pharmacokinetics?
Six men remain in intensive care after being taken ill during a clinical drugs trial in north-west London.

The healthy volunteers were testing an anti-inflammatory drug at a research unit based at Northwick Park Hospital when they suffered a reaction.

Relatives are with the patients, who suffered multiple organ failure. Two men are said to be critically ill.....
The TGN 1412 incident

- March 13, 2006 injection of 6 volunteers in a first-in-man trial
- Within 6 hours all volunteers in intensive care with severe inflammatory reactions and multi-organ failure

Symptoms and timing

- Headache between 50-90 minutes
- All lumbar lumbagia
- Rigors between 58-120 minutes
- Fever between 2.5 to 6.5 hours
- Hypotension between 3.5 to 4.6 hours
- Tachycardia between 2.5 to 4.6 hours
- Nausea, vomiting, dyspnea, bowel disturbances, amnesia
TGN1412

• **Proposed benefit**
  - Binds to subregion of CD28 leading to T-cell activation independent of antigen-presenting cell stimulus
  - B-cell chronic lymphocytic leukemia is expected to benefit from this T-cell activation
  - Lower doses primarily activate regulatory T-helper cells with benefit for T-cell mediated autoimmune diseases (multiple sclerosis and rheumatoid arthritis)

• **Observed adverse effects**
  - Symptoms associated with the cytokine release syndrome (CRS)
Concept paper on the revision of the ‘Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products’ (EMEA/CHMP/SWP/28367/07)
2. Problem statement

The current guideline mainly focuses on non-clinical aspects of drug development and the use of animal data and reflects the practice at the time it was developed which focused on a single ascending dose (SAD) design for first-in-human (FIH) trials.

Since then, integration of the non-clinical data available before FIH administrations and the pharmacokinetic (PK), pharmacodynamic (PD) and human safety data emerging during a trial has also evolved. Consequently, the practice has evolved and many FIH trials are now performed with integrated protocols potentially combining a number of different study parts, e.g. single and multiple ascending doses (SAD and MAD), food interaction, different age groups and early proof of concept or early proof of principle parts. FIH and early phase CTs with multiple study parts are, therefore, increasingly being submitted for regulatory review to National Competent Authorities as part of a single CT application.
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EMA has no position about BIAL, “l’accident de Rennes”

• Under responsibility of ANSM

Solution: Reading between the lines
Extension of the non-clinical aspects of the guideline to address:

- better integration of non-clinical pharmacology data (including PK and PD data evaluated using current PK/PD or physiologically-based pharmacokinetic modelling) and data from the 38 toxicology testing into an overall risk assessment for FIH and early CTs administration;

- translation of non-clinical data to human use by extrapolation and verification of assumptions made;

- expanding on the minimum anticipated biological effect level (MABEL) approach taking all biological effects into account;

- the role of non-clinical data for the:
  - estimated therapeutic dose, maximum human dose level (both for SAD and MAD parts), dose escalation steps and dosing frequency and intervals;
  - definition of stopping criteria for the trial;
  - identification of safety aspects to monitor.
Extension of the clinical part of the guideline with new guidance to address:

- integrated CT designs and study endpoints including decision-making aspects;
- extension of the remit of the guidance beyond single ascending dose FIH trials to incorporate other early phase trials and designs;
- clarification on the choice of trial subjects;
- overall dose/exposure range and scheme including stopping rules;
- rolling review of emerging human data during the study;
- general principles on key scientific information to be included in a CT application;
- safety observations for trial participants
- handling of adverse events in relation to stopping rules and progress to next dosing steps
- general principles on communication to competent authorities and CT subjects.
Evolution of practices for FIH clinical trials

2007

First-in-human SAD design

Dose 1

Dose 2

Dose n

NC data

PD

PK

Safety pharmacology

Toxicology

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2016

Integrated protocols

SAD - Single ascending dose
MAD - Multiple ascending dose
FI - Food interaction
DDI - drug-drug interaction
PoC - Proof of concept

NC data
PD  PK
Safety pharmacology
Toxicology

Single regulatory review (NCAs)
10 November 2016
EMEA/CHMP/SWP/28367/07 Rev. 1
Committee for Medicinal Products for Human Use (CHMP)

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

Draft
2006/7

- This guideline applies to all new chemical and biological investigational medicinal products except gene and cell therapy medicinal products.

2016/7

- The current revision concerns the extension of the existing EU guidance to address FIH and early phase CTs with integrated protocols, and recommendations regarding the non-clinical and emerging clinical PK, PD and safety data to support them.

The guideline applies to all new chemical and biological IMPs.
• While a novel mode of action might not necessarily add to the risk per se, consideration should be given to the novelty and extent of knowledge of the supposed mode of action, as well as the characteristics of the target. This includes the nature and intensity of the effect (e.g. extent, amplification, duration, (ir)reversibility) and other mechanistic effects of the IMP on the Intended target(s) and potential off-targets.

• The usefulness of PD data following repeated dosing testing. While single dose PD data can be used for an initial interpretation of the potential outcome of multiple dosing, consideration should be given to conducting repeated dose pharmacology studies or to include PD endpoints in repeated dose toxicity studies.
Additions

- Potential off-target effects, with particular focus on, but not limited to, targets closely related/similar to the intended one.
Additions

• The primary and secondary PD should be conducted in vitro, using animal and human-derived material and in vivo using animal models, as relevant. These studies should include target interactions preferably linked to functional response, e.g. receptor binding and occupancy, inhibition of enzymes, duration and (ir)reversibility of effect, dose-response relationships and physiological turn-over of the target.

• A state-of-the-art PK/PD modelling approach is recommended, taking into consideration repeated dose applications as to be expected in the clinical situation.
Additions

- Toxicity can be the result of exaggerated pharmacological actions. However, these types of effects should not be ignored when establishing a safe starting dose for humans and the corresponding exposure will contribute to the determination of the dose escalation range to be investigated in humans. Primary and secondary PD can support the generation of mechanistic hypotheses regarding the toxicities seen in vivo and help in the interpretation of the human relevance of these findings.
Dose selection, escalation and maximal dose

- The main changes of the whole GL are made in relation to these aspects.
- A lot more information on these aspects beyond setting the starting dose; which was hardly addressed in the 2007 GL.
- This includes moving from SAD to MAD.
- Emphasis on integration of all available data, including during the CT.
Dose selection, escalation and maximal dose

MABEL vs NOAEL approach
Clinical aspects and monitoring:

- Addition on integrated protocols
- Subject assessments and interventions