White Paper

Inflection Point: How Clinical Trial Results Impact Biopharma Valuations

Understanding the drivers of value creation to navigate an optimal development path

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Introduction

Developing novel therapies to address unmet patient need is the lifeblood of the biopharmaceutical industry. It is also a capital-intensive and high-stakes endeavour, requiring an estimated $3.1 billion to bring a new therapy to market,[1] with a composite success rate of 11% from phase 1 through regulatory submission.[2]

Clinical trial readouts, therefore, represent major inflection points in this journey, as moments of truth, that resolve uncertainty around an asset's future prospects, including its ultimate potential for revenue generation. Consequently, company valuations respond to clinical trial results — positive and negative — as investors re-calibrate their expectations based on the new information becoming available.[3-6]

In this white paper, we will systematically investigate how clinical trial outcomes impact company valuations and explore the underlying drivers, such as how trial results compare to investors' prior expectations, development phase at readout, therapy area or trial design. We focus on emerging biopharma companies (EBPs), in particular those with <$1 billion market capitalisation, because their valuations are highly responsive to trial results, as most of their value is concentrated in their pipeline which often comprises just a single asset. Unsurprisingly, we found that EBP valuations are much more sensitive to clinical trial readouts, by up to two orders of magnitude, compared to big pharma companies.

Furthermore, we will elaborate on the practical implications of understanding those drivers of value inflection. For example, how such insight may inform strategic decisions and help management teams navigate a company's optimal path that balances value upside vs. incremental clinical risk, such as the optimal timing for exploring partnerships or when to pursue an exit via the M&A route.

Methodology: brief overview

IQVIA performed an event study analysis that quantified the share price reaction to clinical outcomes for more than 2,600 trials from 2017 to 2023.

Our analysis defines the event date as the primary endpoint reported date, i.e., the earliest date of public report of results that addresses the primary endpoints of the trial. Positive and negative outcomes at the primary endpoint reported date were allocated based on the company-reported clinical definition.

A robust statistical model was developed to analyse the change in sponsor company share price at the primary endpoint reported date. The change was calculated as the average at the close prices of two days prior and one day prior to the primary endpoint reported date versus the average at the close prices on the day of the event and the day after.

Sponsor companies and therapeutic areas (TAs) were allocated based on IQVIA official classifications.

Further methodological details are documented in the appendix.

The asymmetry of market response

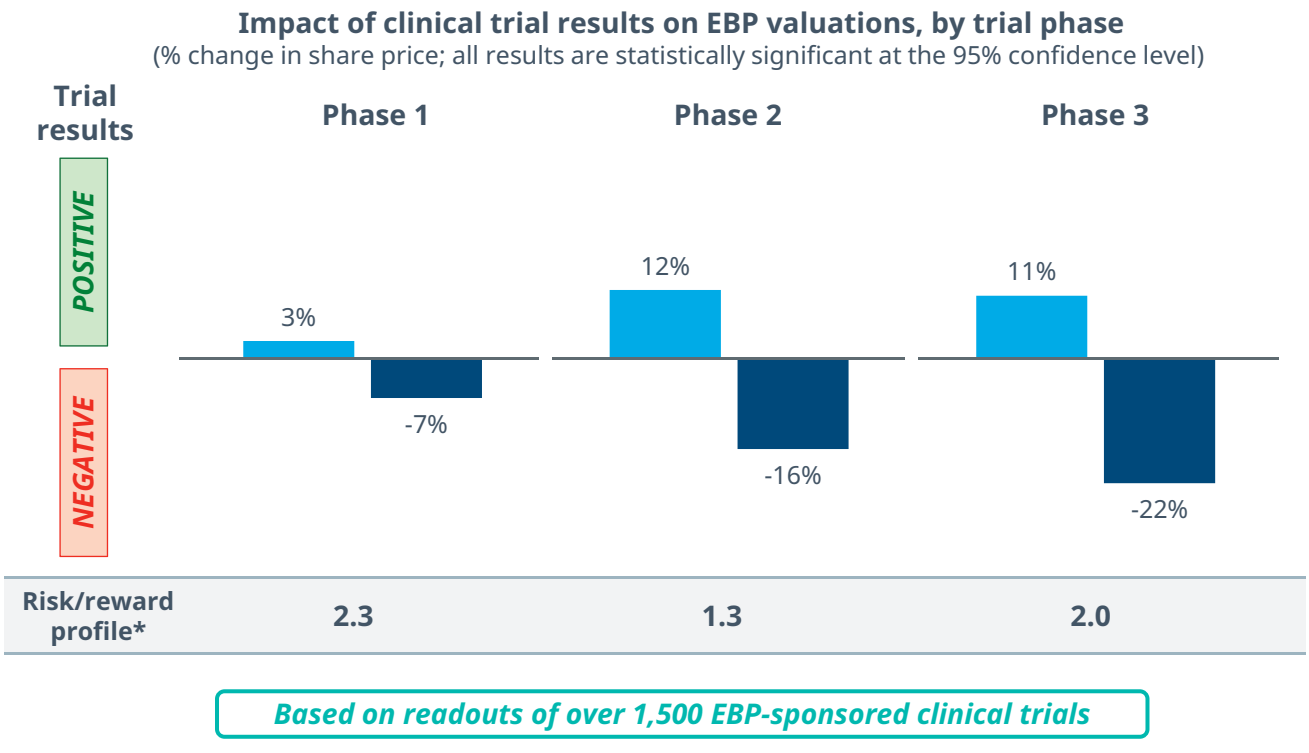
A main focus of our analysis was understanding the market response to positive and negative clinical results for different trial phases along the clinical development path.

