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Translating Science to Medicine

Lessons Learned From 50+ Years of First-in-Human Clinical Experience

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INTRODUCTION

Transitioning an experimental drug from preclinical animal models to the clinic is a critical milestone to bringing new medications to the market. The primary goal of a First-in-Human (FIH) clinical study is to evaluate the safety and tolerability of a new investigational product. An important secondary goal is to assess the pharmacokinetic (PK) profile to confirm human exposure is as expected from animal studies and to help link exposure to biomarkers and target efficacy. These early phase clinical studies have undergone a significant evolution, from a basic "feed-and-bleed" model in the 1970's, to more complex and comprehensive study designs currently being developed. By taking advantage of sophisticated technologies, adaptive designs and the application of biomarkers, Sponsors can obtain early signals of efficacy sooner, while gaining a better understanding of their drug's safety profile. Celerion played a critical role in realizing this advancement. Previously known under the name MDS Pharma, and Harris Labs prior to that, Celerion has more than 50 years of early Phase I clinical trial experience. Over these past 5 decades, the regulatory science has made significant advances in trial safety and expanded guidelines to optimize trial efficiency. Therefore, we gathered our top recommendations as well as pitfalls to be weary of during the set-up and conduct of a FIH study.

FIRST-IN-HUMAN STUDY DESIGNS

A standard single (SAD) and multiple (MAD) ascending dose studies explore 5–7 and 3–5 cohorts, respectively. Healthy volunteers are typically enrolled in these early phase trials and can be randomized 2:1 or 3:1 to active drug or placebo. To limit potential drug toxicities, a sentinel group (1 active- and 1 placebo-dosed subjects) is closely monitored over 24–72 hours prior to administering drug to the remaining subjects in a cohort. With safety and tolerability as main priorities, FIH study participants are typically confined to the clinical research unit (CRU) for observation. Regular safety assessments include clinical chemistries, vitals, cardio-monitoring, and capturing any adverse events (AEs), in addition to frequent blood sampling and occasional urine collection for PK evaluation.

DO'S

1. Seeking a TQT Waiver? Add Holter Monitoring

Exposure levels achieved in a SAD/MAD study often reach up to the maximal tolerated dose (MTD), representing the widest range in doses explored during drug development, and thereby providing an excellent opportunity to collect exposure-response cardiodynamic data. The corrected QT (QTc) interval of an electrocardiogram (ECG) is a well-recognized marker of proarrhythmic risk, and can be collected using 12-lead continuous digital ECG recording with a Holter device [1, 2]. Having cardiac liability data in early stages of development allows Sponsors to decide if they want to continue with the drug development, or how to adjust the future monitoring of their drug product based on the results obtained from the concentration-QTc analysis. Alternatively, Sponsors may choose to analyze these results at a later date, and simply store the data until a decision regarding the fate of the drug program has been made. The advantage of collecting QTc data early, is that the results can be applied towards a thorough QT (TQT) waiver, potentially shortening timelines as well as cost savings later in development, as a dedicated TQT study can cost up towards $1-4 million US dollars. In most cases, Holter monitoring in the SAD portion is sufficient. However, adding intensive ECG monitoring in the MAD may need to be considered in the following cases: MTD or supratherapeutic dose was not achieved in the SAD, the drug/metabolite suggests accumulation and displays a non-linear or time-dependent PK profile. One important consideration for this approach is that an extra day of baseline Holter ECG collection is required, necessitating additional staff support for data collection. For design setup and tips, read: Best Practices for Evaluating Clinical Proarrhythmia Risk in Early Drug Development.

2. Hungry for More! Consider a Food Effect (FE) Cohort

The SAD study also offers an opportunity to gain early and valuable drug bioavailability information. Food intake can influence drug bioavailability by delaying gastric emptying, stimulating bile flow, altering gastrointestinal pH, increasing splanchnic blood flow, blocking drug transporter proteins (involved in drug uptake), or by interacting (physically or chemically) with dosage formulation [3]. Typically, the investigational product is dosed in a fasted state in a SAD study, unless preclinical findings suggest otherwise or the drug is intended to be administered with food. We propose that one SAD cohort (the expected therapeutic dose) will cross-over to be dosed in a fed condition for PK evaluation after a washout period. Data obtained during this early intervention inform fed/fasting conditions for Phase 2 and 3 studies. In addition, the fed state may also mitigate gastrointestinal AEs, which can improve tolerability for proceeding groups. Typically, a standard high-fat breakfast is served prior to drug administration. However, our on-site registered dieticians can design a specialized meal, if needed.

