

De-Risking FIH: *Integrated Strategies for Rapid Proof-of-Concept*

The transition from preclinical to clinical testing is a pivotal moment in drug development. It's also one of the most challenging development milestones, beset by unknown risks, unexpected data and potential regulatory hurdles to overcome. Therefore, proper planning for first-in-human (FIH) studies is critical, since missteps in trial design, CMC, or regulatory planning can cost millions and stall drug development timelines.

Accordingly, it is important to apply practical strategies proven to move molecules efficiently through early clinical assessment, including innovative single ascending dose/multiple ascending dose (SAD/MAD) designs, diverse patient recruitment tactics and fundamentally sound CMC approaches. Doing so can help drug developers avoid common development pitfalls and confidently pursue a fast-tracked path to proof-of-concept (PoC) validation.

How Current Industry Trends Impact R&D Funding

Biotech's funding challenges and currently downward trend in investment necessitate speedy, de-risked early-stage development. Citing data from FactSet, analysts from investment bank Jefferies stated that recent U.S. policies 'aimed at gutting the agencies responsible for conducting and regulating drug research,' have 'exacerbated,' funding challenges by diminishing investor confidence in industry. Additionally, fuelled in part by advances in AI and machine learning, more compound candidates are emerging out of drug discovery, creating more competition for already limited R&D funding. This paradigm forces sponsors to be more selective in the early stages of development, so they do not advance compounds that show limited promise of success – a task that is already challenging due to increasingly complex compounds often beset by formulation challenges, such as poor solubility resulting in suboptimal exposure. However, this approach has contributed to a decline in R&D productivity, despite constantly rising costs associated with drug development.

A 2010 publication exploring the R&D productivity/rising costs dynamic highlighted the high rate of attrition during Phase 2 of development. The researchers stated that only 34% of compounds that enter Phase 2 ever progress to Phase 3. As the focus of Phase 2 is efficacy, these findings reinforce the need to incorporate PoC assessments that examine signals of efficacy earlier in development, enabling quicker wins and faster fails. Subsequent studies have reinforced the 2010 publication's findings.

Thus, it is imperative that drug developers' de-risk and streamline decision-making as well as critical activities during Phase 1. To achieve these goals, developers need to secure conclusive data that supports fundraising and design FIH trial protocols that deliver those data on multiple fronts. Also, it is important to trim the time between the various activities involved in transitioning a molecule from preclinical testing into the clinic. This includes reducing the white space between the drug product development and manufacture (CDMO activities) and clinical dosing (CRO activities).

Enhance FIH Study Design to Bolster Phase 2 Data

An increasingly common way to enable more robust data generation

and time-savings throughout Phase 1 research is the application of hybrid approaches that tighten the gap between Phase 1 and Phase 2. In practice, this strategy comprises an effective FIH study design with meticulous attention to basic considerations, an understanding of options that could expand or enhance the data generated and, when possible, the inclusion of patients in FIH. Initial FIH trial planning considerations include:

- **Consideration of the drug candidate properties** to drive an appropriate formulation strategy for the FIH study and subsequent patient trials.
- **Regulatory and geographic factors** that must align with the developer's go-to-market strategy.
- **Preclinical data** to guide numerous FIH trial decisions, such as starting dose and exposure cap.
- **Safety monitoring** concerns, including whether sentinel dosing will be used and which stopping criteria will be followed.
- **Dose escalation pattern** decisions, including the size of dose escalation steps and how SAD/MAD are interwoven (i.e., sequential or overlapping).
- **Adaptive design approaches** to save time and avoid costly protocol amendments by adding predefined options to the original protocol submission that allow for adjustments as the trial progresses.
- **Molecule specifics** to ensure an appropriate FIH trial design, as the fundamental differences between small molecules and biologics require distinct strategic approaches.

In addition to basic FIH study considerations, trial enhancement options should be applied wherever possible. These options include:

- **Food effect evaluation**, which has essentially become a standard inclusion in modern FIH trials, either incorporated into the SAD or as a stand-alone cohort conducted in parallel with the MAD.
- **QT data collection** to help drug developers collect those data early and potentially avoid running a thorough QT (TQT) study later in development (i.e., receiving a QT waiver).
- **Pharmacokinetics (PK)** in different populations to address differences in gender, ethnicity, and age early in development.
- **Dosage form selection**, as it may be appropriate to use a fit-for-purpose drug product for the initial FIH study but then incorporate formulation flexibility to bridge to an optimised drug product for patient cohorts.
- **Pharmacodynamics (PD) and early data collection** in healthy volunteers to support earlier proof of mechanism of action (MoA). In such cases, it may even be feasible to add a patient cohort to the FIH trial to collect those PD data, providing an opportunity to see early efficacy data as well.
- **Molecule and therapeutic area-specific data**, allowing for the capture of valuable information even when not strictly necessary to support specific clinical endpoints.

