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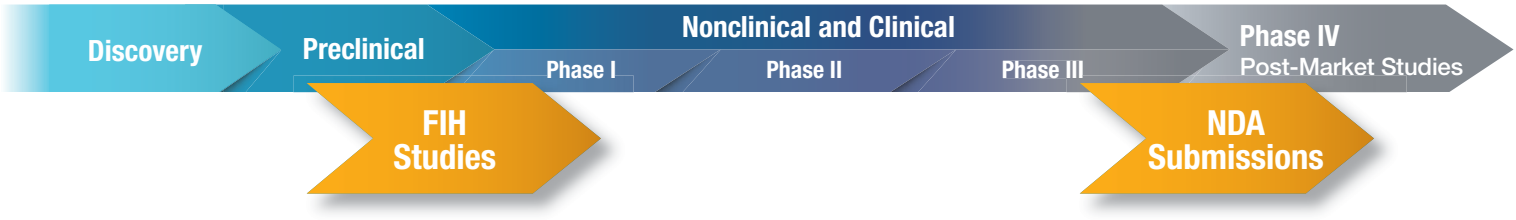
Tackling Early Phase Development Challenges with Effective **FIRST-IN-HUMAN STUDIES**

First-in-human (FIH) trials in the early phases of drug development represent a critical milestone in the approval of medicines. Their purpose is to study the human pharmacology, pharmacokinetics (PK) and pharmacodynamics (PD), tolerability, and safety of an investigational medicinal product (IMP) having already gone through preclinical studies, and to evaluate how the effects translate from animals to humans. They may also include the collection of data on food or drug interactions, different age groups or gender, proof of concept, and relative bioavailability of different formulations. FIH trials allow sponsors to determine potential risks associated to the drug at each step of its development, and determine the safe dose range in the course of its clinical progression.



Both the FDA and the EMA have strict guidelines when it comes to FIH studies. Following two incidents that occurred in the past two decades (Parexel in 2006 and Biotrial in 2016), the EMA revised its **guidance on early FIH clinical trials** to further help stakeholders identify and mitigate risks to ensure the safety of trial participants. These revisions focused mainly on dosing levels and the improvement of strategies in the overall conduct of the clinical trial, including the introduction of sentinel dosing to ensure subject safety.

In recent years, trial protocols have become increasingly complex. In the past, FIH clinical trials consisted of a single ascending dose (SAD) design, which was followed by a multiple ascending dose (MAD) study. Today, most FIH trials combine a number of different study parts (e.g., SAD, MAD, and food effects) which require that the information generated in previous parts be analyzed by the safety review group and integrated into an assessment within a shorter timeframe, prior to making a decision on whether to proceed to the next part.

Designing a Successful FIH Trial

Unexpected toxicity is the primary reason a drug's development is halted or terminated. To maximize the probability that a drug will make it from Phase I to market, sponsors need to ensure the preclinical study results obtained are complete and of the highest quality, and that their clinical study design contains all the vital elements to ensure a successful outcome.

KEY ASPECTS OF FIH TRIAL DESIGNS

Choice of study population

Specific inclusion/exclusion criteria must be clearly identified for both heathy normal volunteers and patient populations.

Number of subjects per cohort

The number of subjects per cohort depends on the variability of both PK and PD parameters and the trial objectives.

Dosing

- **Dose selection:** All available preclinical information should be taken into consideration for the calculation of the starting dose, dose-escalation steps, and maximum exposure. A maximum duration of dosing should be stated in the protocol for every cohort.
- **Route and frequency of administrations:** The route of administration for dosing in humans should be based on the preclinical data, the characteristics of the IMP, and the intended therapeutic use.
- **Dose escalation:** The dose increment between two dose levels should be guided by the dose/exposure-toxicity or the dose/exposure-effect relationship defined in the preclinical studies, and adapted following review of emerging clinical data from previous cohorts.
- **Sequence and interval between dosing of subjects within the same cohort:** There should be an adequate period of time between the administration of treatment to the first subjects in a cohort and the remaining subjects in the cohort to observe for any reactions and adverse events.
- **Transition to next dose increment cohort or next study part:** Administration to the next cohort should not occur before participants in the immediately preceding cohort have been treated, and PK, PD and clinical safety data has been reviewed.

Stopping rules

The protocol should define unambiguous stopping rules which result in an immediate stop to dosing, whether it is temporary or final.