3. Add Flexibility with Adaptive Dose Escalation Decisions

A flexible and adaptive protocol can help select the next dose level based on safety from previous dose levels. Flexibility can be extended to not just increasing a dose level, but also adjusting the dose down, or repeating a level (see Adaptive Trial Designs blog). We recommend including PK data during dose escalation considerations, especially if the toxicokinetic data shows that PK is more than dose-proportional and significant toxicity was observed. By reviewing PK data, insight into dose-proportionality can be gained early. With bioanalytical laboratories located in Lincoln, NE and Zurich, CH, turn-around time for PK analysis can be accomplished within a week of the dose escalation committee meeting. In some cases, it is also important to consider inclusion of pharmacodynamic (PD) results in dose escalation decisions (e.g. target engagement). Celexus® is Celerion's proprietary, secure web-based client port that provides real-time study information. Clinical chemistries, vitals, ECG, AEs and PK can all be reviewed in a blinded matter as data is collected. This enables faster assessment of trends and identification of potential safety signals, as well as a user-friendly platform for dose escalation meetings.

4. The Value of Biomarkers

The nature of a MAD study, with multiple doses over several days or weeks, offers an opportunity to obtain early signals of efficacy or target engagement (see Box 1). Our CRUs have extensive experience with tissue and specimen collection in healthy volunteers or patient panels including skin-, adipose-, muscle-, colon-, and liver-biopsied tissues; as well as saliva, sputum, bronchoalveolar lavage (BAL), urine, feces, semen, and cerebrospinal fluid (CSF) collection. Our bioanalytical lab offers a robust list of validated biomarkers, plus applies a tiered approach for novel biomarker validation depending on the context of use. In addition, the bioanalytical lab in Lincoln, NE is co-located with the CPU, where samples can be collected for immediate processing. This is particularly helpful for peripheral blood mononuclear cell (PBMC) processing and immuno-assays as described in the webinar: Clinical and Bioanalytical Aspects of Immune Monitoring via ELISpot.

Box 1: Examples of Mechanism-of-Action Biomarkers

- **Leukotriene A4 hydrolase inhibition:** Assessment of the inflammatory mediator leukotriene B4 as a biomarker in sputum samples from people with cystic fibrosis [4]
- **Nuclear factor kappa B (NF-κB) inhibition**: Lipopolysaccharide (LPS)-stimulated blood samples to assess NF-kB activity [5]
- **PDE4 inhibition**: Tumor necrosis factor alpha (TNFα) levels in sputum and LPS-stimulated blood [6]
- **Glucagon receptor antagonist:** Oral glucose tolerance test and fasting plasma glucagon, glucagon-like peptide (GLP-1) and insulin [7]
- **Fatty acid synthase inhibition:** *De novo* lipogenesis assessment [8, 9]
- **Formyl peptide receptor agonist:** LPS challenge test [10]

5. Consider a Multi-Part Study

We often assist Sponsors in developing a comprehensive, multi-part FIH study comprising of SAD, FE, MAD and a small proof-of-concept study arm. We find that early patient data can be integral to advancing a program forward. Other "add-on" cohorts can include older adults or a drug-drug interaction assessment. The advantage of combining all study parts under one protocol is that it provides a clear development path. In some cases, study part conduct can occur in parallel to reduce overall timelines, and offers a continuous study team for seamless development.

DON'T

1. No Need to Wait for Finished GMP Drug Product

For a quick and cost-effective study start, our on-site pharmacists offer drug compounding, omitting the need to have a finished GMP product prior to initiating a FIH study. With recent upgrades, our pharmacies have USP <797> compliant clean rooms and individual suites that are USP <795> and <800> compliant for complex extemporaneous compounding of sterile and non-sterile investigational products. An additional advantage of this pharmacy service is the ability to support intermediate dose levels for adaptive trials as well as smaller doses than the available strength when safety assessments suggest a lower dose should be considered. These formulation changes can be done within our Pharmacy suites, without the need to work with multiple vendors. Hear more from our Pharmacist: Onsite Pharmacy Compounding for Your Phase 1 Clinical Study.