Figure 1 combines all these elements, illustrating a complete FIH trial with potential enhancements. The left side of the graphic shows a standard SAD/MAD design, as well as a Holter assessment edit for QT data collections. The right side of the graphic shows enhancements for the trial, including drug-drug interaction (DDI) assessments

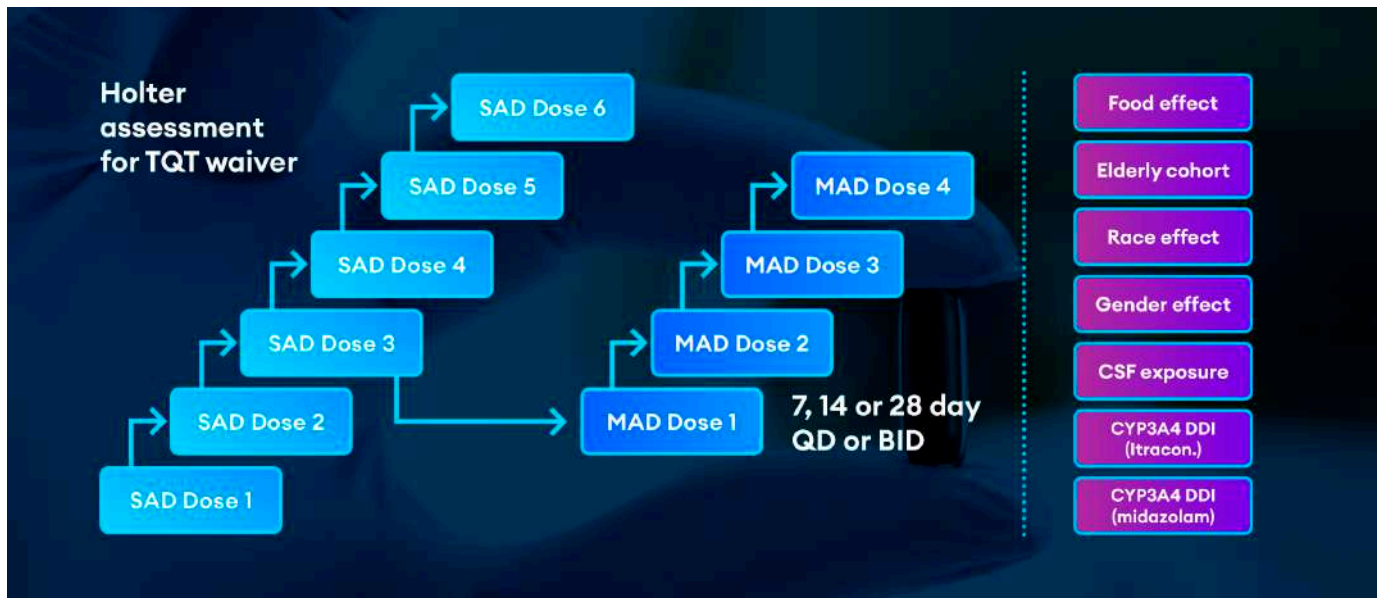


Figure 1

for itraconazole and midazolam. Notably, this example does not include collection of any biomarkers, PD, patient data or formulation assessments.


Additionally, several different strategies can be applied or combined to include patients in early clinical studies. The most straightforward approach is direct advertising, which is most effective for prominent indications like obesity and hypertension. However, for niche therapeutic areas, drug developers may find greater success by partnering with a CRO that specialises in those specific indications. Similarly, academic collaborations can help drug developers identify early clinical trial patients for indications in, for example, rare disease. Once those patients are identified, they can be brought to a Quotient clinic location for dosing and early trial activities, or study activities can be conducted at the patient site under Quotient project management and oversight – depending on the specific circumstances and patient population.


Case Example: Accelerating Through FIH To PoC


Quotient Sciences recently helped a customer navigate a new molecular entity for hereditary angioedema (HAE) through early clinical trials. As an orphan indication, patient recruitment for an HAE trial was a known challenge. To overcome this, we worked with the customer to build a program which facilitated the rapid progression of FIH assessment in healthy volunteers followed by a seamless transition into patients. The study comprised three components: SAD and MAD conducted in healthy volunteers under a single protocol and then dosing of HAE patients under a separate protocol.