We observed an intriguing asymmetry in the statistically significant impact of positive vs. negative clinical trial readouts on company valuations, with negative trial results consistently causing a larger relative market reaction than positive results. This pattern holds true for all trial phases.

Specifically, we found that the impact of negative news was 2.3, 1.3 and 2.0 times higher vs. positive news for clinical trial phases 1, 2 and 3, respectively, implying a most favourable risk-reward profile for phase 2 readouts (see Figure 1).

This consistent asymmetry observed across all trial phases suggests that investors give innovators the benefit of the doubt, on the basis of risk-adjusted expectations. Consequently, any value uplift following

Figure 1: The asymmetry of market response



* Ratio of absolute negative impact / positive impact
Source: IQVIA EMEA Thought Leadership analysis

positive clinical news from an anticipated event is less pronounced as it confirms prior assumptions that are already somewhat reflected in a company's share price.

Conversely, negative trial results defy prior expectations and thus destroy significant value. Taken by surprise, investors fundamentally revise their expectations, including reducing peak sales and possibly lowering assumed overall probabilities of success. This makes negative trial readouts more consequential events for company valuations.

This observation is consistent with the principles of behavioural economics, specifically Prospect Theory, which describes human decision making under risk. One of its key tenets is the asymmetry of how individuals value different outcomes, with losses having a greater emotional effect than equivalent gains.[7]

The asymmetry found in our analysis further extends to the profile and size of the valuation impact observed at different trial phases relative to each other:

- **Positive results:** The value uplift following positive clinical news increases from 3% for phase 1 to 12% for phase 2 and declines slightly to 11% for phase 3. This finding suggests that a positive phase 2 result represents a major value inflection point, as investors firm up their views of an asset's future prospects based on this data, while incremental de-risking following a positive phase 3 readout is not rewarded more highly compared to phase 2, in terms of relative valuation uplift.

  As mentioned earlier, the risk-reward profile is most favourable at phase 2, with an impact ratio for negative vs. positive news of 1.3. Typically, at the start of phase 2 no efficacy data is available yet to anchor investor expectations for one of the key determinants of an asset's future potential. Hence, a positive phase 2 readout removes a lot of uncertainty, which the market rewards disproportionately with the largest valuation upside of all phases, at 12%. At the same time, this lack of robustly anchored investor expectations for efficacy provides downside protection for negative phase 2 outcomes relative to phase 3. It is this favourable combination that singles out phase 2 readouts as a pivotal moment and key value inflection point in the asset journey.

- **Negative results:** The scale of value destruction following negative clinical news rises along successive trial phases, from 7% for phase 1, to 16% for phase 2 and 22% for phase 3. Later-stage disappointments are more detrimental to investor sentiment, because they have already attributed greater value to an asset, based on relatively firmer and more favourable expectations for peak sales and trial success. Consequently, revising those expectations destroys the more value the later such correction occurs in an asset's lifecycle.

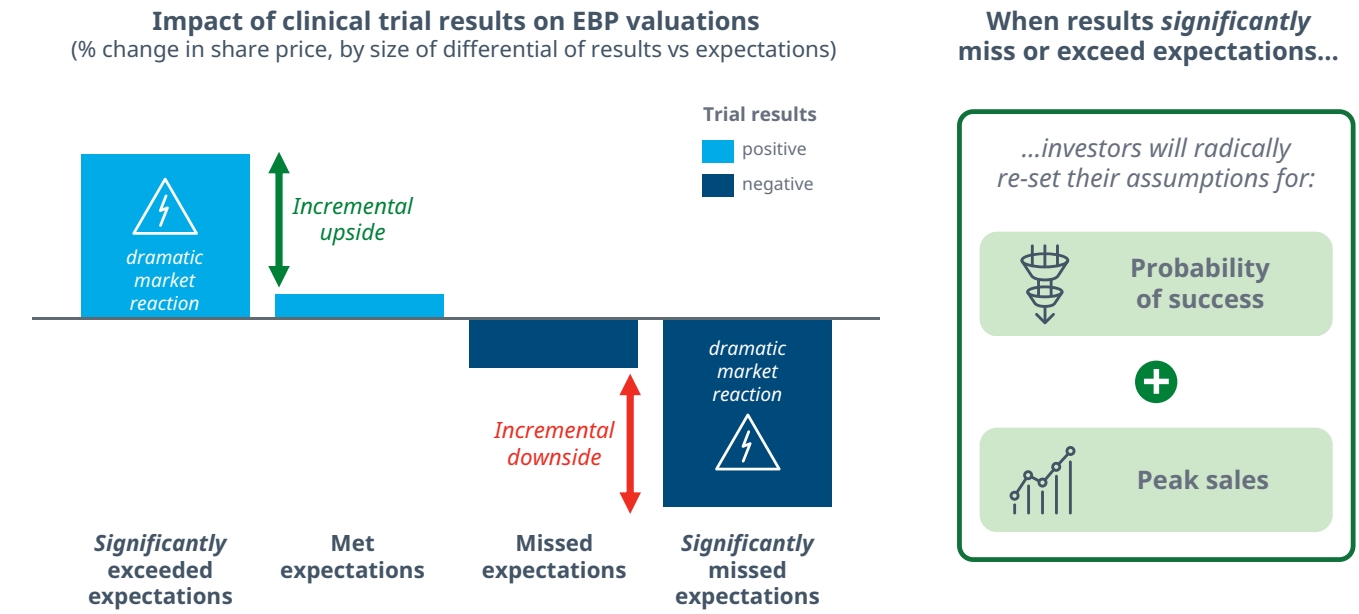
A positive phase 2 result represents a major value inflection point as investors firm up their views on an asset's future prospects.

We also investigated the potential impact of the timing of readouts, specifically when clinical trials were stopped early because of a favourable interim analysis, in a positive scenario, or due to futility or adverse events in a negative scenario.

