Challanges in the Ethical Approval of First-in-man trial/early CT

AGAH Workshop Göttingen

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Ethik-Kommission bei der LÄK RLP

Challanges in the Ethical Approval of First-in-man trial/early CT

- Characteristics of FIM trials
- Requirements of FIM trials
- Responsibilities of the Sponsor
- Responsibilities of the ethics committee
- Examples

Ethical „Aporie“ in Biomedical Research

Es ist unethisch eine Therapie anzuwenden, deren Sicherheit und Wirksamkeit nicht wissenschaftlich geprüft ist.

Es ist aber auch unethisch, die Wirksamkeit einer Therapie wissenschaftlich zu prüfen, wegen des nicht auszuschließenden Risikos einer Schädigung des Patienten/Probanden.

Toellner 1990

Consequences for Biomedical Research

- **Clinical research is unequivocally required from a medicinal point of view!**
- **Research with humans is only justified, when the knowledge cannot be obtained by other ways!**
- **Research with humans must end with robust results involving the minimal possible number of participants and producing the lowest possible levels of risks and burden!**

Characteristics of *first-in-man/early CT*

- First application to humans
- A risk-benefit evalution on the basis of clinical safety values is not available!
- Preclinical data about safety/pharmacokinetics/efficacy are not transferable to humans in a 1 to 1 ratio!
- In FIM the volunteer does not obtain health benefits but risks and burden!
- FIM studies represent human experiments with foreign interest and an uncertainty factor!

FIM study with the humanized antibody TGN 1412 , 13. March 2006

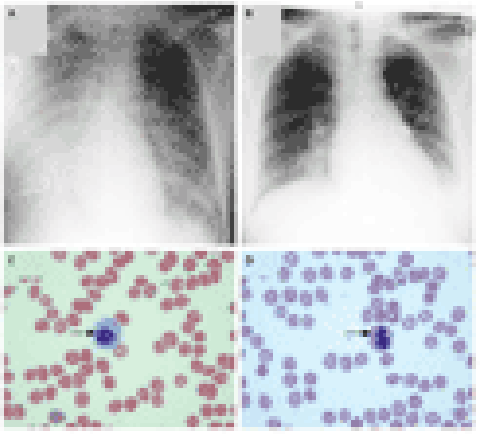
The NEW ENGLAND JOURNAL of MEDICINE

Cytokine Storm in a Phase 1 Trial of the anti-CD28 Monoclonal Antibody TGN1412

Volume 355:1018-1028, 2006

Klinik zur „Hölle auf Erden“

tem Zustand – Polizei beschlagnahmt Unterlagen – Kritik von Ärzten



France: Healthy volunteer died in a MDA cohorte
18.01.2016, 13:38 Uhr | dpa BIA 10-2474 (FAAH Inhibitor)

Since 2005 about 3300 FIM studies have been performed within the EU

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Requirements

- **Clear defined medical indication *(relevance of the planned trial for Medical Care)***
- **Appropriate/extensive preclinical testing *(for example relevance of the animal model, definition of targets, acute and chronic toxicity, gene toxicity, kinetics)***
- **Comprehensive trial protocol with detailed information about benefit-risk evaluation and risk minimisation**
- **Authorisation by the national competent authority**
- **Approval by the ethics committee**
- **Autonomic descision of the volunteer after *„radical“* informed consent**
- **Suitability of trial site and staff**

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Responsibilities of the Sponsor

- **Clear evaluation of the benefit-risk ratio with a statement to:**

  - identifiable and possible risks and burden

  - scientific sound evaluation of the uncertainty/ not-knowledge factor *(to define the degree of uncertainty)*

  - rules how to exclude or minimize risks.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 July 2017
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

Adopted by CHMP for release for consultation	10 November 2016
Start of public consultation	15 November 2016
End of consultation (deadline for comments)	28 February 2017
Adopted by CHMP	20 July 2017
Date of coming into effect	01 February 2018

To mitigate Risks

- **Is a „high uncertainty“ trial planned? (EMEA/CHMP/SWP/2836/07 Rev.1)**

Mode and novelty of action; Nature of target; Relevance of animal models; Characteristics of safety findings; Uncertainities to estimate MABEL, PAD, ATD

- **IMP targets multiple signalling pathways which are ubiquitous expressed in the body**
- **Activated pathways represent amplifyers without endgenous negative feed-back mechanisms**
- **Immunological effects which are not understood in detail**
- **Expression of the target differs between healthy volunteers and patients**
- **Appropriate animal model does not exist**

Responsibilities of the Sponsor:
Consequences for the trial protocol, minimize the risks

- **Trial protocol** (Consider the appropriate quidance documents ICH M3R2; ICH M7; ICH S3A; ICHS3B; ICH S6R1; ICH S7A,B; ICH S9; ENTR/F/2/SF D(2008) 34961 ..):

