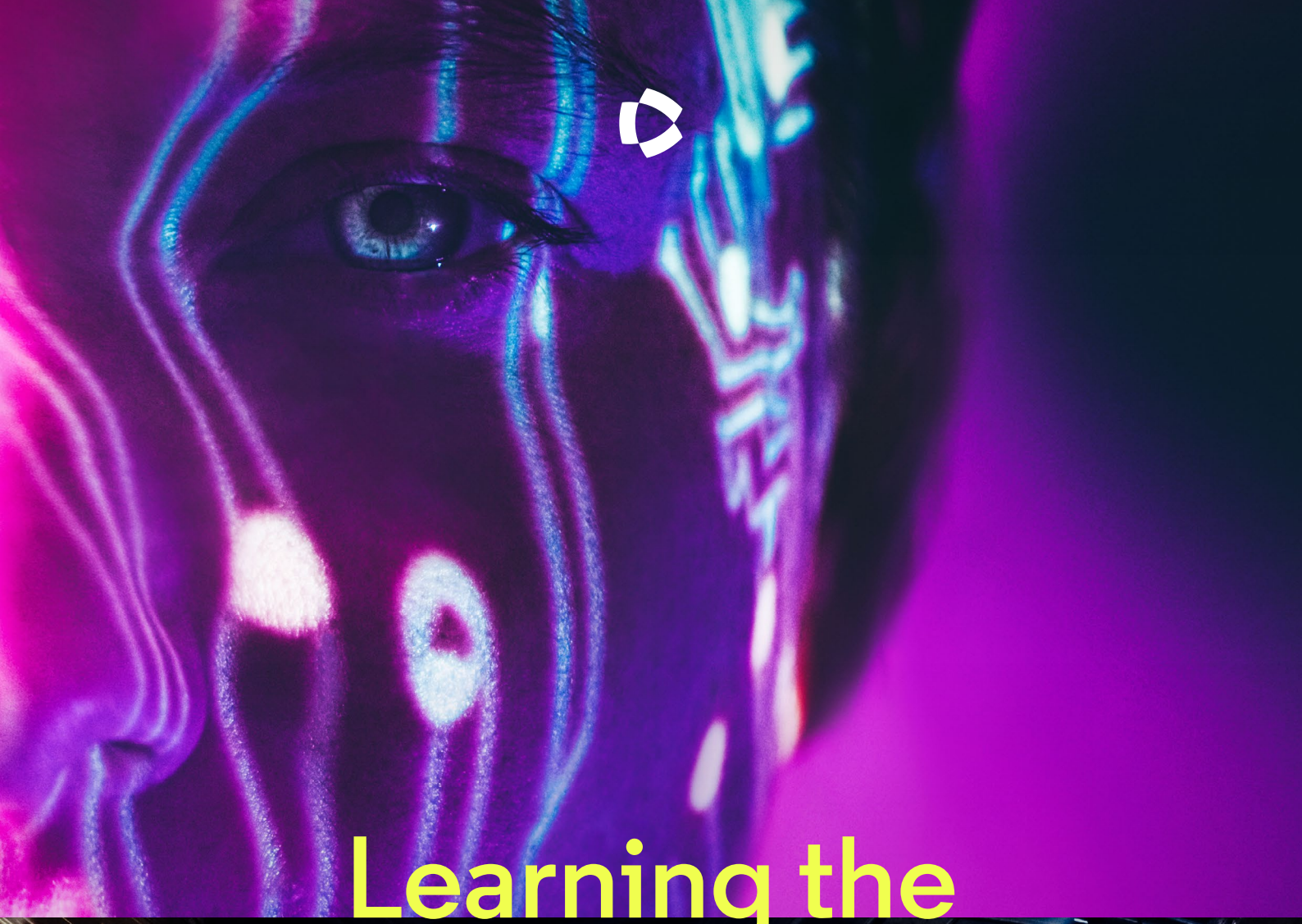


Learning the lessons of failure

How to improve the economics of life sciences R&D

Clarivate™

Contents

Introduction

For biopharma innovators, the path from bench to bedside is often a long and treacherous one, with pitfalls and snares lying in wait at every turn. A quick scan of any biopharma-focused news feed will yield tales of deals falling through, pharmas hitting 'pause' on what seemed like promising programs, failures to launch and drugs languishing in post-marketing doldrums.

How we use these experiences to inform future development determines their role in the iterative process of science.

"Failure is instructive. The person who really thinks learns quite as much from his failures as from his successes."

John Dewey

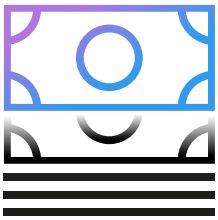
Thalidomide provides perhaps the most well-known cautionary tale for pharma R&D—as well as a more recent redemption arc. From a treatment for morning sickness with devastating fetal side effects in the 1950s to approval in 1998 for the treatment of erythema nodosum leprosum and beyond, thalidomide and its properties have undergone intense scrutiny and become recognized as a valuable (and lucrative) treatment for its approved indication of multiple myeloma as well as off-label applications for HIV complications, Kaposi's sarcoma, gastrointestinal bleeding and more. Its disastrous roll-out in the 1950s spurred greater regulatory oversight of drug development marketing worldwide, introducing legislative changes in the United States that came to form much of the scaffolding of drug safety law in that market and beyond.