Interestingly, investors did not reward early positive trial results more highly. However, the downward market reaction to early negative results was slightly less pronounced compared to negative results that were not early, at -14% vs. -17%, respectively. This suggests positive news is again treated as confirmatory, whereas investors value earlier certainty of downside risk as it allows them to revisit investment decisions sooner, e.g., being able to re-direct funds to potentially more promising opportunities.

When trial results significantly exceed or fall short of investor expectations, the impact on company valuations tends to be dramatic. Big surprises prompt investors to completely re-set their assumptions, including both overall risk and peak sales, which together results in valuations surging or plummeting (see Figure 2).

Figure 2: Significantly missing or exceeding investor expectations



Source: IQVIA EMEA Thought Leadership

When trial results significantly exceed or fall short of investor expectations, the impact on company valuations tends to be dramatic.

The following case examples illustrate how big surprises in trial readouts lead to dramatic market reactions.

- **Karuna Therapeutics:** On 18 November 2019, the company announced results from its phase 2 trial investigating KarXT, an oral co-formulation of novel muscarinic receptor agonist xanomeline and approved muscarinic receptor antagonist trospium, for the treatment of acute psychosis in patients with schizophrenia. KarXT demonstrated statistically significant and clinically meaningful improvement in total PANSS score (Positive and Negative Syndrome Scale for schizophrenia) vs. placebo at all time points over five weeks, reaching an 11.6-point improvement at week 5. KarXT was also well tolerated.[8]

  These outcomes significantly exceeded investors' prior expectations, which were anchored on existing anti-psychotic treatments and had been tempered given common setbacks seen in the challenging field of CNS drug development. Firstly, the 11.6-point improvement in PANSS score considerably outperformed approved anti-psychotic treatments, which typically show 8- to 9-point reductions in PANSS. It was also more than twice the minimum 5-point improvement needed for regulatory approval of current therapies. Secondly, KarXT's favourable safety profile was also surprisingly differentiated vs. first- and second-generation anti-psychotic therapies. The latter suffer from frequent and serious side effects, e.g., extra-pyramidal effects such as acute dyskinesias, dystonic reactions, tardive dyskinesia, Parkinsonism, akinesia, akathisia, weight gain and metabolic side effects, which lead to high discontinuation rates and thus limit those drugs' effectiveness. Finally, the positive trial results for KarXT supported expansion of its development in other CNS disorders.

  In response, Karuna's share price surged by 375% on the day, as investors radically increased peak sales expectations for KarXT and assumed much higher probability of success.[9]

- **Aptinyx:** On 16 January 2019, the company reported negative results from a phase 2 trial of its lead candidate NYX-2925, a novel NMDA receptor modulator, for the treatment of painful diabetic peripheral neuropathy (DPN). The study did not meet its primary endpoint of change in average daily

pain scores (NRS) from baseline at week 4, using a patient-reported scale to assign a numerical pain score from 0 to 10.

This trial failure took investors completely by surprise. NYX-2925's distinct MoA vs. existing and emerging NMDA therapies suggested promising potential for rapid and durable pain resolution with fewer side effects and a lower potential for abuse. Furthermore, investors were encouraged by earlier results from mechanistic proof-of-concept studies of the activity of NYX-2925 in preclinical pain models and an interim analysis from a phase 2 exploratory trial of NYX-2925 in fibromyalgia patients. Therefore, they were cautiously optimistic for NYX-2925 to meet the primary endpoint, with a base case assuming statistical significance or a strong trend of improvement with a -1 point NRS benefit.

Consequently, investors questioned the fundamental viability of NYX-2925 and were forced to dramatically downgrade their expectations for its future prospects. In turn, Aptinyx lost 68% of its value on the day.[10,11]

Our observations for the patterns of typical valuation uplift or depression following clinical trial readouts raise an important question for an asset's development path: How to optimise value creation for incremental clinical risk being taken? We will return to this issue in a later section to discuss the implications and considerations for management teams.

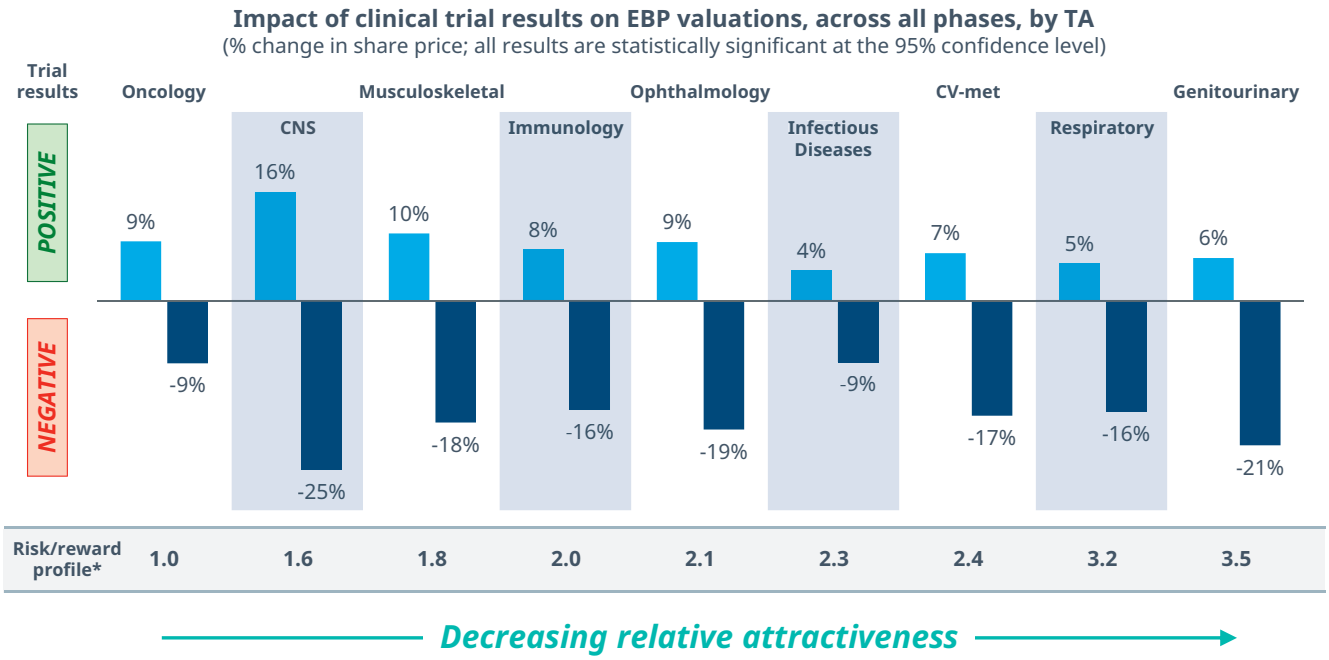
Drivers of valuation impact: therapy areas, trial designs, company size

