Listen to a recording of this issue

The Altascientist
SCIENTIFIC JOURNAL
ISSUE NO. 25

FLEXIBILITY IN PHASE I STUDY TIMING

The structure of an early phase drug development pathway is not set in stone. In fact, certain studies that are generally considered Phase I do not have to be conducted before Phase II commences. Conversely, some studies that are typically done in Phase II can be advanced into a Phase I combined protocol to have access to key data earlier in the program. Early Phase I studies have become increasingly complex, in order to gather comprehensive data related to safety and drug pharmacology. Having early access to trial results and data helps inform decisions later in the development journey, can support funding opportunities, and help solidify the overall plan around sound data.

Partnering with a CRO team that has the knowledge and experience to design each program according to the sponsors' needs, considering flexibility to perform specific analyses early (in Phase I) or later (Phase II and beyond) is ideal. Experts will incorporate and analyze early signals that point to specialized analyses being included or waived, and the development pathway is structured to maximize efficient timelines and budget.

TIMING OF EARLY AND CLINICAL PHARMACOLOGY STUDIES

Phase I clinical pharmacology studies of an investigational drug are designed mainly to:

- investigate safety and tolerability at a range of doses
  - where possible develop target therapeutic dose range
- characterize the pharmacokinetics (PK) and pharmacodynamics (PD)

Therapeutic exploratory studies are required milestones, while clinical pharmacology studies include both mandatory and conditional studies. Conditional studies need only be conducted where specific safety data must be acquired for regulatory approval. These studies can sometimes be scheduled at different stages of the program, depending on the specifics of the investigational product. In some cases, such studies can be waived with supporting data.

Table 1 below lists some of the most common early phase studies, including timing.

Table 1.

STUDY	TYPE	PROJECT TIMING
Healthy Normal SAD/MAD	Human Pharmacology	Phase I
Healthy Normal Food Effect	Human Pharmacology	Phase I
Patient SAD/MAD	Therapeutic Exploratory	Phase Ib
Drug/Drug Interaction	Human Pharmacology	Phase I or II
Cardiac Assessment	Human Pharmacology	• Early QT in Phase I can lead to waiver in later phase(s) • Thorough QT in Phase II or III
Ethnobridging	Human Pharmacology	Phase I
Human Abuse Potential	Human Pharmacology (specialized assessment)	May be required for certain CNS programs, in Phase I or later. Likely needed for end of Phase II.
Renal/Hepatic Impairment	Human Pharmacology (specialized assessment)	May be required where target patient population is likely to be renally or hepatically impaired, in Phase I, II, or III.
Special Populations	Human Pharmacology (specialized assessment)	May be required where target indications are part of a special population (elderly, pediatric, etc.), in Phase II or III.
Absorption, Distribution, Metabolism and Excretion (ADME)	Human Pharmacology (specialized assessment)	Phase II
Dose Response	Therapeutic Exploratory	Phase II
Proof of Concept (POC)	Therapeutic Exploratory	Phase II

DEVELOPMENT PROGRAM OPTIMIZATION

There are a number of strategies that may be implemented to accelerate a drug development program, and/or to potentially waive certain later-phase studies, such as TQT or special population trials.

Phase I Combined Protocols

A combined protocol, as its name suggests, involves planning for and conducting multiple analyses, or including additional cohorts during a single Phase I study. For example, if there is a need to assess food effect for a small molecule, this can be incorporated into the first-in-human or SAD/MAD study conduct. A patient or special population cohort can be included, to gain a deeper understanding of PK/PD or early proof of concept in those groups at the outset of clinical study. Having this data early allows for more informed go/no-go decisions in the program.

Cardiac assessments can also be advanced, by adding early QT assessment in Phase I. Favorable results could be used to support a waiver of a thorough QT study later in development, saving both time and cost.

Because certain molecules exhibit significant differences in metabolism in Asian populations, a drug that is destined for development in the Asian market could be accelerated by the inclusion of an Asian ethnobridging cohort. A study in Asian subjects at Phase I provides important data for a comprehensive and robust regulatory submission.