Definition of the target; relevance of the animal model; transfer of the preclinical data to humans; definition of the the degree of uncertainty; relevance for medical care; definition of the main preclinical IMP parameters (NOAEL, MABEL, PAD, ATD, Kinetics) under consideration of all performed preclincal results/studies; scientific sound rational for estimating MABEL and ascending dose intervals; continuous monitoring of safety; stopping rules for the individual, one cohort and the complete trial; appropriate sentinal monitoring in SAD and MAD; rules for minimizing risks and for safety reporting…

Consequences for the trial protocol

- **EMEA/CHMP/SWP/2836/07 Rev.1: Overlap of SAD and MAD may be acceptable; scientifically justified, supported by decision points and *review of available data* (*Who reviews ? Who defines the amount of available data?)***

- **In view of an ethics committee integrated trial protocols as FIM studies should not be performed, because the degree of uncertainty increases**

- **Unequivocally clear definition of the intended therapeutic indication with specification of PAD/ATD**

- ***Specification and definition of the degree of uncertainty***

Consequences for the trial protocol

- **Exact definition of the first dose (MABEL,** Minimal Anticipated Biological Effect Level**) and the planned dose increments**
- **Definition of the Maximal Dose Level; substantial amendment is required in the case of further increase**
- **Usually no MTD testing; when MTD testing is planned in patients, detailed stopping rules based on clinical conditions are required**
- **Detailed "Safety Monitoring" rules**

Consequences for the trial protocol

- **Clear stopping rules for the individual (one SAR or several AEs of modest or severe intensity [i.e 2 AEs with severe intensity])**
- **Sequential but not simultaneous exposure of the members of one dose cohort, not only in the first dose cohort (appropriate sentinal safety monitoring)**
- **All safety and kinetic data of the preceding dose cohort must be available before starting the next higher dose**
- **Involvement of an independent DSMB**

Investigator`s brochure

- **All preclincial data must be documented!**
- **Detailed and scientific sound evaluation of the benefit – risk relation and the suitability of the animal model tested**
- **Detailed evaluation about the transfer of the preclinical data with respect to safety**
- **Detailed evaluation about the transfer of the preclinical data with respect to efficacy**

Consequences for the trial site

- **Investigator/deputy/staff: Specialists for clinical pharmaco-logy/emergency medicine/experience in the intended clinical indication**
- **Regular training of the whole staff in emergent medicine**
- **Appropriate equipment for emergent medicine including transport facilities**
- **Contact point to a close localized ICU**
- **Communication with the ICU about the planned FIM-trial**

Consequences for the trial site

- **Documentation of SOPs and Quality Monitoring**
- **Definition of the minimal number of staff available throughout the trial procedure**
- **Regular check of the facilities and training programs**

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Responsibilities of the Ethics Committee

- Rational and relevance of the trial for medical care
- Appropriateness of the presumed benefit for medicine and the possibel risks/burden for the individual participant
- The trial protocol
- The inclusion/exclusion/withdrawal criteria
- The investigator`s brochure

Responsibilities of the Ethics Committee

- The complete procedure of getting informed consent
- The suitability of the investigator/deputy/staff
- The suitability of the trial site
- The trial insurance
- The arrangements for compensating subjects
- The contract between Sponsor and trial site

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Ignaz Wessler, Mainz

Trial protocol: To minimize risks
Examples

- **Eur J Clin Pharmacol (2017), 73, 409-416: Who is a healthy subject?**

"The Stopping rules for a cohort are one serious reaction or ≥ 50 % of subjects experiencing any adverse reaction of moderate or severe intensity".

??

not acceptable!

Trial protocol: to minimize risks
Examples

- Safety lab. data 3-21 Tage before randomisation: always actual safety lab. data are required, not older than 3 days.
- Exclusion criteria: clinically relevant deviations of the ECG recording, lab. values, physical investigation: always clear defined criteria.
- Inclusion criterion HF 40/min: Volunteers should represent the common population (HF 50-90/min).

Trial protocol: to minimize risks
Examples

- **"The dose levels will be determined after evaluation of the safety, tolerability and available PK results of previous SAD dose groups":**
  Non-defined doses do not offer an evaluation by the ethics committee.

- **"The MAD part may be starting during the SAD part but only when enough PK and safety data are available":**
  What does "enough" mean, not evaluable by the ethics committee.

Trial protocol: to minimize risks
Examples

- **"The dose should not be escalated further if one of the circumstances listed below occurs in subjects within the same dosage cohort….:**

  Drug related severe AEs of the same character in 4 or more subjects;

  Clinically significant drug-related lab abnormalities or changes in vital signs or the ECG of the same character in 6 or more subjects"

4 (6) or more subjects not acceptable:

- **„or more" does not represent a clear stopping rule**
- **one SAR must cause a stop/hold**
- **2 AEs (suspected, severe intensity) must cause a stop/hold**

Vielen Dank

für

Ihre

Aufmerksamkeit !