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Phase 2 to Phase 3 Clinical Trial Transitions: Reasons for Success and Failure in Immunologic Diseases

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Drug discovery and development is a long and costly endeavor with a rather low overall probability of success. The rates of success for the discovery of a clinical development molecule are difficult to calculate accurately because of the diversity of sources of such projects and molecules, including academia and industry. For molecules that enter clinical development, <10% will eventually be approved by health regulatory authorities (1). During the process of clinical development, the highest level of attrition occurs between Phase 2 (Ph2, "early") and Phase 3 (Ph3, "late") with ~70% of projects failing to progress (Figure 1). The editors of JACI wondered what are the reasons for success or failure in this critical phase, with the hope that factors could be identified to improve the success rate and thus the cost of developing medicines. In this article, we provide insights and perspectives from our collective experience focusing on drug development in allergic and immunologic diseases.

The phase 2 to 3 transition has increasingly become a critical step in clinical drug development. This is the time in the life of a project when it will be evaluated with the most critical eye before embarking on an expensive, resource consuming, and risky pivotal Ph3 program. A recent analysis focused on small molecules shows that the three main reasons for a project to be stopped in Ph2 are: lack of efficacy; safety; and portfolio/commercial considerations (2). These findings can be generalized also to biologics, albeit with fewer discontinuations for safety issues. In our experience, these are loose categories and the decision to continue into Ph3 will vary based on many factors including the indication, risk:benefit profile, and company strategy. The definition of success versus failure is not clear-cut, and depends on the way projects are judged. While unexpected safety issues are difficult to control, there are many other reasons for failure. To begin to identify ways to improve phase transitions, we must first identify many of the reasons for a failure of Ph2 to Ph3 transition (Table 1). While incomplete understanding of the biology of the drug target is a risk for failure at any stage of development, many reasons drugs fail in Phase 2 are due to clinical variables. Potential approaches to improving success in Ph2 are shown in Table 2, and discussed below.

Disease Biology. Immunological diseases are often heterogeneous with respect to molecular or phenotypic differences, and defining target biology in the human disease

setting is critical. Ideally the target should be directly linked to the pathogenesis of the disease and it should be known if target modulation is prognostic for or influences clinical outcome in patient subpopulations, including potential safety concerns.

Increased use of human translational research approaches including modeling and simulation, integrated genomics, and biomarkers have been helpful.

Pharmacodynamics. While obvious that achieving adequate drug exposure is important, drug concentrations often cannot be measured at the site of pathology. Biomarkers associated with the target's pathway or target engagement are key to showing proof of mechanism and aiding dose selection. Absence of such biomarkers increases the risk for failure due to lack of efficacy if the target is not adequately engaged (e.g., poor pharmacokinetics, weak potency, insufficient tissue penetration) or the dose range is too low. Alternatively, if the dose range is too high the drug can fail for safety reasons.

Trial Design and Quantitative Endpoints. One of the most troubling and potentially avoidable consequences of a Ph2 failure is that a useful compound is terminated and not further developed because the clinical trial was not appropriately designed. Clinical trial design is not an easy task, balancing high quality data generation with time and cost. It is important to power Phase 2 trials appropriately, ideally with patient stratification, to estimate the true treatment effect size. Eligibility criteria should only include patients with modifiable disease. For example, asthma trials that include patients with mild disease and few prior exacerbations, or fibrosis trials that have patients with end-stage disease, may risk having a negative outcome even if the drug has clinical activity. While disease-modifying, concomitant medications have the potential to blunt or mask efficacy of the compound being tested, direct comparisons to best available standard of care therapies should be incorporated into study designs when possible. Balanced with the need to make quick decisions and avoid over-investing in Ph2, treatment duration should be long enough to detect a positive outcome. Clinical outcome measures for immunological diseases are complex, often lacking precision and reproducibility. Choosing and standardizing the most appropriate outcomes to test is critical. The greatest opportunities for success come when Ph3/registration endpoints are used in Ph2. This is, however, not always possible

especially in trials studying diseases for which no approved drugs exist. Finally, as responses to placebo and standard-of-care can vary between patients and by geographic region, it is important to make sure these sources of variability are understood and controlled. The importance of clinical trial design cannot be underestimated.

Commercial. Because of many reasons including increasing regulatory requirements, payer demand to quantify benefit over standard of care, and commercial valuation, projects may be stopped despite a positive safety and efficacy outcome. Early involvement of and alignment with patients, providers, payers, and internal marketing is beneficial in improving the transition of positive Ph2 trials.

