Safeguarding public health

UK Experiences with Exploratory Clinical Trials

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Regulatory Developments

CHMP Microdose Guideline	January 2003
PhRMA / FDA discussions US eIND	January 2006
EFPIA / CHMP discussions – concept paper	March 2006
Inclusion of Exploratory Approaches in revision of ICH M3 guideline	October 2006
Belgium Guidance	June 2007

ICH M3 R2 Revision

Revision of ICH M3 initiated in May 2005 and agreed to include new section on exploratory clinical trials (Section 7)

Reached Step 2 consultation in June 2008; adjustments made in response to comments received (Section 7 received 15 pages of consolidated comments!)

Step 4 at Yokohama, June 2009???

There are 5 exploratory clinical approaches described in the revised ICH M3 guideline that can be supported by more limited non-clinical testing programs.

The amount of nonclinical supporting data appropriate in these situations will be dependent on the extent of proposed human exposure, both with respect to the maximum clinical dose used and the duration of dosing.

However, in all cases, nonclinical requirements are reduced compared to those for non-exploratory trials.

Exploratory clinical studies are those intended to be conducted early in Phase 1, involve limited human exposure, have no therapeutic or diagnostic intent, and are not intended to examine maximum tolerated dose.

Can be used to investigate a variety of parameters such as pharmacokinetics, pharmacodynamics and other biomarkers, which could include PET receptor binding and displacement.

Note that Exploratory Clinical Trials should not be viewed as First in Man Trials!

They should be viewed as First in Human Trials

Women, including women of child bearing potential, could be included in Exploratory Clinical Trials.

Approach 1:
Microdose study (with a total dose of ≤ 100ug per subject) which could be useful to investigate target receptor binding or tissue distribution in a PET study or to assess pharmacokinetics with or without the use of an isotopically labelled agent.

Approach 2:
Microdose study (with a total dose of ≤ 500 g per subject) which could be useful for similar applications as described above, but with less active PET ligands

Approach 1: total dose
- ≤ 100ug; and
- ≤ 1/100th of NOAEL; and
- ≤ 1/100th of PAD (scaled on mg·kg^{-1} or mg·m^{-2} for iv or oral)

Maximum of 5 administrations (no restriction on inter-dose interval)
Starting dose can be same as maximum dose

Approach 2: total dose
- ≤ 500ug; and
- each dose ≤ 100ug; and
- each dose ≤ 1/100th of NOAEL; and
- each dose ≤ 1/100th of PAD (scaled on mg·kg^{-1} or mg·m^{-2} for iv or oral)

Maximum of 5 administrations with wash-out period between doses (6x predicted T1/2)
Starting dose can be same as maximum dose

Approaches 3: Single Dose Studies at Sub-therapeutic Doses or **into Anticipated Therapeutic Range**

Involves a single dose clinical study typically starting at subtherapeutic doses and possibly escalating into the pharmacological or anticipated therapeutic range
This approach is not intended to support the determination of maximum tolerated clinical dose (except possibly in US).

Approaches 4 and 5: multiple dose clinical studies

Two different nonclinical approaches to support multiple dose clinical studies of up to 14 days duration
Could be useful for determination of pharmacokinetics and pharmacodynamics in human in the therapeutic dose range,
Not intended to support the determination of maximum tolerated clinical dose.

The fourth approach involves 2 week repeat dose toxicity studies in rodents and non-rodents where dose selection in animals is based on exposure multiples of anticipated AUC at the maximum clinical dose.

The fifth approach involves a 2-week toxicity study in a rodent species up to a maximum tolerated dose, and a confirmatory non-rodent study that seeks to demonstrate that the NOAEL in the rodent is also not a toxic dose in the non-rodent.

Other approaches not described in this guidance may be acceptable and should be discussed with the appropriate Regulatory Authorities.

Remember, following Regulatory Guidance is only one way of achieving an objective. There might be a better way!

The secret of health for both mind and body is not to mourn for the past, nor to worry about the future, but to live the present moment wisely and earnestly.

Buddha

So, has any one tried these approaches in the UK yet?

The MHRA authorises approximately 1200 clinical trials per year – more than any other Competent Authority in the EU.

Approximately 40% of all FTIH trials conducted in EU are performed in the UK.

Between 1 April 2008 and end February 2009, the MHRA assessed 57 FTIH Trials with novel compounds. About a third of these were "biologicals"

Although we've seen a number of Phase 1 micro-dose studies, we've only seen one FTIM micro-dose.

The non-clinical programme followed the revised procedure for a multiple dose micro-dose study (approach 2).

Another 9 trials were supported by nonclinical programmes similar to those described in the revised ICH M3, only 4 from "large" Pharmaceutical Companies.

2 of these were up to MTD (Option 3).

6 were SAD studies (Option 4)

1 was a SAD study (Option 5)

Another 4 trials were supported by "non-standard" non-clinical programmes argued on a scientific rationale.

We have also seen a great number of other Phase 1 trials, where the FTIH was conducted outside the UK and was supported by an Exploratory Trial Design.

The MHRA has also has a number of "Regulatory Advice" meetings with companies/charities/ academics to discuss Exploratory Clinical Trial Designs.

MHRA has also provided speakers at a number of other Clinical Trial conferences to discuss the subject.

Take home message – Exploratory Clinical Trials supported by "novel" nonclinical packages are already being conducted.

Significant interest being shown by Sponsors.

MHRA convinced more and more trials will follow these designs – saving money in the short term, but hopefully animals and resources long term.

Any Questions

Don't be shy!

There's no such thing as a silly question to a Regulator!

And I promise I won't take note of your names!!