PHASE I HYBRID TRIALS WHITE PAPER

A guide to successful planning and execution.

Contributors

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Phase I hybrid trials are early clinical studies combining both healthy normal volunteers (HNVs) and patients from the target indication in one protocol. These trials can be extraordinarily valuable, as they can deliver important insights regarding a drug's pharmacodynamic (PD) effects and therapeutic potential at a very early stage in development. Traditionally, HNV and patient populations were enrolled in sequential studies, referenced as Phase Ia (including HNVs) and Phase Ib (including patients), respectively.

Given that our industry has witnessed a steadily increasing interest in these types of combined trials over the past three to five years, this white paper provides an overview of hybrid trial background and feasibility, and discusses considerations around potential value, study design options, biomarker strategies and regulatory aspects with a few case studies to illustrate the successful execution of hybrid studies.

Evolving early clinical development

In certain ways, there is nothing new about conducting Phase I trials in patients. Where drug candidates are cytotoxic or highly immunosuppressive, for example, it would be unethical to expose HNVs to such drugs. Thus, most early-stage oncology studies have been conducted in patient populations. However, over the past decade the way in which most early clinical development trials that would normally be conducted in HNVs have been designed and executed has changed significantly. Historically, a stepwise approach was taken where each study had one primary focus that had to be completed before the next study was started. Now, we see a more parallel, or at least overlapping, approach where multiple objectives are included in a single protocol, resulting in increased trial complexity.[1] A major driver behind this development can be attributed to a desire to generate PD data earlier, which can help prioritize more promising pipeline candidates and also may dramatically affect the net present value of an early-stage asset.

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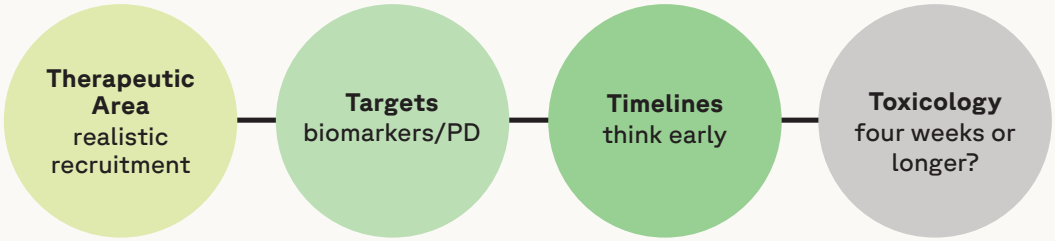
Traditional HNV trials still represent the majority of Phase I trials – and while this is not likely to change, adding patient cohorts within these programs has become increasingly common. Potentially shortening timelines, providing confidence in the asset and the rising costs for drug development, are the main drivers that encourage companies to consider hybrid trials. Lack of efficacy remains the most important reason for failure in Phase II[2], therefore, it makes sense to look at the PD response and mechanism of action earlier. While this sometimes is possible in healthy volunteers, in most cases these endpoints are best evaluated in the target patient population.

Sponsors must approach hybrid trials in Phase I with some caution and strategic considerations. The saying of "one size does not fit all" is particularly true for hybrid trials and sponsors should carefully consider the pros and cons of such an approach to ensure this is the correct route for their molecule. Simply put: will a hybrid trial add value or detract?

Hybrid trial elements

Hybrid trial planning and design encompasses several intertwined and often fluid elements that must be evaluated to determine if a hybrid trial adds value, as compared to a traditional HNV trial.



Determining the added value of a hybrid trial

Although hybrid trials are not designed to reach conclusions with statistical significance, a signal can provide a degree of confidence. The other and most relevant aspect is that Phase I trials are primarily designed to determine safety, tolerability and attain pharmacokinetic (PK) data; these objectives should always remain the primary focus of the trial.

Beyond the limited sample size, demonstrating a potential PD signal remains exploratory in Phase I due to the shorter duration of dosing compared to later stage trials. Dosing duration cannot exceed the duration of Good Laboratory Practice (GLP) toxicology studies, which is often limited to 28 days. Therefore, adding exploratory endpoints to the standard safety and PK assessments – such as biomarkers to evaluate parameters related to mechanism of action, target engagement or PD signals – are important to consider early in designing hybrid trials and maximizing the value gained from incorporating patients.

Timelines are another important factor to consider regardless of whether a sponsor is performing a hybrid study. The overarching consideration starts with a sponsor's overall drug development timeline. They must evaluate if adding a patient cohort will advance the asset within the original timeline and increase value or if this addition could prolong the timeline and potentially impact the overall development strategy. The whole premise of the Phase I space centers on agility and attainment of crucial data to move an asset forward quickly, minimizing time to initiation of Phase II and beyond. Therefore, the consideration of undertaking a hybrid trial in Phase I should be debated early on and integrated into the overall drug development timeline.

Certain indications such as rare and orphan diseases and common but more complex chronic conditions, do fit a hybrid model particularly well. This can be attributed to the challenges in recruitment for these indications in Phase II trials, which are often costly, lengthy and, therefore, require a multi-geography/multi-site approach. In these areas, a hybrid trial can add real value, especially for smaller companies facing funding constraints, since in an ideal scenario, strong PD/efficacy data from a hybrid trial may justify omitting Phase IIa and moving straight into Phase IIb, as discussed later in Case Study 2.

