TRIANGLE INSIGHTS GROUP by mercalis

The Importance of Early Positioning in Drug Development

Introduction

For some, product positioning is reactionary and established largely after data from a pivotal trial is ready. After all, how can a product's positioning be established without knowing how the data stacks up to competitors? While it is true a product's positioning will be constrained by the data submitted to the FDA, early positioning work can reveal opportunities for a novel treatment to differentiate itself from standard of care (SOC) through creative pivotal trial design. What we hope to convey here is that an asset does not need to be all things for all patients to be a success.

Improving upon the SOC's efficacy is not the only way to become a market leader. Instead, as examples, designing a pivotal trial with a distinct dosing schedule, new safety endpoints, or a differentiated trial population are all ways to show additional value and carve out a meaningful share of the market. There is ample research to date showing that even a relative 10% improvement over the SOC's primary endpoint may not be enough to overcome incumbency advantages. Fortunately, conducting positioning research early in clinical development can show many ways to move away from this head-to-head comparison and allow for tailoring of a product to segments not fully served by SOC.

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WHITE PAPER

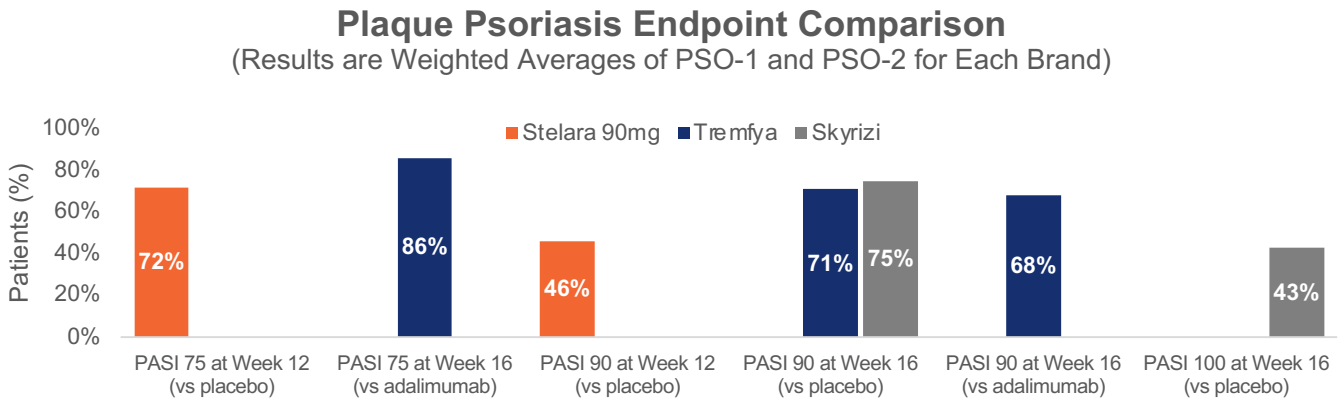
Endpoint Selection

It is well understood in life sciences that minimal therapeutic advance over the SOC does not always guarantee market leadership or commercial success. Incumbency advantages, such as high prescriber awareness and quality market access, can often overshadow a novel entrant's marginal improvement within the same core endpoints. As such, the question companies need to be asking of their development pipeline is not just whether they can beat SOC, but what degree of improvement would be required for meaningful uptake. After POC trials, a program would benefit from endeavoring to conduct endpoint and threshold testing with target prescribers, with the goal of understanding what level of efficacy is required to supplant SOC. If that research suggests a threshold that will be a technical risk to achieve, creating as many opportunities as possible for differentiation can be important. Incorporating additional endpoints can provide the flexibility to "break the tie" if your primary endpoint data is similar or decouple your asset from direct endpoint comparison with the SOC if data falls short of expectations.

