First in human studies: Practical aspects of design and controls

ASCPT

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Goals of FIH study planning

To facilitate swift and efficient transition from preclinical to clinical arena

To ensure subject safety

To optimise data sets obtained, with compound specific endpoints evaluated

To increase confidence in molecule and/or obtain early NO GO decision based upon Target Product Profile (TPP) criteria

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Multicomponent FIH Study Design to Maximise Efficiency

Typical format (all in healthy volunteers)

- ▶ Part A: SAD (with food effect)
- ▶ Part B: MAD
- ▶ Part C: additional secondary objectives (eg population, formulation comparisons)

Primary objective remains safety and tolerability

- ▶ Secondary/exploratory objectives are compound/class specific

Hybrid studies becoming more prevalent

- ▶ Normal Healthy Volunteers (NHV; low doses) + patients (high doses)
- ▶ SAD run in NHV transition to MAD in patients
- ▶ SADMAD completed in NHV, with "Proof of Principle" run in patients
- ▶ SADMAD in patients

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Where to start?

Starting dose defined in accordance with preclinical data:

- ► Guidance given in:
    - ► ICH M3R2,
    - ► FDA and EMA guidance

- ► Maximum recommended starting dose
    - ► Generally start with NOAEL in most appropriate (sensitive) species
    - ► If molecule "high risk" use MABEL (minimal anticipated biological effect level)
- ► Convert to HED – allometric scaling
- ► Apply appropriate safety factor – usually minimum of 10

- ► Modify according to safety pharmacology, metabolism/binding, pharmacology

Minimally pharmacologically active first dose

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Dose Escalation Planning

Provisional (SAD) doses entered into protocol

Flexible protocols allow doses to be adjusted based upon emerging data

Possible Dose Escalation Schemes:

► Linear Series – constant dose increment. E.g. 1, 2, 3, 4, 5 mg

► Logarithmic Series – increasing absolute dose increment, constant relative dose increment. E.g. 1, 2, 4, 8, 16 mg

► Fibonacci Series – increasing absolute dose increment, decreasing relative dose increment. E.g. 1, 2, 3, 5, 8 mg

In Practice:

► Combination of the above:

  ► E.g. Max five fold escalations below predicted therapeutic dose/exposure

  ► Max two to threefold escalations once predicted therapeutic dose/exposure reached

Dose escalation increments should not increase

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Dose Escalation Decisions

Data required for dose escalation need to be clearly defined:

▶ Ideally in the protocol, can be elsewhere (ICH GCP)

  ▶ Minimum number of subjects needed (e.g. 6 out of cohort of 8)

  ▶ Which assessments - safety and tolerability, anything else?

  ▶ Out to which timepoint?

  ▶ PK?

▶ Who is required to make decision?

▶ Dose Escalation Meeting

▶ Documentation of decisions, QC of data

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When to stop?

Use objective stopping criteria:

Based upon known class effects and/or preclinical findings

- ► Typically includes reference to SAEs/severe AEs
- ► Upper dose level ceiling given in terms of mg or systemic exposure

Quantify

- ► Limit (either as an absolute value or change from baseline)
- ► Frequency (number of subjects/cohort and/or number of occasions/time interval)

Consider

- ► Target Saturation

Define stopping criteria for: individuals, cohorts, study

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Intervals between subjects

Use of sentinel subjects (dose leaders):

- ► Typically two subjects (1 active, 1 placebo)
- ► Appropriate observation period prior to dosing remainder of cohort (e.g. 24h, 48h, 2 weeks)
- ► Usually investigator decision to continue (but may include sponsor)
- ► Different approaches depending on level of risk
  - ► 1st cohort of SAD only
  - ► All cohorts in SAD
  - ► All cohorts in SAD and MAD

Staggering within cohorts

- ► May dose 2 subjects on Day 1, 2 subjects on Day 2, and 4 subjects on Day 3

Interval between subjects within a cohort

- ► Oral doses often 5 minute interval
- ► IV doses longer intervals – often 10 minutes, maybe several hours
- ► IV doses – also need to consider infusion rates

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Introduce flexibility where appropriate

Cohort size

► Option to increase if emerging data suggest higher numbers needed for robust evaluation

Cohort number

► Option to increase if more dose levels needed

Dose levels

► SAD: provisional doses can be increased or decreased based upon emerging data

► MAD selected based upon data from Part A

Assessments

► Option to alter timing and frequency or include additional assessments based upon emerging data

Limits of flexibility should be clearly defined in the protocol

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Key safety conclusions

Consideration of all preclinical data during study design

Risk based approach to study design

Well defined flexibility within protocols to allow timely reaction to emerging data

Expanded designs to address molecule specific concerns

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