Safety monitoring

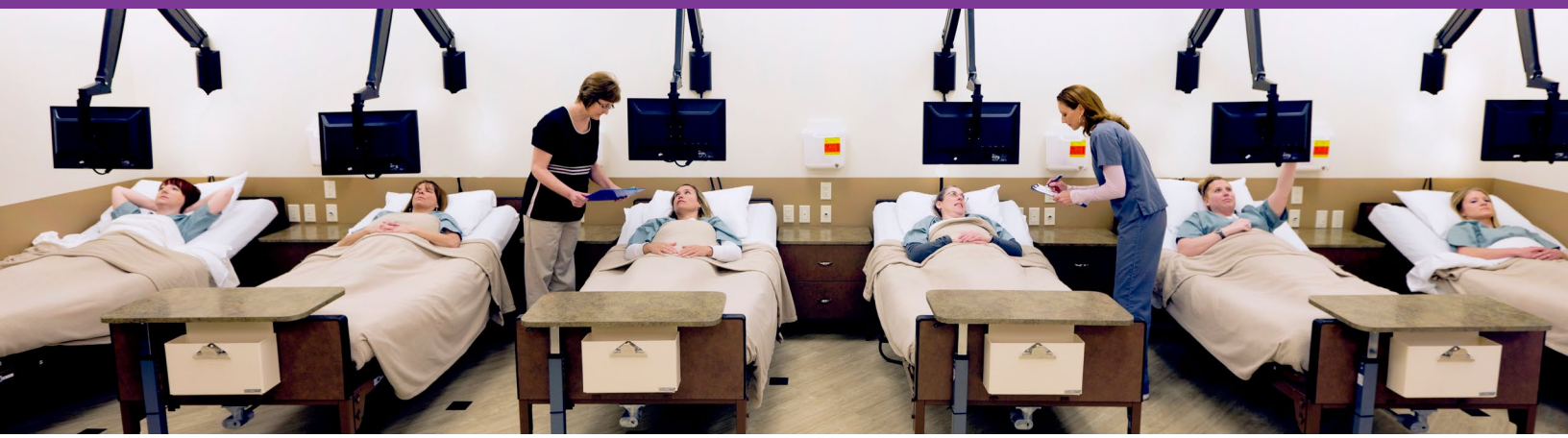
The protocol must have a plan for prompt communication of serious adverse events and suspected unexpected serious adverse reactions (SUSARs) or serious safety-related protocol deviations between the sponsor, all study sites, investigators and trial subjects, particularly in the case of multi-center trials.

Trial sites

Factors contributing to the decision on study site/country selection for FIH trials include where the sponsors operate, regulatory requirements, ease of enrollment, and distribution of target patient population. It is recommended that FIH trials be conducted at a single site. If multiple sites are involved, early interaction with local health authorities is advised.

Inclusion of a placebo

When the study design includes the use of a placebo, it would be appropriate to allow for one subject on active and one on placebo to be dosed simultaneously prior to dosing the remaining subjects in the cohort to minimize the risk of adverse events.



When designing FIH trials, participant safety is of utmost importance since researchers are evaluating the effects of a drug in humans for the first time and do not yet know the effects the medicine will have on them. In addition to the key aspects listed above, appropriate strategies to identify and minimize potential risks must be put in place to ensure participant safety and a successful trial outcome.

Bridging the Gap from Preclinical to Clinical

Altasciences provides an integrated and collaborative approach across our preclinical and clinical units to ensure the successful conduct and outcome of your FIH trials while ensuring the safety of participants, whether they are patients and/or healthy normal volunteers (HNVs). Our early phase clinical facilities employ over **1,000 scientific experts** and have a capacity of over **500 beds** across our **clinical pharmacology units in the U.S. and Canada.** Our diverse locations allow us to run multiple studies simultaneously, give us two different regulatory agency perspectives, and enable us to conduct FIH studies prior to IND submission by using one of our Canadian clinical sites.

Since 2003, we have designed, conducted, analyzed, and reported on over 360 studies for small molecules and biologics, including various dosage forms and high-risk, novel targets. Our clinical pharmacologists are proficient at designing SAD and MAD studies, as well as testing for various effects, such as age, gender, and food. With the latest technologies and diagnostic tools, our toxicologists work with our clinicians to determine the best clinical study monitoring practices for effects observed during the preclinical trials. By leveraging the preclinical data in the design of your FIH studies, we take your programs all the way through to proof of concept (POC).

