First-in-Human (FIH) and other Phase 1 clinical trials are usually conducted in healthy volunteers (HV). Patients with the target indication may be used in Phase 1 trials for some medicinal products, notably anticancer drugs, but such trials are outside the scope of this guidance document.

The first step in the clinical development of an investigational drug usually involves the administration of single doses in increasing amounts to small groups of participants (cohorts). This trial design is called a single ascending dose (SAD) study. The usual intent would be to follow this with a multiple dose ascending (MAD) study.

Definitions

DSMB: Data Safety Monitoring Board

FIH: First-in-Human

HVs: Healthy Volunteers

ICH: International Conference on Harmonisation

IP: Investigational Product

MABEL: Minimal Anticipated Biological Effect Level

MAD: Multiple Ascending Dose

MTD: Maximum Tolerated Dose

NOAEL: No Observed Adverse Effect Level

PD: Pharmacodynamics

PICF: Participant Information and Consent Form

PK: Pharmacokinetics

SAD: Single Ascending Dose

SAD Study Designs

The aims of a SAD study are to assess tolerability, safety, pharmacokinetics (PK) and can incorporate, the pharmacodynamic (PD) effects of a single dose of the investigational drug.

A safe starting dose for use in cohort 1 of a SAD study is determined from the results of animal toxicology studies and can involve consideration of the pharmacology and cell interaction of the investigational product (IP). A commonly used method to determine a safe starting dose is based on allometric scaling of a no observed adverse effect level (NOAEL) in animal studies to a human equivalent dose and incorporating an appropriate safety factor. In cases where the IP is considered ‘high risk’ an alternative method, the ‘Minimal Anticipated Biological Effect Level’ (MABEL) (EMEA/CHMP/SWP/28367/07), is often used to calculate an acceptable safe starting dose. The magnitude at which the dose is escalated between cohorts should be largely guided by the results of nonclinical toxicology studies. The dose is successively escalated following a review of safety outcomes (usually by an independent drug safety monitoring board) observed within a defined period after dosing at each dose level.

SAD study designs typically involve 5-7 ascending dose levels. Dose increments may vary between 3 to 5-fold at low doses of the investigational drug, decreasing to 2-fold or less around the expected therapeutic range. Sentinel participants should be included at the initial dose level in first in human (FIH) studies. Dose increases may also be guided by PK data as a measure of systemic exposure to the drug.

The maximum dose in a SAD study design may be specified in the protocol, based on the results of animal toxicity tests, or can exceed the maximum dose tested in nonclinical toxicology studies depending on the data (to include assessment of the study toxicokinetic data). An attempt to identify a maximum tolerated dose (MTD)

is often the aim of the SAD portion of a Phase 1 study. Alternative Phase 1 study designs are described in the International Conference on Harmonisation (ICH) guideline document ICH M3(R2) and may, for example, involve testing to a pharmacologically active dose rather than establishing a MTD.

SAD studies may be open-label or may include a small number of participants in each cohort (usually 2) who receive placebo formulation instead of active drug in a randomised, double-blind design.

MAD Study Designs

The aims of a MAD study are to assess the tolerability, safety, PK and, if possible, the PD effects of repeated (multiple) doses of the investigational drug. Like the SAD study design, MAD studies usually involve small cohorts of participants, with appropriate review of safety data for each cohort before escalating the dose in the second cohort.

The starting dose may:

- Be the same as for the SAD study, or
- Be based on the MTD (e.g. one or two dose levels below the MTD), or
- Be based on the minimum anticipated efficacious dose (provided this is lower than the MTD established in the SAD study) all with considerations of PK and/or PD data obtained during the SAD stage.

Sentinel participants are not usually included in MAD study designs. Like SAD studies, MAD studies may either be open-label, or include a small number of participants in each cohort who receive placebo formulation in randomised, double-blind fashion.

Conventional SAD-MAD Study Designs

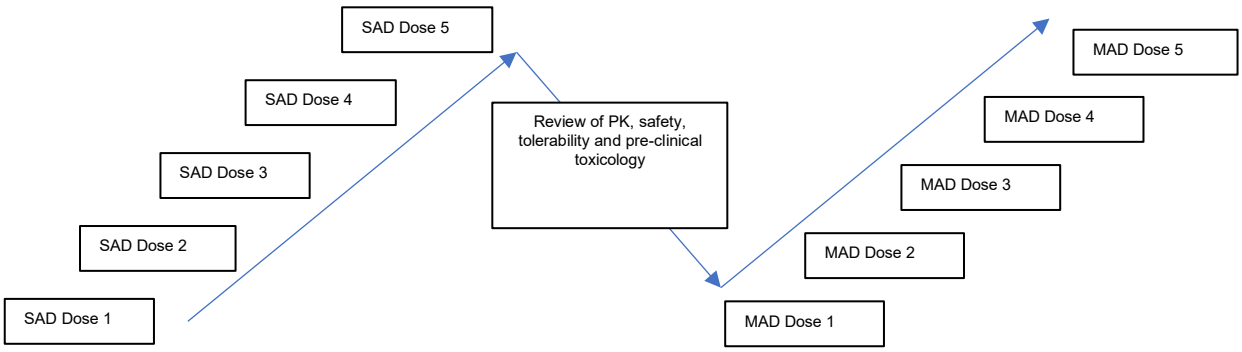
In the conventional combined SAD MAD study design, the SAD portion is completed before the MAD part is initiated. Safety and PK data (and PD data if available) from all single-dose cohorts are reviewed to establish an appropriate starting dose for the MAD part of the combination study.