It is important to emphasize that the data from Phase I studies should be interpreted with caution due to the small sample size. However, a hybrid approach may provide a degree of reassurance – even if it is only to say the drug was safe and well tolerated in a patient population with some potentially useful PK data – which may assist and inform the Phase II design.

Evaluating hybrid study design options

The study design of Phase I hybrid trials is another very important aspect to consider. The general approach to designing a hybrid trial does not differ from that of conventional healthy subject first-in-human (FIH) trials, including a single ascending dose (SAD) part, followed by a multiple ascending dose (MAD) part. Additional elements may be included, such as a food effect component; beyond these "standard" FIH components, a hybrid trial would also include at least one patient cohort, typically enrolled upon completion of the HNV MAD part.

Hybrid designs could also include more than one patient cohort to allow assessment of dose linearity of PK and PD parameters. Even the entire MAD may be conducted in patients, in lieu of a healthy subject MAD, but this is only feasible if supported by an appropriate scientific and ethical rationale. In this case, patients are exposed to multiple doses, when safety and tolerability in HNV subjects is based on SAD data only. If there is uncertainty with this approach, a compromise may be to run just one MAD cohort in HNVs to ensure human safety of a multiple dosing regimen, before moving into patients.

Regardless of using one or multiple patient cohorts, sponsors must consider the dosing duration in these patient cohorts. As discussed earlier, the purpose of including patient cohorts is to have a first look at potential PD signals, such as biomarkers associated with target engagement or a PD endpoint. Therefore, in most cases, the patient cohort(s) will include a multiple dosing regimen, where the study drug is dosed at least to steady state (SS), and preferably beyond, so that the above endpoints can be assessed at the time of maximized drug effect. Sponsors must keep in mind that drug effect often lags behind the drug's kinetics, i.e. it usually takes longer than attainment of SS for the full drug effect to emerge. It may be feasible for patient cohorts to have longer dosing durations than HNV multiple dosing cohorts – where the focus is primarily on safety and PK – without the need to dose significantly longer than what is needed for SS attainment.

The limiting factor in terms of dosing duration for the patient cohorts, however, are supporting pre-clinical data, in particular GLP toxicology studies. Multiple dosing duration in humans cannot exceed the longest toxicology dosing duration, which typically ranges from two to four weeks, but, in some cases, may be as long as 13 weeks. This timeline is important to keep in mind when planning the toxicology program, and it may be worthwhile to go with longer study durations that will allow for more study design flexibility in early clinical development.

One further consideration for maximizing the data output from hybrid studies is to conduct not only the MAD but also part of the SAD in patients for those compounds where a PD effect can be expected even after a single dose. A study design following this approach may have the lower SAD doses conducted in HNVs and the higher SAD doses (i.e. those with pharmacological activity) in patients. In such a design, however, patients have to be monitored very closely, given that they are exposed to dose levels where safety has not been first established in HNV subjects.

Another operational consideration regarding SAD cohorts in patients relates to recruitment, which may be more challenging unless there is an anticipated therapeutic benefit following a single dose. And finally, enrolling patients into SAD cohorts when there is no expected therapeutic benefit from a single dose may also raise questions around ethics. Consequently, the more common approach has been to limit the inclusion of patient cohorts to the MAD part of Phase I hybrid studies, although there are exceptions.

In cases with strong evidence of single doses yielding PD signals, enrolling patients in both parts of the study will allow for comparison of single versus multiple dose PD data, which may generate useful information for the design of later stage studies. However, if there is any doubt whether or not a single dose will yield a measurable PD response, it may be better to limit PD data collection to the MAD as there is usually a greater likelihood of capturing stronger PD and efficacy signals, for reasons discussed above. Strategically, it actually would be preferable to have no PD data from the SAD than weak or ambiguous PD data that may raise questions or may create doubt in the asset. The main premise behind a hybrid approach is to yield confidence and provide reassurance of a drug's potential for success early on in clinical development, which is best supported by clear and robust data collected in patients of the drug's target indication.

Biomarkers and the value of thinking early

As described in the BIO Industry Analysis report[3], the probability of successful transition from Phase I to regulatory approval for all therapeutic areas is nearly three-fold higher with a predictive biomarker. As it is not always possible to show real therapeutic benefit in a Phase I patient study due to the limited sample size and limited duration of dosing, considering biomarkers will at least enable the ability to detect "potential" PD responses and supplement those efficacy endpoints lacking robustness.

Ideally, such biomarker models and associated assays should be explored, developed and refined during preclinical development, using animal disease models. The applicability of such models to humans may need to be validated in a pilot study before use in the hybrid trial. Incorporating validated biomarkers may assist greatly and add robust and objective exploratory endpoints to a Phase I study. From a regulatory and ethical perspective, a hybrid design that includes biomarkers may also provide reassurance that a company has a science-driven strategy and is attempting to maximize the data output by moving into patients early in clinical development.