Our full-service bioanalytical laboratories are staffed by highly skilled analysts with experience that spans a wide spectrum of biological matrices in both animals and humans, and can process over **60,000 study samples per month.** Our large method development team is skilled in developing new methods and/or adapting preclinical ones to clinical to support FIH trials. We have an extensive in-house database of **over** 620 assays **covering 600 molecules,** and we use the latest instrumentation in LC/MS and Ligand Binding to perform our analysis. We also conduct the analysis of PK and biomarkers that allow us to make critical decisions in FIH trials and establish proof of concept, without relying solely on safety data such as dose escalation.

Access to Patient Populations

Our access to special and patient populations is enhanced through long-standing partnerships with an extensive network of investigators, research teams, and hospitals. Thus, Altasciences can deliver faster and better pharmacology data to sponsors looking to obtain data as early as possible in the drug development process. Our medical and clinical operations staff also support study conduct at external hospitals, thereby enabling a Phase I/II setting at sites with direct access to patient populations.

Our robust database of 345,000 participants (including HNVs and patient populations) leads to quick study startups, excellent retention rates, and allows Altasciences to conduct not only FIH studies, but POC studies in Phase I versus Phase II, where a larger number of cohorts would be required. This allows sponsors to secure patient safety, efficacy data, and de-risk their compound as soon as possible, which in turn leads to shorter timelines and reduced costs.

Special and Patient Populations

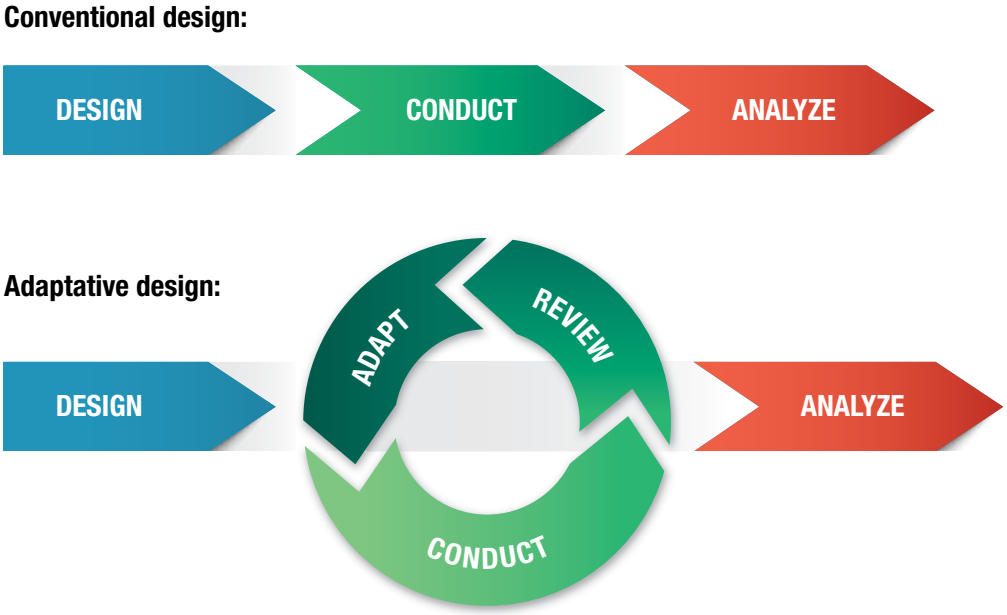
- ADHD
  - Adult
  - Pediatric
  - Adult Workplace Environment (AWE)
  - Analog Classroom
- Allergy
- Anxiety
- Asthma
- Atopic Dermatitis
- Binge Eating Disorder
- Chronic Obstructive
- Pulmonary Disease
- Constipation
- Depression
- Diabetes (Type I and II)
- Dyslipidemia
- Elderly
- Fibromyalgia
- Gastroesophageal Reflux Disease
- Generalized Anxiety Disorder
- Glaucoma
- Gout
- Hepatitis C
- Hypercholesterolemia
- Hypertension
- Lupus
- Migraine
- Non-Alcoholic Fatty Liver Disease (NAFLD)
- Non-Alcoholic Steatohepatitis (NASH)
- Obesity
- Osteoarthritis
- Osteopenia
- Overactive Bladder
- Pain and Inflammation
- Panic Disorder
- Post-Menopausal Women
- Premenstrual Dysphoric Disorder
- Psoriasis
- Restless Legs Syndrome
- Sleep Disorders
- Smoking
- Substance Abuse (recreational and dependent)

Integrating Adaptive Designs in FIH trials

Traditional study designs, particularly in the later stages of drug development, are often criticized for being too rigid, requiring large sample sizes (often thousands of patients), having study timelines that run for years, and costing drug developers millions of dollars until the success or failure rate of the study drug is established. Since 2006, the FDA and EMA have encouraged the development and implementation of adaptive designs to increase trial efficiencies. The FDA released a 2018 guidance entitled *Adaptive Design Clinical Trials for Drug and Biologics* which outlines several examples of possible adaptations that could take place during the course of a trial.