Developing a combined protocol, with its different assessments, requires flexible protocol language, clearly defined assessments, and a deep knowledge of the molecule and applicable regulatory guidance. The goal of a combined protocol is to have early access to data, with the intention of eliminating certain clinical pharmacology studies and reducing requests for additional information, and/or to obtain waivers for certain analyses that usually occur later in the program. Such protocols should be developed with the support of experts who have insight on the regulatory environment, as well as a broad understanding of the scientific and clinical considerations that have a measurable impact on the success of a drug development program.

Special Populations

Including a cohort for special populations that are likely to be treated with the investigational drug is another way to strengthen the data collected in Phase I, and optimize the submission package. Typically, this additional cohort would be studied after the conduct of the SAD and MAD cohorts in healthy normal participants. Special populations could include elderly people, pediatric patients, or individuals with a concomitant chronic disease or medication regimen (i.e., diabetes, hypertension, depression, etc.)

Resource Allocation

Decisions regarding acceleration of study timing are frequently influenced by resource availability. Sponsors with several medications in development may opt to balance timelines between those drugs in order to maximize revenue streams, and use funds from approved drugs to fund new discoveries.

When preclinical and early clinical signals do not strongly point to the need for supplemental analysis, sponsors may also choose to wait until later in development to complete those assessments. In such a situation, it can be prudent to wait for the regulatory authorities to specify precisely which additional data is necessary before dedicating resources to specialized assessments.

Resource allocation may also vary depending on whether the same sponsor intends to complete the drug development all the way through to commercialization. Sponsors who intend to sell or license the drug prior to authorization may choose to delay certain trials, allowing the licensee to determine the trajectory and timing of the program.

SCENARIOS

Top-tier drug development partners will take the unique needs of each sponsor and project into account when designing a program. No two programs will be conducted in exactly the same manner, or on the same timeline. In the scenarios below, we demonstrate how a program for the same molecule can be conducted in two different ways. These scenarios are for demonstration purposes only; more options are possible.

The molecules and parameters are fictitious, while the potential program designs are real; assuming there are no special demands from the regulatory bodies and no unequivocal signals from preclinical data that would demand specific timing.

Scenario 1:

- **Sponsor:** Virtual biotech
- **Class of drug:** Small molecule
- **Indication:** Novel analgesic
- **Resource allocation:** Limited budget, released at milestones.
- **Preclinical/other signals:** See table below

TYPE OF STUDY	SIGNAL	STATUS	COMMENTS
*Abuse potential	Evidence of abuse-related adverse events	Required	Mandatory even if signals are present or if mechanism of action is related to drugs with known abuse potential.
*Physical dependence	Unknown	Required	Evaluation may be required if investigational drug is administered chronically.
*Cognitive effects	Weak, inconclusive, strong	Required	May be mandatory if prior data suggests cognitive impairment or safety concerns.
Drug/drug interactions	Weak, inconclusive, strong	Recommended under certain conditions	
Drug/alcohol interactions	Weak, inconclusive, strong	Recommended under certain conditions	
Renal/hepatic impact	Weak, inconclusive, strong	Recommended under certain conditions	

*These analyses cannot be waived for CNS-active drugs, even if the preclinical signals are weak and other evidence indicates low potential/impact.

A) Typical Non-Accelerated Drug Development Program Structure

This structure is designed for the initial discovery sponsor to complete the development program through to market authorization. Studies listed in blue have flexible timing, and have been scheduled here as a "typical, routine" development program.

TYPE	PHASE I	PHASE II	Phase III	Phase IV
Therapeutic confirmatory			1° efficacy	2° efficacy
Therapeutic exploratory	Patient SAD/MAD	POC Dose response		
Human clinical pharmacology	Healthy normal SAD/MAD	DDI, ADME	BA/BE, TQT, Renal/Hepatic	Postmarketing commitments (PMCs)
Specialized assessments		HAL/HAP, Driving		

B) Alternate Drug Development Program Structure

In this version of the program, the initial sponsor has combined certain of the key studies in Phase I, to license the drug after proof of concept. The "flexible" studies, listed in blue, have been scheduled to maximize available data in support of licensing efforts for this fictitious novel analgesic.