2. Don't Always Assume NOAEL When Determining Starting Dose

There are several approaches to determining the first-time in human starting dose of a new investigational product. The 'dose factor' method is an empirical approach using preclinical data to determine the No Observed Adverse Effect Level (NOAEL) and then a human equivalent dose (HED) is applied as an arbitrary safety factor. This technique is easy to calculate and generally has a good safety record. However, retrospective investigations into the BIA 10-2474 and TGN1412 disasters revealed that NOAEL overestimated a safe starting dose (reviewed in [11]). In these instances, a PK-guided approach such as Minimal Anticipated Biological Effect Level (MABEL) or pharmacological active dose (PAD) that accounts for drug activity would have resulted in starting doses that were magnitudes lower than actually studied. Moreover, the NOAEL approach may lead to a starting dose that overshoots the PAD or the predicted efficacy dose based on animal models, and in this case a lower starting dose may be planned. In addition, the planned dose levels can be bracketed around the PAD or predicted efficacy dose or concentrations and provide more useful PK and PD data [12]. Typically, MABEL or PAD are applied for high-risk candidates and immune system targets. Other approaches include PK or PK/PD modeling to establish the starting dose, or if a drug with a similar mechanism of action is already approved, the marketed dose can be investigated [13].

3. Don't Exclude Women

For the majority of new investigational products, the anticipated target population will include women. Therefore, (healthy) women should not be excluded from early studies exploring the PK (and PD) of new drugs in development to ensure that clinical trials adequately account for gender-specific differences. While relatively little is known about a drug's bioavailability and safety during the early development phase, new investigational products can be administered to women of non-childbearing potential (WONCBP) to mitigate a potential teratogenic risk. WONCBP are defined as having undergone a sterilization procedure (such as hysteroscopic sterilization, bilateral tubal ligation, bilateral salpingectomy, hysterectomy or bilateral oophorectomy) or as being postmenopausal as confirmed by follicle stimulating hormone blood test. In certain circumstances, women of childbearing potential (WOCBP) may participate in Phase 1 studies if highly effective contraceptive measures are employed. Pregnancy testing should occur during treatment and at the end of systemic exposure. In addition, lactating women should be excluded from such studies. Investigational products with a negative preclinical reproductive toxicity finding, topical drugs or drugs with a localized site of action may also consider the inclusion of WOCBP. Men participating in a clinical trial should also take steps to avoid impregnating their partner and should agree to not donate sperm during and after dosing [14, 15].

4. Avoid Vague Stopping Rules

Dose escalation and study stopping rules are a key part of study risk mitigation and represent a set of safety criteria that indicate when a trial should be suspended, or when a cohort or individual subject should halt drug administration. These criteria often consist of meeting a number of significant AEs or any serious adverse event (SAE). Safety stopping rules should be robust, easily understandable and effective for decision-making. The European Medicines Agency (EMA) recommends clearly defining when the following events should occur: trial termination, stopping of a cohort, stopping of an individual subject, and progression to the next step or escalation of the dose [16]. Safety dose escalation and study stopping rule scenarios could include halting subject dosing or trial enrollment until toxicity data can be further studied; addition of subjects or cohorts (without exposing to higher doses) to fully characterize AE data; or implementation of smaller dose increases between dose cohorts. Another option may exclude participants with characteristics thought to be more at-risk for a particular AE [17]. The ICH guidelines also indicate that Sponsors should provide a list of acceptable (and known) toxicities that if observed within specific parameters do not alter participant enrollment or dosing [17].

CONCLUSION

Safety and tolerability are the primary goal of a Phase 1 FIH study, however, an optimized study design can also provide early signals of efficacy and bioavailability. With more than 50 years of clinical trial conduct experience, Celerion has the knowledge and expertise to support your FIH study.

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