The story of Viagra® (sildenafil) is rightly regarded as a triumph rather than a failure, but the drug's early history offers valuable lessons for pharma R&D. Sildenafil was first developed in the mid-1990s to treat hypertension and angina pectoris, but Pfizer soon spotted a broader commercial opportunity in the drug's secondary effect of rapid (30-60 minutes) inducement of penile erections and subsequently patented and marketed the molecule as Viagra for the treatment of erectile dysfunction (ED) in the U.S. and Europe. With near-instantaneous blockbuster status, Viagra impacted more than just the pharma development world. Pfizer's pioneering use of direct-to-consumer outreach in its U.S. sales and marketing of Viagra blazed a trail for today's commercialization strategies in that market. Since its launch in 1998 through to the loss of its last U.S. patents in 2020, Viagra was able to retain massive market share and remains synonymous with ED treatment much as Kleenex does with facial tissues in the U.S. or Hoover with vacuuming in the U.K. Sildenafil has also won approval for other indications, such as pulmonary arterial hypertension (REVATIO™), capitalizing on its prior success to fund development for other medical conditions.

In today's biopharma environment, it's only by working across typically siloed departments that potential failures can be detected and rectified before they sideline entire programs that, if executed well, have the potential to positively impact patient health, the company's bottom line and future deals potential. With stiffer competition, smaller margins, legislative activities impacting the expected ROI, greater regulatory scrutiny of patient outcomes and increasing expectations around the cost-to-benefit ratio from patients, clinicians and payers, biopharma companies need to recognize that a scientific breakthrough itself is not enough to guarantee market success. The keys to success are developing products that have relevance in the real world and making the right decisions early in development that influence the drug's safety and effectiveness, so they are acceptable to patients and clinicians and reimbursed by payers. Robust strategic planning from the beginning minimizes the use of resources to address avoidable issues later in the lifecycle and allows for the adjustments needed to keep development on track.

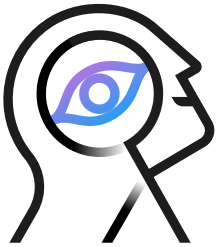
This paper details eight examples of development programs that experienced, and in some cases overcame, hurdles from pre-discovery through commercialization or that missed or downplayed red flags to their detriment, with the aim of learning lessons that can help advance science for future generations.

Considerations throughout the development lifecycle to maximize scientific and commercial success



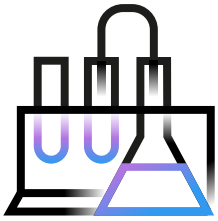
Company's financial health

- Ability to future-proof development plans
- Contingency planning for slow development, delays in regulatory approval or poor initial uptake
- Diversified assets and portfolio to offset losses in a single area
- Appropriate budgeting for all activities from discovery through commercialization



Discovery/pre-clinical development

- Level at which the mechanism of action is understood
- Early indicators of potential future issues with safety and efficacy
- Potential off-target effects
- Biomarkers that can be used during clinical trials to identify patient segments or monitor drug effectiveness
- Strength of biological evidence linking a drug target to disease



Clinical development

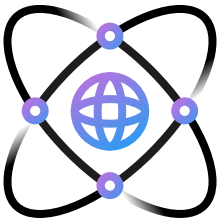
- Study population (i.e., inclusion/exclusion criteria)
- Choice of comparator
- Endpoint selection, including surrogate endpoints
- Collection of quality of life and other patient-centric data
- Single-country or multinational site locations, including disease prevalence
- Adherence to the latest regulatory and good clinical practice guidelines
- Use of available biomarkers to identify patient segments
- Status of competitors' development plans and findings from clinical trials
- Parallel development of companion diagnostics for simultaneous regulatory approval
- Patient selection criteria based on knowledge of drug candidate's mechanism and potential risks
- Legislative and regulatory changes, such as U.S. Inflation Reduction Act (IRA)
- The impact of legislation such as the U.S. IRA on product financials and revenue from new assets

Regulatory approval

- Outcomes of prior submissions in the same drug class or therapeutic area
- Regulatory acceptance of methods or companion diagnostics
- Post-marketing surveillance plan
- Input from regulatory agencies earlier in development, such as to the study design or endpoints
- Regulatory requirements for target markets
- Acceptance of foreign data

Addressing patient needs

- Appropriate characterization of the unmet needs of the target patient population
- The endpoints that matter to patients, including the impact on their daily lives
- Barriers to adherence, such as a lack of insurance, burdensome monitoring, lack of diagnostic or treatment centers nearby
- Acceptability of administration method, timing or frequency
- Impact of side effects, including how they compare with the symptoms of the disease/condition itself
- Satisfaction with current treatments