Adaptive trial designs are extremely helpful in improving clinical trial efficiency by identifying the optimal dose earlier on, reducing the sample population size, shortening timelines, and getting drugs to market faster, especially in the case of certain therapeutic areas, such as oncology, where failure rates are high. While conventional trials focus on rapid recruitment and study start up, adaptive trials favor slower patient enrollment as they allow for changes to be made to recruitment based on how the patients are responding to the study drug. By securing specific sub-groups of patients more likely to yield the desired results, and suffer less adverse effects, the overall timeline of the trial can be accelerated.

These flexible trial designs allow researchers to analyze data at interim timepoints throughout the trial, and use the results to make adjustments as the study proceeds, to produce a more positive overall outcome. Expertise with statistical methodology, previous experience with the logistics and conduct of adaptive trials, a team able to work across disciplines, and profound knowledge of regulatory affairs are imperative to running an adaptive trial successfully.



Altasciences has long been designing and implementing flexible adaptive trials in the course of our Phase I/II studies through the use of technologies such as electronic data capture (EDC) and real-time data access, allowing us to change certain aspects of the study during the course of the trial as it moves forward, and hence, help to reduce failure rates in Phase III. If the changes are well outlined in the protocol, they may occur without requiring additional regulatory or IRB approval, leading to fewer protocol amendments.

The latter approach accelerates early stage clinical results for earlier entry into Phase II, and overlaps the SAD, MAD, and food effect parts, allowing for the inclusion of a POC arm in patients. This adaptability also allows for the incorporation of other objectives, such as drug-drug interaction (DDI) and QTC studies.

Common adaptations allowed in FIH adaptive trials include:

Number of cohorts: optional cohorts or stopping confirmed cohorts

Size of cohorts: start initial cohorts with fewer participants and increase when a biological effect is seen

Patient populations: identify groups based on response to the drug, and adjust recruitment of patients accordingly

Doses: adjust doses during the trial to identify the most optimal dose for the Phase III trial

Trial termination: study can be stopped early if interim data analysis shows lack of utility, which can save millions in program cost

Altasciences has designed and conducted adaptive trials for drugs that treat several types of therapeutic indications which have yielded successful results:

1. **Cannabis FIH study for chronic pain** – adaptions based on PK and safety
2. **Immune modulator FIH for an autoimmune disease** – adaptation based on PD
3. **Anti-viral for Hepatitis C infection** – adaptation based on efficacy

Other examples of adaptive trial designs used for our clinical pharmacology studies:

PK endpoint – adjust sample size based on initial cohort

Renal or Hepatic Impaired – start with most severe and stop study if no change is seen

DDI – start with the CYP that has the strongest inhibition or perform a cocktail study and follow up with individual interactions based on results

POC – adjust sample size based on initial cohort

The benefits of adaptive trials often lead to shorter study timelines and reduced drug development costs by providing sponsors with quicker go/no-go decisions, greater safety measures for participants, the ability to determine the optimal dose selection and frequency at a faster pace, fewer protocol amendments, and even the ability to combine multiple protocols into one — all resulting in reduced time-to-market for the drug.

However, if adaptive trials are conducted across global sites, there may be challenges that could affect their outcome. For example, the interim data may not be analyzed as quickly, consistently, or accurately as in a single-site trial. Therefore, it is important to ensure effective site monitoring across all sites when planning an adaptive trial, especially when it involves bioanalytical samples. Standards of care also vary from one country to another, making it pivotal to understand the differences in patients from different regions and how they may impact the results of the trial. Regulatory considerations can also vary. During the course of your adaptive trials, Altasciences' regulatory team is always on hand to ensure the integrity and quality of our scientific data is maintained at the highest standards, and that our clinical study protocols and designs adhere to both FDA and EMA guidelines.