Fast-track/Integrated/Adaptive/Umbrella study designs

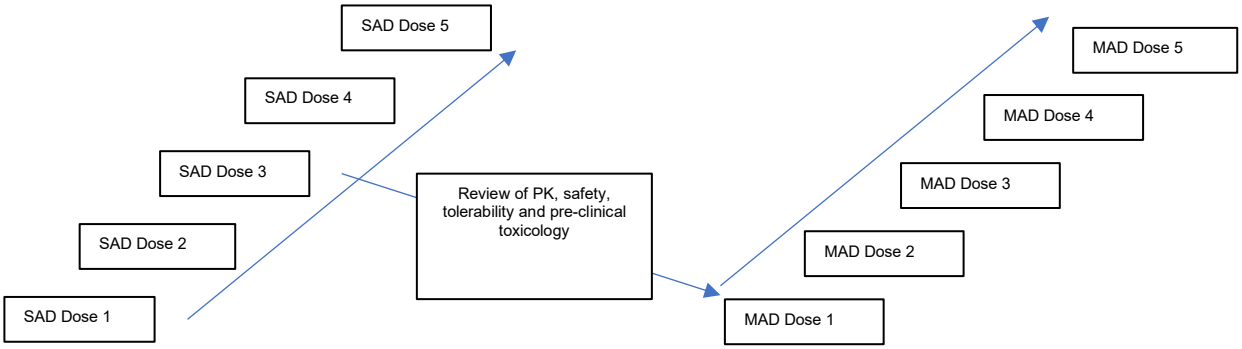
In recent years, various alternative study designs have been used to accelerate Phase 1 development of new medicines and to enable earlier commencement of Phase 1b or Phase 2a studies in the target patient population. Umbrella protocols typically allow for multiple doses to be investigated before completion of the SAD component, as soon as sufficient data are available from the SAD stage to demonstrate safety of the starting dose in the MAD stage. They may also include investigation of food effect at a single dose level (again starting before completion of the SAD stage, assuming sufficient safety data are available from the SAD stage to support the selected dose). Other components may also be included, such as evaluation of PD biomarkers, PK-PD relationship, population differences (elderly, ethnic groups, gender differences), different drug formulations, and investigation of potential drug-drug interactions. Adaptive Phase 1 protocol designs allow for many aspects of the study to be modified based upon emerging data; by incorporating clear decision points in the protocol, dose levels, cohort sizes, sampling times and other design parameters can be modified without the need for formal protocol amendment (although HREC approval may still be required; see below).

The following figures illustrate umbrella study designs in comparison with conventional SAD-MAD designs:

Traditional or Sequential design



Adaptive / Integrated / Umbrella design



Consideration for HREC Approval

Healthy subjects who volunteer to participate in phase 1 trials receive no therapeutic benefit from the investigational drug and so the risk of harm must be minimal. This overarching principle applies equally to multi-stage phase 1 studies as it does to simpler, single-stage study designs.

For both the sequential and adaptive study designs, the HREC will generally approve all aspects of a multi-stage phase 1 protocol at the time of initial review. Information regarding dosing changes must be provided to the HREC via an amendment in eProtocol (e.g. when progressing from the SAD to the MAD stage). Because of this, Bellberry HRECs do not generally require a caveat to be placed on sequential and adaptive study designs.

Caveats

In exceptional circumstances, the HREC may impose a caveat to indicate certain limitations or restrictions on the progression of the research. For example, if, upon review, the HREC determines that the study does not have adequate DSMB arrangements or stopping rules in place, a caveat may be considered. In these circumstances, specific requirements of the caveat will be outlined in the approval letter. The approval letter will confirm:

- The approval of the applicable stage of the study.
- The point at which further information is required before progressing.

For sites that wish to screen in a part of the study that is not yet approved, the site must produce the PICF for the part in question, whether it be at initial review or as an amendment.

If important safety data such as new dose-limiting toxicities emerge during the ongoing SAD stage, this information must be submitted to the HREC for review and should be incorporated into revised PIS documents for all study parts that are still in progress.

References

EMA Guideline on strategies to identify and mitigate risks for first-in-human and early clinical trials with investigational products
ICH guideline M3(R2)