Considering the diversity of biopharmaceutical innovation efforts undertaken by EBPs, a more differentiated understanding is needed of the drivers of valuation impact, beyond development phase. Therefore, we explored differences between therapy areas, the impact of trial designs and EBP size.

Therapy areas

We analysed the nine, most common therapy areas (TAs) in focus of EBP-sponsored clinical trials. These TAs showed considerable variation in their respective, aggregate risk-reward profiles across all trial phases, ranging from 1.0 for oncology to 3.5 for genitourinary (see Figure 3). This pattern equates to notable differences in relative TA attractiveness from an investor perspective, with oncology standing out as offering the most attractive prospects.

Figure 3: Wide variation in aggregate risk-reward profiles across TAs



* Ratio of absolute negative impact / positive impact
Source: IQVIA EMEA Thought Leadership analysis

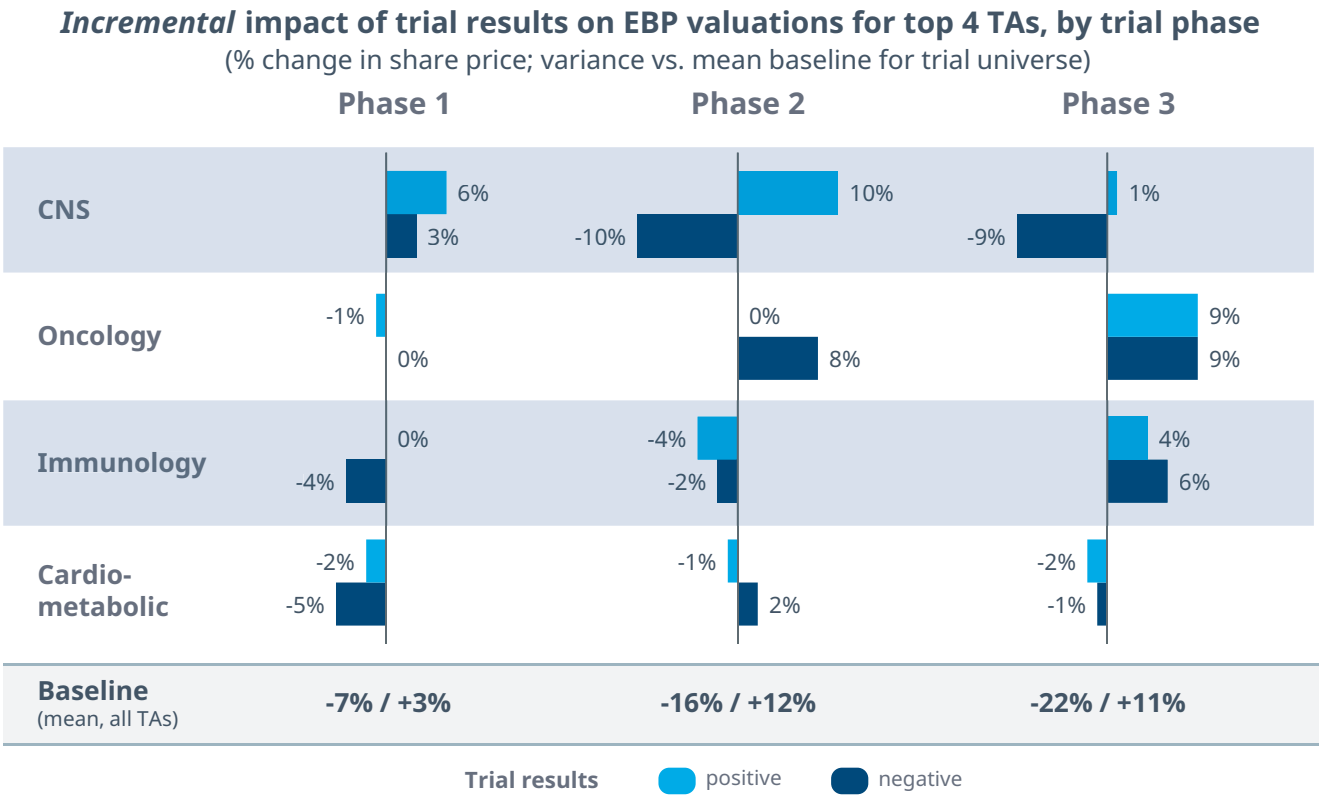
The asymmetry of market response to positive and negative trial results discussed earlier applies across TAs, with the exception of oncology. As we will discuss later, the unique profile of oncology is partially associated with its high share of single-arm trials, which have lower downside risk.