The entire program was underpinned by a flexible manufacturing strategy, which enabled the FIH study to start quickly. Because of the small HAE patient numbers and difficulty in enrolment, the manufacturing supply chain needed to be capable of delivering capsule formulations for the patients in real time. In this case, a manufacturing

Phase 1 healthy volunteers to initial patient trial

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Molecule Overview
 - New chemical entity
 - Hereditary angioedema (HAE), orphan indication

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Project Scope
 - Integrated healthy volunteer study & real-time adaptive manufacturing to support POC trials

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Development & Manufacturing
 - Capsule formulation manufactured by Quotient for healthy volunteer phase
 - POC product manufactured “on demand” as patients enrolled with 14-day lead time

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Outcome
 - Project initiation to positive POC in 18 months

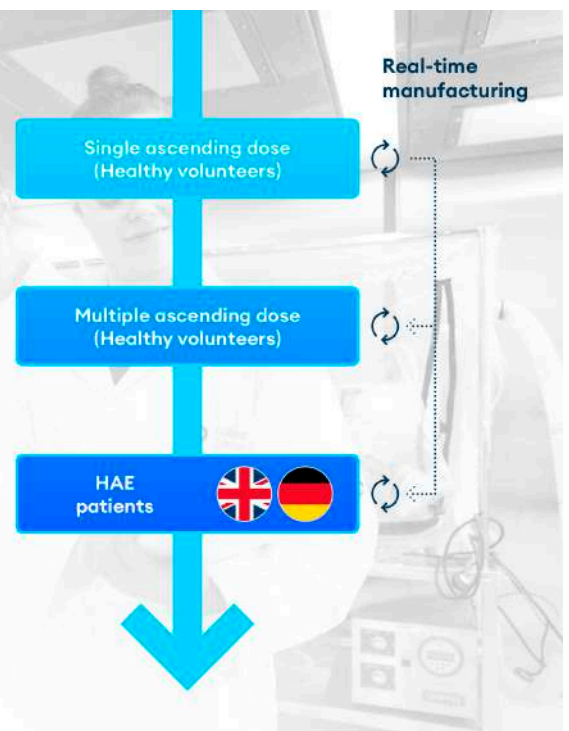


Figure 2



Background

- R552 being developed for autoimmune and inflammatory disorders
- Physicochemical and nonclinical PK suggest poor solubility
- Enhanced formulations to be evaluated in FIH study to achieve desired exposure levels



Integrated Program

- Establish safety tolerability, exposure, efficacy and food effect within a single study
- Evaluate lipidic and SDD formulation alternatives to mitigate risks from potential sub-optimal bioavailability
- Define lead solid oral dosage formulation for patient proof of concept (POC) trial



Outcome

- FIH and Phase II drug product selection
- Seamless supply of SDD tablet for patient POC studies
- Timeline < 15 months

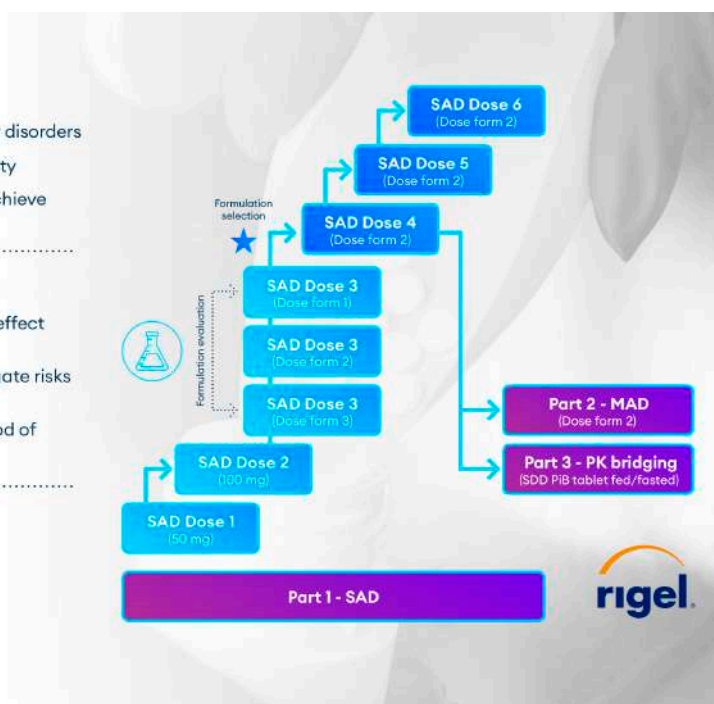


Figure 3

process was established that fulfilled a 14-day lead time for shipment to HAE patients in both the UK and in Germany.

This was accomplished using Translational Pharmaceuticals®, a process by which Quotient seamlessly integrates manufacturing into the clinical supply chain, benefiting project initiation and execution by helping customers bring drugs into the clinic faster and reach decision points earlier (Figure 2).