There are several case studies where a biomarker-driven approach has led to a complete re-evaluation of a sponsor's overall Phase I strategy and the adoption of a hybrid approach over a traditional Phase I design. This is now becoming common practice and can provide a degree of confidence that a molecule may be impactful in that disease area, despite there being only a short dosing period in these patients. This strategy has been applied in both rare diseases and more common indications, such as NASH and Alzheimer's Disease.

CASE STUDY 1: A biomarker-driven approach in idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a condition with high rates of morbidity and mortality. Preclinical work in animal models identified biomarkers in bronchoalveolar lavage specimens, which were then applied to a human IPF study.

Prior to design and execution of the human trial, an academic assay validation study of the biomarker from bronchoalveolar lavage was performed in patients with IPF. The Phase I program then incorporated these validated bronchoalveolar lavage assays as endpoints to enable some demonstration of response over 28 days of dosing, providing early insight into the drug's mechanism of action.

The additional effort of performing the initial validation study enabled traction with sites and investigators for the actual hybrid design trial and enabled first-time approval by regulators.

The importance of the regulatory environment

When considering a Phase I hybrid design, geography is a key question. Despite an increased prevalence of these trials, not all regulatory environments are comfortable with adding patients early in Phase I FIH studies. Phase I still bears the highest risk in the clinical trial pathway, so both sponsors and regulators must ensure that the well-being of participants is given the highest priority.

For example, the TGN1412 disaster[4] was a harsh reminder of the risks to healthy volunteers. If this molecule had gone into the target patient population with chronic pathology, the outcome could have been even worse. Sponsors must proceed with caution and remain vigilant when conducting any early clinical trial, including hybrid studies. It is useful for sponsors to consider obtaining regulatory feedback early on, for example, in a Pre-Investigational New Drug Application (Pre-IND) meeting if submitting to the U.S. Food and Drug Administration (FDA), or during a discussion with the Medicines and Healthcare Products Regulatory Agency (MHRA) ahead of a Clinical Trial Authorization (CTA) application submission.

Whatever the outcome of such an early regulatory interaction may be, the design also has to be consistent with the guidelines set out by regulatory agencies to mitigate risks to subjects in Phase I. The two main areas of safety vigilance, as with any FIH study, are dose escalation and dose stopping criteria. For the latter, this means criteria for individual subjects and criteria applicable to the entire study. These are the boundaries that need to be predefined in any protocol involving dose escalations regardless of the regulatory environment, and as such have to be adhered to.

A further nuance related to regulatory environments has been the requirement to submit HNV data for interim agency review, in some cases, before being allowed to proceed to dose patients in Phase I. This request is sometimes made in the absence of an obvious scientific/safety rationale, which underlines the general caution around Phase I. Sponsors, therefore, should carefully decide if it is worth pursuing this route as it may ultimately prolong timelines to proceed to Phase II. Consequently, a sponsor should weigh these arguments first, and then select a trial location associated with a regulatory environment that is more familiar and thus comfortable with Phase I hybrid designs.

CASE STUDY 2: Overcoming geographic regulatory challenges

For a molecule targeting patients with moderate to severe psoriasis, the sponsor experienced resistance from the local regulatory agency with using a hybrid approach in Phase I development due to early exposure of patients. The Phase I program was subsequently moved to a location with greater regulatory familiarity with hybrid designs and received authorization. The PD response in patients produced impressive data, which enabled advancement of their asset straight into Phase IIb trials.

Summary

As sponsors attempt to gain an earlier understanding if their drug works in its target indication, the prevalence of Phase I hybrid trials continues to increase. Despite this rising interest in early signals of potential efficacy, however, such studies first and foremost should focus on safety of participants and only involve clearly justified patient cohorts. Understanding that hybrid trials do not supersede the need for HNV trials and that "one size does not fit all," sponsors undertaking this approach should carefully evaluate the potential advantages and risks of conducting a hybrid trial. Planning for a hybrid trial requires aligning the right therapeutic area with the right molecule and the right study design that also needs to align with any applicable regulatory requirements. To potentially optimize their drug development plan with a hybrid trial, sponsors are advised to evaluate their strategy early on in the compound's development timeline, carefully consider a potential hybrid trial's endpoints, and continually monitor its progress to ensure that patient safety is maintained throughout the study at all times.

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References

1. Tufts CSDD (Center for the Study of Drug Development) Impact Reports. *Rising Protocol Complexity is Hindering Study Performance, Cost, and Efficiency.* July/August 2018;20(4). https://csdd.tufts.edu/impact-reports Accessed October 1, 2019.
2. Arrowsmith J, Miller P. *Phase II and Phase III Attrition Rates, 2011-2012*. Nature Reviews Drug Discovery 2013;12:569
3. Biotechnology Innovation Organization (BIO) Industry Analysis Reports. *Clinical Development Success Rates 2006-2015*. https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf Accessed October 1, 2019.
4. Attarwala H. *TGN1412: From Discovery to Disaster.* J Young Pharm. 2010;2(3):332–336. doi:10.4103/0975-1483.66810

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