As already explored in the previous section, risk-reward profiles differ by development phase. We therefore conducted a more granular analysis for a subset of the top 4 most common TAs in EBP-sponsored clinical trials, which have a sufficiently large sample size to allow meaningful stratification of observed impact by trial phase.

Figure 4 shows the incremental impact of positive and negative trial readouts by trial phase for each of the top 4 therapy areas, expressed as variance vs. the baseline of mean impact by phase observed across our entire EBP-sponsored trial universe.

- **CNS** exhibits the highest sensitivity to trial outcomes, with more incremental upside and downside across nearly all phases compared to the baseline. This finding reflects the high degree of risk and uncertainty associated with clinical development in CNS indications, where high-profile setbacks are not uncommon.
- **Oncology** rewards innovators with its favourable risk-reward profile, showing more incremental upside and less downside vs. the baseline across all phases. Oncology assets benefit from opportunities for label expansions within an indication, potential multi-indicationality and, in an area of high unmet need, may be granted accelerated approval based on less mature data. This makes any positive clinical data, even on surrogate endpoints such as objective overall response rate (ORR) or pathological complete response (pCR), more valuable compared to other TAs. At the same time, the high share of single arm trials in oncology, with their distinct risk-reward profile, contributes to lower downside risk.

Figure 4: TA-specific sensitivity and risk-reward profiles by trial phase



Source: IQVIA EMEA Thought Leadership

- **Immunology** exhibits an unfavourable risk-reward profile for trial phases 1 and 2, with more incremental downside risk and less upside vs. the baseline. Conversely, it rewards innovators in phase 3 with more incremental upside and less downside vs. the baseline. Innovators need to clear a high bar in immunology as an increasingly mature and competitive TA which skews the impact of earlier stage readouts towards the downside. Once assets progress to phase 3, markets reward greater clarity of where an asset may fit into a crowded immunology treatment landscape.

- **Cardio-metabolic** has an overall unfavourable risk-reward profile, with less incremental upside vs. baseline across all trial phases, and more incremental downside in phases 1 and 3. This pessimistic overall sentiment is a reflection of the struggles many innovators have faced in achieving commercial success with cardio-metabolic assets, e.g., entering a highly genericised environment, with a 'good enough' mindset not recognising unmet need or rewarding innovators, while payers de-prioritise funding cardio-metabolic innovation.[12] Furthermore, typical early-stage and pivotal cardio-metabolic trials do not address stakeholder demand for CV outcomes data, which requires large outcomes trials, run for extended periods of time. This translates into a the less favourable upside.

  However, it is worth noting that this is an aggregated TA view which masks more buoyant, recent dynamics in some of the underlying indications.

Within these macro-therapy areas we can find 'attractiveness hotspots' at indication level, with more favourable risk-reward profiles compared to the respective TA overall. Examples include inflammatory bowel disease within immunology, or obesity within cardio-metabolic, where unmet need remains high, proof-of-concept for several potential technologies already exists and the market opportunity has been validated by earlier therapies.

Hype cycles

Another important consideration for understanding market reactions is the impact of potential hype cycles which can dramatically influence investor sentiment and lead to exaggerated market response to news. Hype cycles are time-dependent and typically rise and fade during a particular time period. In the context of biopharmaceutical innovation they are driven by exuberance linked to a specific therapy area and/or technology, e.g., obesity, rare diseases, mRNA during the Covid pandemic, antibody drug conjugates in oncology or GLP-1s in various cardio-metabolic conditions today.

The following examples illustrate the impact of great excitement surrounding particular themes on investor sentiment and the resulting amplification of market response.

- **Viking Therapeutics:** In positive top-line results for its phase 2 VENTURE trial announced on 27 February 2024, dual GLP-1/GIP receptor agonist VK2735 met all primary and secondary endpoints in obese patients. Specifically, VK2735 demonstrated statistically significant weight loss of up to 14.7% after 13 weeks of treatment.

This result exceeded investor expectations by numerically beating the weight loss delivered at the same time point by their benchmark, Lilly's top-performing brand Zepbound, the most potent, on-market obesity therapy to date with the same MoA as VK2735. This outcome established Viking as a credible, future contender in the much-hyped obesity space.

In response, Viking's share price surged by 80% on the day, well above the typical market reaction of 11% to phase 2 readouts for cardiometabolic assets.[13,14]

- **Revolution Medicines:** On 9 April 2024, the company presented preclinical data and additional clinical case studies at the American Association for Cancer Research Annual Meeting 2024 (AACR24). In an ongoing phase 1 trial, its asset RMC-6236, an oral, multi-selective RAS inhibitor, demonstrated complete response in two patients with KRAS G12D-expressing pancreatic cancer and KRAS G12V-positive non-small cell lung cancer, respectively.

  Despite the very early-stage nature of the presented data, investors interpreted this as first validation of the company's tri-complex inhibitor platform, with increased confidence in expanding and advancing the asset's clinical development programme, including pivotal studies.

  In response, Revolution Medicines' share price rose by 14% on the day, well above the typical market reaction of 2% to phase 1 readouts in oncology.[15,16]

Our findings clearly demonstrate that therapy area context is important to develop a meaningful and accurate understanding of value inflection along an asset's development path. It is therefore essential that innovators carefully calibrate their assumptions for TA-specific drivers and patterns of potential market response.

Therapy area context is important to develop a meaningful and accurate understanding of value inflection along an asset's development path.