Areas for Endpoint Differentiation: Industry Examples

- **Pivotal Endpoint Selection**: In plaque psoriasis, one of Stelara's primary endpoints was the proportion of subjects who achieved at least a 75% reduction in PASI (psoriasis area and severity index) score (PASI 75) from baseline to Week 12. When Tremfya and Skyrizi were being studied, to differentiate from Stelara (and because healthcare providers began expecting it), each utilized "the proportion of subjects who achieved at least a 90% reduction in PASI score (PASI 90) from baseline to Week 16." This alternative endpoint allowed for perceptions of clinical differentiation to existing SOC. **(See chart 1)**

Chart 1.



Source:
EvaluatePharma, accessed October 2024
ClinicalTrials.gov accessed October 2024

- **Day/Week of Measurement:** Opzelura and Zoryve are both approved to treat moderate to severe atopic dermatitis. Opzelura measures its pivotal endpoint at week 4, while Zoryve measures at week 8. Both are topical treatments and utilize very similar pivotal endpoints. However, simply measuring at two different points allows Opzelura to imply higher efficacy (at week 8) and Zorvye to imply faster response (week 4) to counterbalance lower scores. Each has a way to uniquely position and avoid direct comparison against each other despite the fact their data could have been very similar if measured at the same points.
- **Safety Endpoints**: Eliquis, an oral blood thinner, captured all-cause mortality, a safety endpoint not captured in the pivotal trials for Pradaxa or Xarelto which helped provide further differentiation. In some cases, the mere inclusion of an additional safety endpoint can imply heightened safety: "that treatment is safer because they explored safety more deeply than the standard of care."

Put simply, adjusting endpoints to allow for additional areas of differentiation to SOC allows for more flexibility in positioning and the ability to carve out pockets of opportunity. This practice is not without its own risks. Particularly, if prescribers have been conditioned to expect certain endpoints and will perceive new endpoints unfavorably. Early market research can tease out how entrenched expectations are surrounding endpoints; if there is little flexibility in endpoint selection, the subsequent sections of this paper show there are other ways to differentiate.

Route of Administration (ROA) / Dosing Frequency

Intuitively, oral treatments are often more favorable than infused therapeutics and less frequent dosing is preferred over more frequent. However, a deeper exploration of an indication and its unique dynamics frequently reveal these generalities can have exceptions. Is daily oral therapy truly more favorable than a once quarterly injection? Is at-home administration of a subcutaneous therapy (avoiding a visit to the doctor) favorable to patients if they are not comfortable with needles? What benefit is there to a monthly injection if it is in combination with a treatment that requires weekly injection? Putting aside the notion that formulation and dosing can impact the efficacy and safety of a product, each indication presents unique circumstances and warrants thorough exploration to understand administration preferences.

Treatment Administration Factors to Consider:

1. Site of Administration
2. Provider or Patient Administration
3. (If Applicable) Combination Regimen ROA

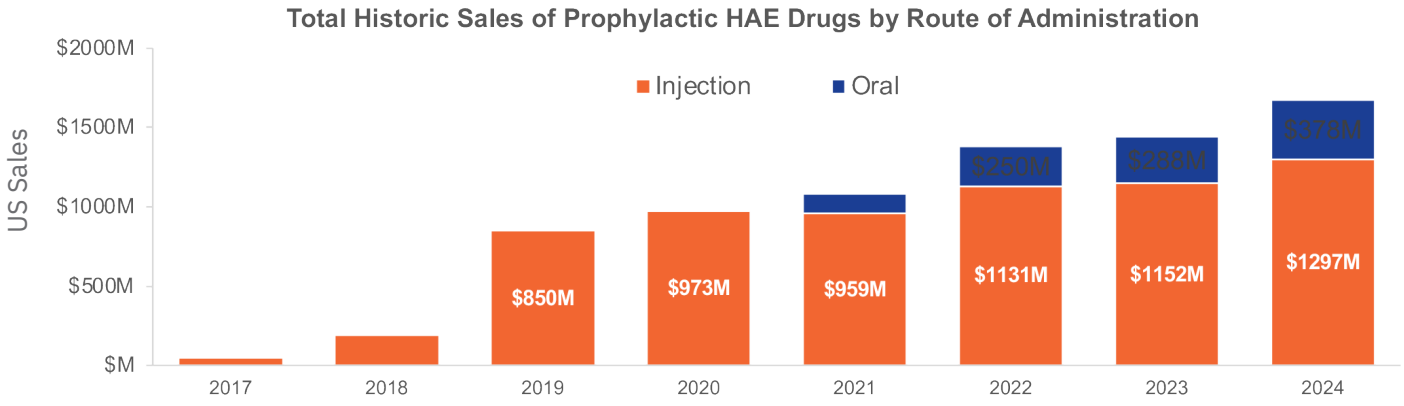
Real World Examples:

- **Combinations with Pebrolizumab**
  - **IV Formulation:** A product with weekly dosing used in combination with pembrolizumab may be perceived unfavorably by prescribers and patients in contrast to pembrolizumab's Q3W (every three weeks) dosing. Given how challenging it can be to arrange for infusions (e.g., patient travel, time away from work and family, scheduling), the weekly dosing of the product implicitly makes the entire combination a Q1W (once weekly) regimen.
  - **Subcutaneous (SQ) Formulation:** If pembrolizumab offers an SQ formulation, infused combination products may be perceived less favorably as somewhat defeating the purpose of switching patients to the SQ formulation.
- **Chronic Treatment of Hereditary Angioedema (HAE):** In HAE, patients generally have a choice between Q2W (every two weeks) injection of Takhzyro or QD (once daily) oral administration of Oraldeyo. At present, each has a place because different patient types fall on different sides of the spectrum in the preferences for oral versus injection (given the frequencies offered). However, pipeline therapies such as Navenibart (STAR-0215) offer the potential for once quarterly or even biannual dosing.

There is an open question surrounding whether QD oral will hold the same positioning in the face of less frequent injection. **(See chart 2)**

In practice, the route of administration and dosing frequency can often be more impactful than a 5-10% relative efficacy improvement over standard of care. Drug developers would do well to take the pulse of prescribers early, as it may reveal improved dosing/ROA are the chief unmet needs within the market.

Chart 2.



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Clinical Trial Population

One often overlooked opportunity for differentiation comes from the composition of the clinical trial population – instead of competing directly with an incumbent, it may be beneficial to attempt to contextualize efficacy in such a way that the incumbent's efficacy is not an absolute measuring stick. We are not speaking so broadly as line of therapy differences, but rather marginal distinctions in study population. A simple example is selecting harder-to-treat patients than were in the incumbent's pivotal trial – "Our product may not outdo the incumbent directly, but we studied our therapy in tougher-to-treat patients; if the incumbent did the same, they may not have gotten as good of results as we have achieved." The challenge, of course, is making sure prescribers draw the conclusions the developer hopes for from the trial population differences. Early target product profile (TPP) testing can reveal that the harder-to-treat patient faces greater unmet need and that prescribers will relax their efficacy expectations if you can target those patients. The challenge, of course, is making sure prescribers draw the conclusions the developer hopes for from the trial population differences.

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Examples of Marginal Trial Population Distinctions

1. **Patient Health:** Across therapeutic areas (TAs) there are well-accepted metrics that correlate with patient health that allow a manufacturer to say, "we studied in a sicker (or healthier) patient population than our competitor":
   a. **Respiratory** – Forced Expiratory Volume (FEV1)
   b. **Oncology** – Performance Status
   c. **Diabetes** – HbA1c
   d. **Various** – hospitalization rate, frequency of exacerbations
2. **Concomitant Treatment:** For depression, the incumbent requires patients to cycle off antidepressants, but an alternative may be to run a trial for which patients continue their antidepressant regimen.

3. **Translating Unmet Need into a New Indication:** Within atopic dermatitis/eczema, body surface area involvement significantly influences treatment selection. For patients with a small area of involvement, a branded topical treatment may be most suitable while for a more diffuse case, systemic therapy may be necessary. However, not all body surfaces are equally treatable. Patients with hand eczema face unique challenges both physiologically and environmentally. As such, we've seen companies developing therapies specifically for chronic hand eczema) as a differentiator/carving out a new sub-market.