ALTASCIENCES' CASE STUDY:

A Single-Center, Double-Blind, Placebo-Controlled, Randomized, Adaptive, FIH Study to Assess Safety, Tolerability, Pharmacokinetics, and Food Effect of Single and Multiple Ascending Doses of a Novel Small Molecule Administered Orally in Healthy Male and Female Subjects

Study Overview

This study was a single-center, randomized, placebo-controlled, double-blind, adaptive, FIH study in healthy subjects. The primary objective was to demonstrate the safety, tolerability, and pharmacokinetics of a novel small molecule compound. The study was conducted in two parts. The first part consisted of a SAD design (combined with a food effect evaluation) performed at six dose levels. The second part consisted of a MAD design performed at three dose levels. Both parts had adaptive design features allowing for flexibility in doses given, frequency of dosing, and other elements integral to subject safety and risk mitigation.

Study Details

- **Class of Drug:** Small molecule
- **Population Type:** Healthy normal subjects
- **# of Participants:** 90 randomized
- **Time to Recruit Panel at Altasciences:**
  SAD – 8 weeks (FSFV Cohort 1 – LSLV Cohort 6)
  MAD – 8 weeks (FSFV Cohort 1 – LSLV Cohort 3)
- **Study Design:** Single-center, randomized, placebo-controlled, double-blind, adaptive.
- **Key Inclusion Criteria:**
  - Males and females 18 to 55 years old
  - Non or ex-smoker
  - Clinical laboratory values within laboratory's stated normal range
  - No clinically significant diseases captured in Med Hx or evidence of clinically significant findings on the physical examination and/or ECG
- **Key Exclusion Criteria:**
  - Pregnant or breastfeeding
  - Presence or history of significant gastrointestinal, liver, or kidney disease
  - Presence of clinically significant ECG abnormalities at screening
  - Any clinically significant illness in the 28 days prior to the first study drug administration
  - Use of any prescription drugs in the 28 days prior to the first study drug administration that would put into question the status of the subject as healthy (per investigator judgement)
- **Services Provided:** Clinical and supporting research services (project management, medical writing, data management, and statistics)

Study Purpose

To investigate the safety, tolerability, and pharmacokinetic profile of a novel small molecule compound, when administered orally at ascending dose levels as a single dose in the absence and presence of a high-fat meal, and after multiple doses.

Methods

In Part A (SAD), 10 subjects were randomized in each of the 6 ascending dose cohorts to receive either one oral dose of the study compound or matching placebo in a 8:2 ratio. A sentinel group of 2 subjects (assigned 1:1 to study compound or placebo) was dosed at least 1 day prior to dosing the remaining subjects in each cohort. All subjects were confined at our clinical research unit for 48 hours after dosing. Dosing between cohorts was separated by at least 7 calendar days in order for a blinded safety data review to be performed by the Safety Review Committee (SRC). The food effect evaluation was conducted in the third cohort after a 10-day washout period, as decided by the SRC.

In Part B (MAD), 10 subjects were randomized in a similar fashion to Part A, in each of the 3 ascending dose cohorts. Each subject was dosed the assigned treatment twice daily for 7 consecutive days. All subjects were confined for 48 hours after the last study drug administration, and discharged on Day 9.

In both parts of the study, dose stopping and study stopping rules were established *a priori* and followed by the SRC to ensure subject safety. In addition, adaptive features, including allowance of dose adjustments, maximum dose allowed, and number of dose cohorts allowed in each part of the study, were defined to allow informed decision making on emerging clinical data.

Conclusions

The compound was shown to be safe and well tolerated up to 1200mg under single-dose conditions and up to 400 mg under twice daily-dose conditions. The adaptive design allowed doses to be adjusted as data was made available. The incidence of treatment-emergent adverse events was comparable to placebo and most adverse events were mild in severity. This FIH study demonstrated the compound to be a safe drug candidate at the doses evaluated and has continued to the next phase in drug development.

THE FINAL STEP: CHOOSING THE RIGHT CRO

One of the most pivotal steps in the course of drug development is the FIH trial. When selecting a CRO partner, it is paramount to seek one that can ensure participant safety while prioritizing science and the collection of accurate clinical data. They need to have the required expertise, a strong project management team, and the operational and technological capabilities to implement adaptive trial designs whenever possible. An added benefit would be to partner with a CRO, such as Altasciences, that has in-depth experience with both preclinical and clinical operations, that allows you to work with a single, integrated CRO that can carry your early phase trials from lead candidate selection to preclinical testing to proof of concept, seamlessly across disciplines, and in the most time- and cost-efficient way possible.

ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.

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