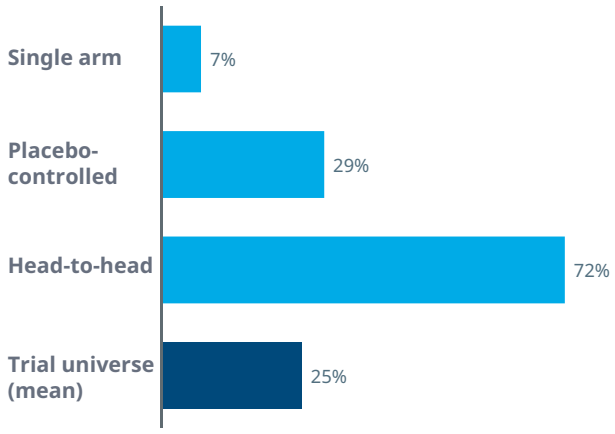
Trial designs

In a further analysis, we explored differences in market reaction to the readouts from three clinical trial designs: single arm, placebo-controlled and head-to-head trials.

The observed market sensitivity to clinical news corresponds directly to the richness/robustness of the underlying evidence, increasing from single arm to placebo-controlled and further to head-to-head trials, with an impact amplitude between positive and negative results, across all phases, of 7%, 29% and 72%, respectively (see Figure 5).

Figure 5: Impact of trial designs corresponds to robustness of evidence

Sensitivity of EBP valuations to readouts, by trial design
(Impact amplitude: delta negative-positive change in share price)



***Case study*: An ophthalmology-focused biotech**
(Significant downside risk of head-to-head trials)

Trial design
- Phase 3 **head-to-head trial** of biotech's asset vs. the market leader
- Primary endpoint: Non-inferiority in improving visual function

Trial result
- **Missed primary endpoint**: Biotech's asset failed to demonstrate non-inferiority vs. market leader
- Also showed numerically higher side effects

Impact
- Major setback for biotech's path towards approval
- Investors doubted ability to carve out a viable position for biotech's asset in the marketplace
- Biotech's **shares plummeted by >80%** on the day

Source: Company press release; IQVIA EMEA Thought Leadership analysis

- **Single arm trials:** The absence of context, even in the form of a placebo comparator, makes it difficult for investors to calibrate their interpretations of results from single arm trials. As such, they do not resolve as much uncertainty as placebo-controlled trials, resulting in a more tempered market reaction. While not statistically significant in our analysis, single arm trials appear to have a skewed risk-reward profile with lower downside risk relative to their upside. As mentioned in an earlier section, the high share of single-arm trials in oncology is one reason behind its unusual risk-reward profile, which lacks the asymmetry consistently observed across all other TAs.

- **Placebo-controlled trials:** A placebo comparator enables contextualisation and thus provides investors with richer, more robust evidence to confirm or re-calibrate their expectations. Investors also often rely on making cross-trial comparisons based on placebo-controlled trials to inform their views on an asset's differentiation, notwithstanding the clear, inherent limitations of that approach. Therefore, readouts from placebo-controlled trials lead to a stronger market response compared to single arm trials.

- **Head-to-head trials:** Readouts from these trials provide the most comprehensive evidence to investors, including a methodologically robust, like-for-like, direct comparison vs. a competitor. Unsurprisingly, market reactions show the highest level of sensitivity to head-to-head (H2H) trial results. Crucially, this higher sensitivity is strongly skewed towards the downside, with negative H2H trial readouts in phase 3 having an impact of -73% vs. -22% for the mean negative impact seen for phase 3 across our trial universe.

  This pattern reflects the interplay of several factors. Firstly, H2H trials use a meaningful, active comparator, such as the standard of care or a relevant competitor, with the aim to demonstrate at least non-inferiority, and ideally superiority. Consequently, a negative H2H trial result fundamentally undermines an asset's future prospects, raising serious questions about why it should have a place in the treatment landscape. Secondly, innovators who embark on a high-stakes H2H trial signal to investors a strong conviction that such trial will succeed. Therefore, a negative H2H trial outcome inevitably falls significantly short of investor expectations, leading to a dramatic market response, as we discussed earlier, while any upside from a positive H2H readout has already been priced in to a large extent.

The example of an ophthalmology-focused biotech highlights the substantial downside risk of head-to-head trials:

- The biotech was running a phase 3 head-to-head trial investigating its asset against the market leader. The study did not meet its primary endpoint of demonstrating non-inferiority in improving visual function.

- This trial failure represented a major setback for the company's path towards regulatory approval and its ability to carve out a viable position for its asset in the marketplace. Investors were alarmed, with the biotech's shares trading down by over 80% on the day the trial results were announced.

Company size

The relative shape of observed impact patterns that we have discussed so far was broadly consistent across the EBP size spectrum. However, the size of an EBP matters as a factor determining the extent to which clinical news impacts companies' valuations.

As expected, valuations of larger EBPs with commercial-stage asset(s) tend to be less sensitive to trial results, because less of such companies' value is concentrated in their pipeline asset(s).

Even among pre-commercial EBPs company size provides some shelter against market reactions.

Even among pre-commercial EBPs company size provides some shelter against market reactions. EBPs with <$1 billion market cap are more sensitive to clinical news than EBPs with ≥$1 billion market cap, by a factor of 13.3, 9.5 and 6.2 for readouts at phases 1, 2 and 3, respectively.

