EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Regulatory Perspective

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Disclaimer

The views expressed in this presentation are the personal views of the speaker and may not be understood nor quoted as being made on behalf of or reflecting the position of EMA or one of its committees or working parties or any of the national agencies.

Other positions:

- Vice Chair of the Psychopharmacology Special Committee of the Council of the Royal College of Psychiatrists, UK.

- Previous : Consultant Psychiatrist & Co-Director of Psychopharmacology Evaluation Unit at the South London & Maudsley NHS trust in London and Honorary Senior Lecturer in the Department of Forensic and Neurodevelopmental Sciences at the Institute of Psychiatry, Kings College London, UK.

Discuss the regulatory landscape and the evidence needed for regulatory agencies to consider trials in humans in the absence of predictive animal models of disease.

Explore areas within the drug development pipeline where new and emerging tools, technologies, and techniques might be subject to regulatory processes.

Discuss how accelerating to human trials would alter the drug development pipeline. Consider potential challenges to such approach.

What evidence is needed to conduct efficacy trials in humans? What constitutes a feasible outcome measure and what is the role of surrogates?

1-Discuss the regulatory landscape and the evidence needed for regulatory agencies to consider trials in humans in the absence of predictive animal models of disease.

Non clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (ICH M3 (R2), EMA/CPMP/ICH/286/1995). ICH guideline M3 (R2) - questions and answers (EMA/CHMP/ICH/507008/2011).

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Guideline on strategies to identify and mitigate risks for first-in-human clinical trials with investigational medicinal products' (EMEA/CHMP/SWP/28367/07)

The requirements for progression from the conduct of non-clinical studies to clinical trials for investigational medicinal products in humans are extensively addressed as part of ICH M3 (R2) and the related Q&A document.

In addition, in 2007, EMA published the 'Guideline on strategies to identify and mitigate risks for first-in-human clinical trials (CTs) with investigational medicinal products' (EMEA/CHMP/SWP/28367/07), which is now proposed for revision.

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.

Some specific discussion points have been defined (non-exhaustive) when reviewing the current guideline:

- Extension of the guidance to early phase CTs including single study or integrated protocol designs.

- 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 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 FIH:

o estimated therapeutic dose, maximum human dose level (both for SAD and MAD parts), dose escalation steps and dosing frequency and intervals;

o definition of stopping criteria for the trial;

o identification of safety aspects to monitor.

– 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.

Given the diversity in type of investigational medicinal products being developed and clinical trial designs, and considering the complexity in interpretation of relevance of animal toxicology findings for human use, it is considered that the guidelines should continue to be followed in conjunction with all applicable national and international guidance in an integrated, risk-based approach. In addition, there is a need to emphasise that the guideline is applicable for all molecules and not only for biotechnology-derived proteins.

The most important anticipated impact of the revised guideline will be the enhancement of the current strategies to identify and mitigate risks for trial-participants.

This is to facilitate the conduct of these trials in a safe, efficient and transparent manner to the benefit of public health and further harmonise practice in EU Member States.

Explore areas within the drug development pipeline where new and emerging tools, technologies, and techniques might be subject to regulatory processes.

Discuss how accelerating to human trials would alter the drug development pipeline. Consider potential challenges to such approach.

What evidence is needed to conduct efficacy trials in humans? What constitutes a feasible outcome measure and what is the role of surrogates?

Qualification of novel methodologies for medicine development

The European Medicines Agency offers scientific advice to support the qualification of innovative development methods for a specific intended use in the context of research and development into pharmaceuticals.

The advice is given by the Committee for Medicinal Products for Human Use (CHMP) on the basis of recommendations by the Scientific Advice Working Party (SAWP). This qualification process leads to a CHMP **qualification opinion** or CHMP **qualification advice**.

CHMP qualification opinions

The CHMP can issue an opinion on the **acceptability of a specific use of a method**, such as the use of a novel methodology or an imaging method in the context of research and development. The method can apply to non-clinical or to clinical studies, such as the use of a novel biomarker.

The opinion is based on the assessment of data submitted to the Agency.

Before final adoption of qualification opinion, the CHMP makes its evaluation open for **public consultation** by the scientific community. This ensures that the CHMP shares information, as agreed with the applicant, and is open to scientific scrutiny and discussion.

CHMP qualification advice

The CHMP can issue **advice on protocols and methods** that are intended to develop a novel method with the aim of moving towards qualification.

The advice is based on the evaluation of the **scientific rationale** and on the **preliminary data** submitted to the Agency.

Table of contents

Dose finding

The dose levels proposed for the two indications differ, being xxx mg, xx mg and xxx mg administered every 4 weeks for the early AD indication and xxx mg and xxx mg every 4 weeks (with an additional dose at 2 weeks) in PSP.