In considering approaches to improve the Ph2 to Ph3 transition, the parameters that define improvement are important. Simply increasing the proportion of drugs that progress from Ph2 to Ph3 is not a productive solution if success rates in costly Ph3 programs are decreased. It is reasonable to conclude that attrition rates in Ph2 should be higher if this reduced the rate of late stage failures. An overall definition of success in the steps leading up through Ph2 studies must optimize the probability of advancing drugs that have the greatest likelihood of being effective and safe, in the shortest possible timeframe, and in the most economically efficient manner. It is balancing these competing demands that is the conundrum of drug development.

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FIGURE LEGENDS

Figure 1. Phase transition success rates for immunologic diseases compared to all indications. Shown in Panel A are the clinical trial phases and key milestones in the drug approval process. Prior to testing of an Investigational New Drug (IND) in humans, relevant regulatory authorities including the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in Europe must approve an IND application. IND testing consists of three phases. Phase 1 clinical trials are generally conducted in healthy volunteers (or for oncology, in cancer patients) to find a safe dose and the most effective way to deliver the drug. Phase 2 studies are designed to determine whether the drug is effective in a disease setting, while continuing to assess safety. Phase 2 trials are usually divided into two components: Ph2a to define a proof of concept that the drug may be beneficial, and Ph2b to find the optimal range of therapeutic doses (dose range finding). Phase 3 (also called registration or pivotal) studies are larger studies testing effectiveness and safety (often being compared to standard treatments), to define the drug's value in clinical practice. After a successful Ph3 program, a New Drug Application (NDA) for small molecules or a Biologic License Application (BLA) for protein and cellular therapeutics is submitted to regulatory authorities for approval (marketing authorization). Panel B shows the phase transition success rates for immunologic (defined as combination of allergy, respiratory and autoimmune; dark blue) compared to all (light blue) indications, occurring between 2006 and 2015 (reanalyzed from Ref 1). Success rates for immunologic indications were: 65.7% for Ph1 to Ph2 (n=484); 30.8% for Ph2 to Ph3 (n=555); 64.9% for Ph3 to NDA/BLA submission (194); and 89.2% for NDA/BLA to approval (n=139). Success rates for all indications were: 63.2% for Ph1 to Ph2 (n=3582); 30.7% for Ph2 to Ph3 (n=3862); 58.1% for Ph3 to NDA/BLA submission (n=1491); and 85.3% for NDA/BLA to approval (n=1050).

Table 1. Reasons for failure in Phase 2.

Variable	Reason for Failure
<i>Drug target and pharmacodynamic biomarkers</i>	Poor understanding of the target biology and target/pathway-associated biomarkers
<i>Disease heterogeneity</i>	Unknown or known interpatient differences in disease not properly controlled, and absence of a predictive biomarker
<i>Dose</i>	Dose range too low or too high
<i>Treatment duration</i>	Treatment duration too short for efficacy
<i>Concomitant medications</i>	Medications that suppress or mask the response to active treatment
<i>Response to placebo or standard-of-care</i>	Imbalance in confounding patient factors between active and control arms Geographical differences in treatment standards
<i>Clinical endpoints</i>	Not consistent or reproducible

Table 2. Steps Prior to and During Ph2 Trials to Improve the Ph2 to Ph3 Success Rate.

Variable	Opportunity for Improvement
<i>Disease Biology</i>	Better understand the contribution of the drug target to disease onset/activity of human vs. animal model disease Characterize the degree to which variation in drug target activity influences clinical outcomes in patient subpopulations
<i>Pharmacology/ Pharmacodynamics</i>	Develop pharmacodynamic markers of drug activity for use in Ph2 More in depth assessment of level of drug exposure at site of pathology (e.g., peripheral blood vs. lung) Explore adequate range of doses to accurately assess efficacy and safety concerns
<i>Trial Design and Quantitative Endpoints</i>	Characterize natural variability of outcome measures in patient populations prior to conducting clinical trials (i.e., to minimize high placebo response rates) Develop surrogate endpoints that accurately link drug target modulation with clinical outcomes Increase duration of study drug administration Employ adaptive study designs that allow efficient modification of drug dosing and outcome assessments during Ph2 Larger sample size Ensure that Ph2 patient population represents the planned Ph3 patient population Assess Ph3 endpoints in Ph2
<i>Commercial</i>	Define competitive efficacy and safety profile needed prior to initiating Ph2