TYPE	PHASE I	PHASE II	Phase III	Phase IV
Therapeutic confirmatory			1° efficacy	2° efficacy
Therapeutic exploratory		POC Dose response		
Human clinical pharmacology	Healthy normal SAD/MAD/Food Effect, DDI, Patient Cohort	ADME	BA/BE Renal/Hepatic	PK Special Populations
Specialized assessments	EPQT, Special Population (Elderly), Early Cognitive Assessments		Driving HAL/HAP	

Scenario 2:

- **Sponsor:** Large-scale pharmaceutical
- **Class of drug:** Small molecule
- **Indication:** Cardiology/Pulmonary – Pulmonary arterial hypertension (PAH)
- **Resource allocation:** Flexible budget, available as required.
- **Preclinical/other signals:** See table below

TYPE OF STUDY	SIGNAL	STATUS	COMMENTS
*Abuse potential	Weak	Required	Mandatory even if signals are weak or inconclusive.
*Physical dependence	Weak, inconclusive, strong	Required	
Drug/drug interactions	Weak, inconclusive, strong	Recommended under certain conditions	
Drug/alcohol interactions	Weak, inconclusive, strong	Recommended under certain conditions	
Renal/hepatic impact	Weak, inconclusive, strong	Recommended under certain conditions	

*These analyses cannot be waived for CNS-active drugs, even if the preclinical signals are weak and other evidence indicates low potential/impact.

A) Typical Non-Accelerated Drug Development Program Structure

In this version of the program, the studies are planned in a "typical" fashion, with no specialized assessments scheduled.

TYPE	PHASE I	PHASE II	Phase III	Phase IV
Therapeutic confirmatory			1° efficacy	2° efficacy
Therapeutic exploratory	Patient SAD/MAD	POC Dose response		
Human clinical pharmacology	Healthy normal SAD/MAD	Food effect, DDI, ADME	BA/BE, TQT, Renal/Hepatic	Postmarketing commitments (PMCs)
Specialized assessments				

B) Alternate Drug Development Program Structure

In this version of the development program, food effect has been included in a combined protocol in Phase I. QT assessment has been advanced, in hopes of obtaining a waiver for later-phase cardiac assessments.

TYPE	PHASE I	PHASE II	Phase III	Phase IV
Therapeutic confirmatory			1° efficacy	2° efficacy
Therapeutic exploratory		POC Dose response		
Human clinical pharmacology	SAD/MAD/Food Effect	ADME, DDI	BA/BE Renal/Hepatic	PK Special Populations
Specialized assessments	EPQT, Post-Menopausal Females instead of Healthy Subjects			

SUMMARY

Altasciences has vast expertise and integrated services to help sponsors determine the unique roadmap for their molecule and program parameters. Our Proactive Drug Development platform transforms the traditional outsourcing paradigm by providing you with expertly designed, customized roadmaps that seamlessly bring you from lead candidate selection to clinical proof of concept, and beyond.

Proactive Drug Development accelerates decision-making by providing expert guidance and synchronized early-phase services, which can reduce timelines by up to 40%. The integrated solution drives success with a tailored program that coordinates bioanalytical services, preclinical safety evaluation, formulation development, clinic-ready manufacturing, on-demand clinical pharmacy, and clinical testing to proof of concept, all within one organization. With drug development managed by a single CRO/CDMO partner, several segments of a program can be run in parallel.

Proactive Drug Development provides comprehensive communication plans and expertly designed roadmaps to get you to clinical proof of concept faster. Our unique organizational structure and integrated processes reinforce our ability to anticipate specific program needs. A centralized scheduling system facilitates active timeline management and immediate responses. The synergistic relationship we develop with each client translates into a results-driven exchange of information that maximizes opportunities for success.

ALTASCIENCES' RESOURCES

Webpage

Comprehensive Early Clinical Development Solutions

Fact Sheet

Development Program

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.