Utilizing clinical trial population differences is a good form of risk mitigation. If an asset demonstrates efficacy similar to the standard of care, the manufacturer can point to the fact that the product achieved results in harder-to-treat patients. Whereas, if efficacy falls short of standard of care, it is possible to assert that the results cannot be directly compared to SOC because the trial populations were different. An asset can benefit from this positioning either by being studied in a differentiated population or creating another arm to the trial with a differentiated population.

Choice of Combination Therapy

Particularly in oncology, the choice of combination therapy is one of the most important decisions in clinical development. The choice takes many development variables out of the manufacturer's hands and ties the novel product's success to that of the other treatment within the combination. Of course, the benefit of combining with a marketed therapy is that the product can borrow from the credibility of that asset and "piggyback" on the favorable perceptions HCPs already have for that product. On the other hand, a combination regimen means the novel product can be profoundly impacted just as much by in-class competition as competition affecting the other half of the combination.

As an example, one case study involves a company that developed Product X for liquid tumors to be combined with Product Y (a mature product within the indication). However, in recent years, a new treatment (Product Z) has become the new SOC and a core component of most combination regimens within the indication. After completing a Phase II trial, the company conducted market research that showed if Product X was not also combined with Product Z, overall uptake could be limited. In response, the company is left weighing whether it must run new clinical trials that it may not be able to afford or push the Product X/Y combination into pivotal trials in the interest of time to market. Critically, early HCP research may have revealed the strong preference for Product Z combinations and given the company time to adjust its development approach.

Key Questions to Inform Choice of Combination Therapy:

1. How expensive is the product(s) which is/are being studied as a part of the combination? If priced high, will you be able to price at the level you hope for your own product?
2. How will the planned ROA and dosing schedule mesh with the other products within the combination?
3. How much patent life remains for the other half of the combination and what will be impact of generic/biosimilar entry (or that of competitive treatments)?
4. Does the development pipeline include promising treatments that compete directly with the other portion of the combination? If the other therapy lost its position in the paradigm to a competitor, how would that impact the commercial viability of your overall combination?

Many of these questions can and should be answered as early as possible during clinical development. Otherwise, a manufacturer may be put in the position of running new trials for their asset with another therapy (all while the treatment landscape can continue to evolve), a timely and expensive process that some companies may be unable to endure with existing cash runways and pressures on time to revenue.

Conclusion

To close, there are multiple ways to differentiate a novel therapy and create value outside of strict, direct comparisons to the current SOC on a single efficacy measure. Early research exploring product positioning can create branching roads to success. Instead of one "shot on goal" to exceed the SOC's primary endpoint by a sufficient margin, thoughtful pivotal trial design allows for multiple shots.

Can alternative endpoints be used to further support clinical differentiation? Should a manufacturer invest to match the therapy backbone dosing schedule, or will an alternative route of administration compensate for non-congruent dosing regiments? Are there specific patient segments which could be considered for trial inclusion? Early research to identify lingering unmet needs can show that prescribers are looking to understand new therapies in ways the SOC has yet to show. The key takeaway we hope comes from this paper is that early positioning creates flexibility (risk mitigation) in comparison to reactionary positioning conducted following the conclusion of pivotal trials.

Key Questions to Inform Choice of Combination Therapy:

What is the price range for the other product(s) being studied in the combination? If priced particularly high or low, will that impact the ability to price your own product as planned?

How well will the intended route of administration (ROA) and dosing schedule of your product align with those of the other product(s) in the combination?

How much patent life remains for the other product(s) in the combination, and what impact might generic or biosimilar competition—or that of alternative treatments—have?

Does the development pipeline include treatments that could directly compete with the other product(s) in the combination? If a competitor therapy replaces the other combination product in the treatment paradigm, how might that affect the commercial viability of your combination?

About Mercalis

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