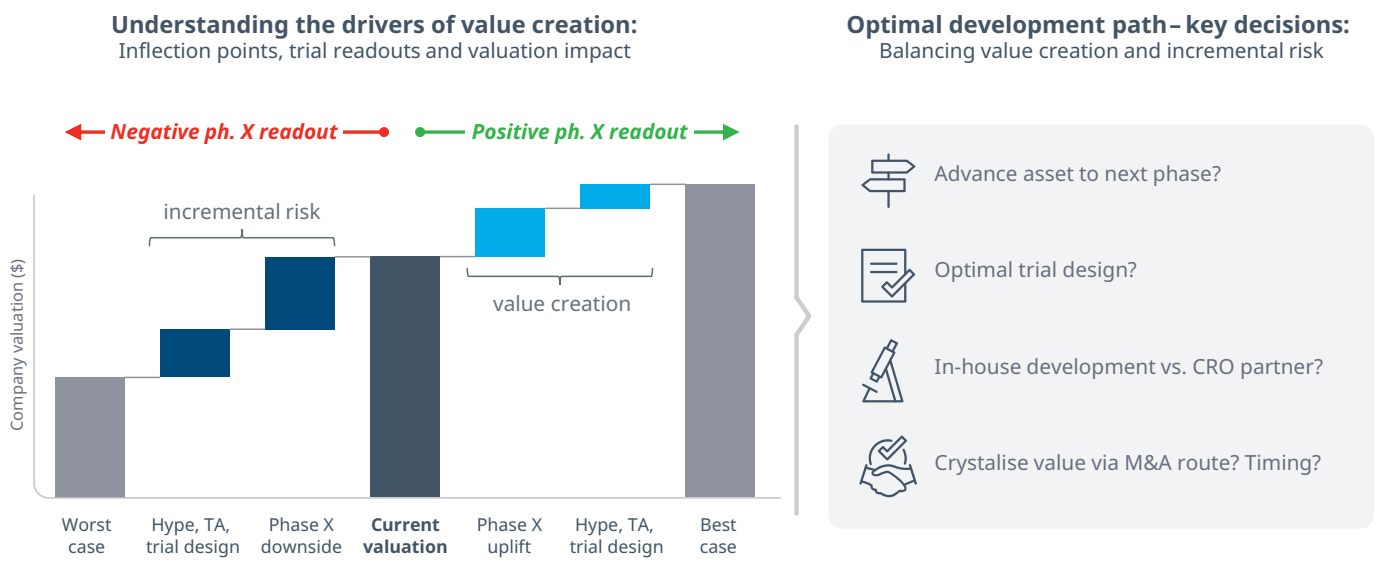
A plausible explanation may be that smaller EBPs, as nascent companies, have less of a track record and fewer proof points to support their equity story. Therefore, any additional, new information becoming available is relatively more impactful on how the market responds, as investors still make up their minds. That differential should narrow towards higher trial phases, because even nascent companies will have established some track record by that point.

Considerations for management teams

Steering a company along a path that optimally balances value creation and risk is among the most important tasks for management teams across companies of all sizes. In the case of emerging biopharma companies with pre-commercial asset(s), this requires strategic decisions that are aligned with pivotal value inflection points in an asset's development journey (see Figure 6).

For example, as our research identified, phase 2 readouts have the most favourable risk-reward profile for how markets respond to positive vs. negative clinical news. Understanding the drivers of value inflection, such as differences between TAs in the relative sensitivity of EBP valuations to trial results, or the impact of different trial designs, provides further insight to inform critical trade-offs and their timing. For example, it helps management teams decide whether to take on incremental clinical risk by moving into the next development phase for an expected value upside vs. prioritising a near-term exit via the M&A route to lock in value for investors that was gained on the back of recent positive data.

Figure 6: Considerations for management teams



Source: IQVIA EMEA Thought Leadership analysis

Case study: Prometheus Biosciences

On 7 December 2022, Prometheus Biosciences announced positive results from two clinical trials, phase 2 ARTEMIS-UC and phase 2a APOLLO-CD. Those studies investigated its key asset, anti-TL1A monoclonal antibody PRA023, for the treatment of patients with moderate-to-severely active ulcerative colitis and Crohn's disease, respectively.

PRA023 demonstrated strong efficacy and favourable safety in both studies. In particular, the placebo-adjusted clinical remission rate of 25% at week 12 in ulcerative colitis significantly exceeded investors' prior expectations of 15%, which were anchored on standard of care biologics. It also compared favourably to potent JAK inhibitor Rinvoq, with a seemingly cleaner safety profile. Furthermore, results in Crohn's disease provided important proof-of-concept in addition to early validation of a novel biomarker strategy.[17] In response, Prometheus Biosciences' share price surged by 257% on the day.

Only four months later, on 16 April 2023, Prometheus Biosciences entered into a definitive agreement with Merck to be acquired for a total equity value of $10.8 billion, representing a premium of 75.4%.[18]

This example illustrates strategic decision making on the optimal path for an EBP that is aligned with a pivotal value inflection point following a positive phase 2 readout. For investors in Prometheus Biosciences, this timely transaction removed exposure to future risk from phase 3 trials and potential self-commercialisation efforts. At the same time, the sizable deal premium crystallised the substantial value uplift from both the recent phase 2 results and the acquirer's subsequent, bullish expectations for the future potential of PRA023.

Closing thoughts

Investors ultimately look for a compelling equity story. Therefore, it is critical for EBP management teams to be able to clearly articulate the rationale behind key strategic choices that determine a company's path and how it is linked to optimal value creation from its asset(s) adjusted for risk.

A successful asset journey begins with developing a clear asset strategy, subsequently translated into a comprehensive clinical development plan, which provides assurance to investors.

Transitioning from typically smaller, early phase studies to the critical phase 2, a major value inflection point as we discussed earlier, presents many challenges for EBPs. For example, EBP sponsors will need to master patient recruitment at a much larger scale, requiring a broader, often global approach, while more complex protocols and competing trials compound the risks to completing the study successfully and on time.

Funding constraints may tempt EBP sponsors to size their clinical trials too conservatively, thereby risking to underpower phase 2 studies for the objectives they seek to achieve to deliver on investor expectations.