The choice of doses is based on PK data from 2 dose panels in currently ongoing single ascending dose (SAD) study and a 4-week duration repeat-dose toxicity study in mice.

The 4-week toxicity study in non-transgenic mice only covers off target-related effects.

Pharmacologically mediated toxicity will be addressed in the transgenic mice model, and the results (including TK) of this study are considered of key importance to establish the safety of the antibody before proceeding into phase 2.

Dose finding

It is noted that the dose studied in the mice model Pxxxxx (xxx mg/kg) translates to a humanized dose of xxx mg/kg, which is well below the proposed xxxx mg/kg dose in the phase 2 study.

The ongoing SAD study is testing 5 dose levels with the two top dose levels corresponding to the proposed doses in the phase 2 PSP study.

Preliminary pharmacokinetic data indicate non-linear pharmacokinetics, which implies that a population based PK modelling approach would be appropriate.

Since the current dose proposal is based on the assumption of linear pharmacokinetics, the final dose selection should be based on all available data and awaiting a complete data set analysis is recommended.

Dose finding

Various compartmental models (1, 2, and 3) and combinations of inter-individual and residual error models should be evaluated.

Once the final plasma PK model is established, CSF data can be added with fixed plasma PK model parameters at the previously estimated values to develop a CSF PK model.

Exposure-response analyses are also recommended.

PK/PD modelling can help to determine the most appropriate exposure-response model and estimate the impact of disease-relevant covariates (e.g. baseline biomarker value, baseline disease status as measured by cognitive score).

For the dose selection, the Applicant assumes that tau concentrations in the CSF of PSP and AD patients are xxxxx pg/ml.

Dose finding

For the dose selection, the Applicant assumes that tau concentrations in the CSF of PSP and AD patients are xxx pg/ml. The validity of such assumption is questioned, since: 1) total tau concentration depends a lot on method used to measure it and the Applicant provides no details on methodology, 2) the same assumption is used for AD patients and it is known that total tau concentration in CSF is 2-3 fold higher in AD patients compared to PSP patients.

It is noted that the proposed highest dose in the phase 2 PSP study is twice as high as compared to the highest proposed dose in the phase 2 AD study.

Having in mind the difference in total tau levels in the CSF and the different tau isoform ratios in the two diseases this proposal seems not supported by data. Therefore, the Applicant is requested to clarify the assumptions and available data to support the dose selection.

LOI - Preclinical

The applicant should discuss the lack of repeat dose toxicity studies and possible additional methods to generate safety data such as:

Possible development of an xxx surrogate antibody targeting tau in animals

Whether the neurotoxicity study planned in transgenic mice expressing mutant human tau could be longer than just 8 weeks

Whether other studies in genetically modified animals would be informative.

Preclinical

Please discuss further the characteristics of MAB including:

whether MAB tau binding occurs in a non-disease state

how much crosses the placenta

Pre-clinical

The Applicant is proposing to omit developmental/reproductive toxicology (DART) studies and carcinogenicity studies. PSP may develop in the 5th decade thus subjects may still be fertile. Difficulties in generating relevant toxicological data for MAB, due to the lack of cross-reactivity with tau in the standard non-clinical species are acknowledged, however, alternative approaches have not been adequately discussed.

No rationale was provided for why these relatively short term-studies are considered sufficient to support chronic dosing in humans or the value of using a non-responsive animal species (wild-type mice).

Please justify in more detail the approach to defer the completion of the carcinogenicity studies post-approval in case the benefit of treatment with XXXXX would be minimal.

The possible contribution of the active metabolite XXXX to the cardiovascular safety of XXXX should be clarified.

The dependence potential of novel CNS-active compounds should generally be evaluated in accordance with the tiered approach delineated in the pertinent European guideline (EMEA/CHMP/SWP/94227/2004).

The corresponding study results should be available upon MAA, except further clinical investigations with continued drug exposure are required beforehand.

Further interaction with the EMA regarding the outcome of the non-clinical dependence evaluation is appreciated.

Dose finding The Applicant is requested to clarify the assumptions for the dose levels proposed based on toxicokinetic data from the study in transgenic mice,

total tau concentrations in the CSF,

and available data including PK data from SAD study (preferentially all dose panels tested) to support the dose selection.

The discussion should include specificity of the choice of the dose for the two indications.

Non Clinical Studies should inform:

– integrated CT designs and study endpoints including decision-making aspects;

– 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 handling of adverse events in relation to stopping rules and progress to next dosing steps;

Links

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Qualification of novel methodologies for drug developments

http://www.emea.europa.eu/pdfs/human/biomarkers/7289408en.pdf

Scientific guidelines Http://www.emea.europa.eu/htms/human/humanguidelines/background.htm

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