In this case, Translational Pharmaceuticals was used to support the FIH study and streamlined the process from SAD initiation to positive PoC in patients in just 18 months. This speed is possible because Quotient has simplified its integrated manufacturing and distribution processes to overcome the challenges of on-demand production. This capability is critical because drug developers need fast, reliable supply of the appropriate materials to quickly generate understanding within the Phase 1 human trial and reach FIH clinical endpoints.

Another recent example of Translational Pharmaceuticals' effectiveness involved designing a FIH study to address suboptimal biopharmaceutical properties and preclinical data for a molecule targeting autoimmune and inflammatory disorders. Early in development, the molecule was found to have poor solubility and bioavailability due to its chemical properties. This forced the developer to manage conflicting goals: the need to advance rapidly to Phase 2 while also characterising and overcoming the compound's perceived liabilities.

Quotient's solution started with traditional elements of a SAD/MAD study (Figure 3). The study started dosing with an oral lipid formulation that had previously been used for toxicology studies. However, the lipid could only be given at a top dose of 180 mg in the clinic due to the RDA of the lipidic excipients. The lipid formulation was dosed in SAD 1, 2 and 3. Quotient proactively developed two additional SDD suspension formulations, with the aim to match the lipid exposure and provide linear exposure. These enhanced formulations were strategically integrated into the trial during cohort three. The two enhanced SDD formulations were assessed at the same dose level and in the same subjects as the lipid formulation in SAD cohort 3, after appropriate washout.

The blue star in Figure 3 marks the decision point after SAD dose 3 to designate an SDD formulation to progress, as well as set the dose level for SAD cohort 4. The SDD that was easier to manufacture was selected. The SAD phase continued by using the SDD to dose escalate while simultaneously being dosed in the MAD trial. After the MAD phase, researchers examined the comparative performance of the SDD as a rudimentary powder-in-bottle formulation against a final tablet formulation to bridge PK between the two.

Additionally, a fed/fasted arm was built into that element of the trial to understand potential food effects relevant to the spray dried formulation.

The study progressed quickly, advancing from FIH to the final Phase 2 drug product selection decision point in under 15 months. Further, the post-MAD comparative performance element of the trial enabled Quotient's customer to rapidly move into Phase 2 with an optimised formulation, an SDD tablet.

Accelerating Development Through the Power of Integration

In today's highly competitive industry, there is intense pressure on drug developers to progress studies faster into the clinical development timeline with fewer financial resources. While generating reliable data faster and more cost-effectively is inherently challenging, Quotient's Translational Pharmaceuticals® approach is proven to accelerate development programs by leveraging a purpose-built infrastructure to develop formulations, provide GMP or compounded drug products to deliver quality clinical data. Quotient's approach has evolved to deliver integrated programs under one organisation, steered through a single project management point of contact. This is exemplified by their unique platform, Translational Pharmaceuticals®, which simplifies program design and enhances decision-making on every project while also significantly reducing clients' R&D spend. To learn more, contact the authors and visit www.quotientsciences.com/early-clinical-development.

About Quotient Sciences

Quotient Sciences is a clinical development and manufacturing accelerator, helping biotech and pharma companies bring new medicines to patients faster. With over 35 years of experience and a



track record of success, we provide drug product (CDMO) and clinical (CRO) services across the entire development pathway, including formulation development, clinical pharmacology, clinical trial and commercial product manufacturing. Our proprietary and disruptive platform – “Translational Pharmaceuticals®” – integrates drug product manufacturing and clinical testing to eliminate silos in the drug development process. This in turn reduces costs, improves outcomes and significantly accelerates drug development times.

To learn more, visit www.quotientsciences.com.

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Dr. Andreas Reichl

Dr. Andreas Reichl has over 25 years of pharmaceutical industry experience, featuring a diverse background comprising of a medical doctorate and key positions held across clinical operations, project management and medical science. Andreas’ expertise lies in Clinical Pharmacology, where he has been advising many clients on time and cost-effective study designs, streamlined project execution and reporting. At Quotient Sciences, Andreas holds a Senior Drug Development Consultant position. Prior to his tenure at Quotient, Andreas gained extensive CRO experience at Fortrea, Labcorp Drug Development, Covance and Radiant Research, after having spent two years in academia (at University of Florida).



Dr. Kevin Schaab

Dr. Kevin Schaab has over 25 years of experience in helping develop innovative pharmaceutical therapies, with significant experience in roles spanning pharmaceutical sciences (CMC), non-clinical development, FIH to PoC clinical studies and business development. At Quotient Sciences, Kevin is a member of the drug development consultancy team and is responsible for working with our internal teams to help design and deliver early phase programs along with customer teams. Kevin holds a PhD in Chemistry from the Florida State University, a Master’s degree in Business Administration from San Diego State University, and a Bachelor of Science degree in Chemistry from the University of Cincinnati.