Partnering with a third-party clinical solutions provider must form a key consideration for EBPs to create and execute a winning clinical development roadmap that delivers the right data. Such a partner can bring global reach, deep therapeutic, regulatory and operational expertise, combined with relevant technology and analytics capabilities, to de-risk clinical delivery, ensure it is cost-effective and to accelerate timelines.[19]

Biotech companies maximise value for their investors when the stars align: delivering the right clinical data, at critical inflection points in the development path, driving optimally timed strategic decisions that balance value creation and risk.

Their management teams must accurately identify this risk-reward sweet spot. Understanding the patterns and drivers of value inflection is a prerequisite for doing so.

Biotech companies maximise value for their investors when the stars align: delivering the right clinical data, at critical inflection points in the development path, driving optimally timed strategic decisions that balance value creation and risk.

Appendix: additional methodology details

I. Data

Our analysis utilized a dataset provided by Citeline, which contains many datapoints about clinical trials conducted between 2017 and 2023. The dataset comprises trials sponsored by government, academia, cooperative groups, and industry.

To ensure the data was fit for purpose, IQVIA performed multiple data cleaning steps. The first step involved removing all trials with invalid and/or missing clinical trial termination reasons. The second step removed trials with no event date information. The third step removed trials with non-industry sponsors, such as academic institutions. Sponsors were then grouped into the following classifications:

COMPANY TYPE	CLASSIFICATION
Large pharma	Top 20 pharma companies e.g., AstraZeneca, Roche etc.
Large EBP	Based on maturity e.g., business focus, in-line portfolio
Mid-size pharma	Excluded from analysis

The remaining companies were categorized as the EBP universe, the focus of this analysis. These were further classified as follows:

COMPANY TYPE	CLASSIFICATION
Small EBP	<$1Bn market capitalisation
Mid-size EBP	≥$1Bn market capitalisation

In many instances, the Citeline dataset listed multiple TAs for each trial. Hence, TAs were re-categorized based on the disease allocation, using disease to TA classifications per the methodology in IQVIA MIDAS Disease. Further groupings were made to increase the number of trials by TA for the robustness of the sample size. For example, obesity, cardiovascular, and endocrine were grouped into CV-met, and immunology included autoimmune, inflammation, dermatology, and gastroenterology.

Once the final clinical dataset was built, it underwent a rigorous manual checking process, for example, validation that all EBPs were indeed EBPs and not another type of business profile, such as a CDMO, which was then removed from the dataset.

To incorporate the value creation proxy into the analysis, Refinitiv, a financial workflow tool, was utilized to source sponsor market capitalisations recorded in USD at close prices on the event date. This data was then merged with the clinical dataset, such that the resulting final database included key clinical characteristics, as well as the value creation metric, market capitalisation. This final blended dataset included datapoints on 1,502 publicly listed EBP-sponsored clinical trials. The split of EBPs in our sample is 70/30 in favour of small EBPs.

II. Methodology

A robust statistical model was developed to analyse the change in EBP market capitalization at the event date. The event is the primary endpoint reported date, i.e., the earliest date of public report of results that addresses the primary endpoints of the trial. A positive clinical outcome is denoted when the primary endpoint is met and vice versa for negative when the primary endpoint is not met.

The change in market capitalisation, i.e., the value creation/destruction proxy, was calculated as the average at the close prices of two days prior and one day prior to the primary endpoint reported date versus the average at the close prices on the day of the event and the day after.

The change in market capitalisation was used as the dependent variable. The analysis tested the effect of several independent variables on the market capitalisation in case of positive vs negative clinical outcomes using the t-test. The average impact of clinical trial phase, TA, and trial design (placebo vs single-arm vs head-to-head) was assessed, as well as the effect of TA and trial design within each phase. Results were checked for robustness considering the disease-level hype, the year of result release, and the number of patients included in the trial. This was conducted using SPSS version 28.

Furthermore, within the results, there are two sub-analyses which have marginally different methodologies:

EARLY OUTCOMES

For the analysis of early outcomes, the event date was moved to the primary completion date, i.e., the date when the final subject was examined or received intervention for data collection for evaluating the primary endpoints of the trial. Clinical outcomes and their event dates are listed below:

CLINICAL OUTCOME	EVENT DATE
Positive	Primary endpoint reported date
Negative	Primary endpoint reported date
Early positive	Primary completion date
Early negative	Primary completion date

An example of an early negative outcome is when a trial has initial efficacy and/or safety concerns and vice versa for early positive outcomes.

WHEN TRIALS MISS OR EXCEED INVESTOR EXPECTATIONS

This sub-analysis is about clinical outcomes versus investor expectations. Investor expectations of a clinical outcome could be anchored on many datapoints, for example previous trial data, competitor results (with the same MoA) or data from pre-clinical models. When a clinical outcome is released, that outcome will be compared to what investors predicted it would be, causing them to make amendments to their previous assumptions. Consequently, significantly exceeding, or missing expectations can have a dramatic impact on a sponsor's value. A brief explanation by outcome type is provided below:

CLASSIFICATION	DESCRIPTOR	RESULT
Significantly exceeded expectations	Positive clinical outcome which significantly exceeds investor expectations	Large increase in market cap
Met expectations	Positive clinical outcome which is in-line with investor expectations	Increase in market cap
Missed expectations	Positive clinical outcome but results are below investor expectations OR negative clinical outcome but positive sub-population results	Decrease in market cap
Significantly missed expectations	Unambiguous negative clinical outcome which is far below investor expectations	Large decrease in market cap

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Markus has over 20 years of experience in life sciences, advising clients in all major geographies on a broad range of topics, including real world evidence strategy, launch readiness, go-to-market models, brand and commercial strategies, and building enabling organisational capabilities.

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