Market access

- The competitive landscape and how the drug/device compares with others in development or already on the market
- Emerging changes in the standard of care
- Whether key payer questions have been addressed and how those differ country by country
- Manufacturing or formulation challenges that could impact product quality, stability or scalability
- If patient support is needed to pay for and access treatment
- The need for education for clinicians or patients to understand and use the product
- Adequate explanation of the value of the product, especially if it is priced higher than current options
- Understanding formulary inclusions/exclusions
- For conditions with a well-established treatment paradigm, patient and clinician satisfaction with existing treatments and level of effort to convince them to switch
- The impact of legislation and government regulations, such as the U.S. IRA on the expected manufacturer market access expenditures and pricing considerations of any new or existing asset

01

Bortezomib and carfilzomib

Velcade® and KYPROLIS®

Under-valued assets in the discovery/pre-clinical phase persevered to achieve blockbuster status

Overview

Producers

Takeda Pharmaceutical Co Ltd (Velcade)

Amgen (KYPROLIS)

Type

Selective proteasome inhibitor

Usage

Velcade: injection to treat mantle cell lymphoma and multiple myeloma (newly diagnosed and relapsed or refractory [R/R])

KYPROLIS: injection to treat R/R multiple myeloma

Velcade

- 1994: First evaluations of the anticancer properties of MG-341 (bortezomib/ Velcade), a proteasome inhibitor, at MyoGenetics
- 1995: MyoGenetics became ProScript; MG-341 became PS-341; findings suggested a novel mechanism of action by PS-341 for antitumor activity
- June 1999: Acquisition of ProScript by LeukoSite for $2.7 million
- September 1999: Acquisition of LeukoSite by Millennium Pharmaceuticals for $635 million
- 2002 and later: Clinical development of bortezomib
- May 2003: Food & Drug Administration (FDA) approval for the third-line treatment of multiple myeloma, with several subsequent label expansions for multiple myeloma and mantle cell lymphoma
- April 2004: European Medicines Agency (EMA) approval to treat multiple myeloma, with several subsequent label expansions
- October 2006: Japan Pharmaceuticals and Medical Devices Agency (PMDA) approval to treat R/R multiple myeloma
- April 2008: Millennium Pharmaceuticals acquired by Takeda Pharmaceutical Co Ltd for $8.8 billion

KYPROLIS

- December 2003: Proteolix Inc founded to investigate and develop proteasome inhibitors
- June 2004: PR-171 (carfilzomib/ KYPROLIS) developed as a novel molecule and investigated in clinical trials
- June 2008: EMA orphan designation (to Interface International Consultancy Ltd)
- October 2009: Proteolix Inc acquired by Onyx Pharmaceuticals for up to $851 million
- July 2012: FDA accelerated approval to treat R/R multiple myeloma, with several subsequent label expansions
- August 2013: Onyx Pharmaceuticals acquired by Amgen for $10.4 billion
- November 2015: EMA marketing authorization

An orphan drug across multiple acquisitions finally has its day(s) to shine

Patients with multiple myeloma often experience severe, debilitating pain, and Velcade was not only the first treatment option for multiple myeloma but also the first-in-class proteasome inhibitor. Prior to its approval, the prognosis with multiple myeloma was poor, and yet, this paradigm-shifting drug nearly did not come into being.

MyoGenetics was co-founded by Alfred Goldberg, the discoverer of the proteasome, and led by Julian Adams, a medicinal chemist, who was instrumental in sustaining the Velcade program. First developing Velcade for HIV- and muscular dystrophy-associated muscle weakness, the company pivoted to oncology treatments after recognizing the role of proteasomes in cell survival and growth. Despite impressive suppression of cancer growth in preclinical studies, everyone except Adams placed little faith in the commercial success of Velcade, including executives at all three companies that held the rights to Velcade throughout its development. In fact, Velcade held little interest for Millennium Pharmaceuticals in its acquisition of ProScript/LeukoSite.

Adams persevered to overcome obstacles such as high toxicity-induced side effects, finding the right oncology target (eventually, multiple myeloma), developing a suitable formulation, financial difficulties at ProScript and internal resistance, and more. He accomplished this through strategic partnerships with the U.S. National Cancer Institute (NCI), Dana Farber Cancer Institute and The University of North Carolina, (which funded the first clinical trial of Velcade). This trial showed no serious side effects, demonstrated Velcade's efficacy in terms of its ability to slow the progression of multiple myeloma, and documented the success of combination treatment in patients for whom previous treatments had not worked.

Partnerships with multiple myeloma patient organizations also proved pivotal to convincing stakeholders of the importance of Velcade for this patient population, who did not have access to an effective therapy. Convinced of its value, Millennium Pharmaceuticals fully committed to further development, along with the NCI, and engaged closely with the FDA to provide the data needed for regulatory submissions. After its first approval in 2003 in the U.S. and 2004 in Europe, Velcade has accumulated multiple approvals, altered the fabric of multiple myeloma treatment and achieved blockbuster status—all through dogged perseverance.

Reluctant funders delayed, but did not stop, the development of a key cancer therapy

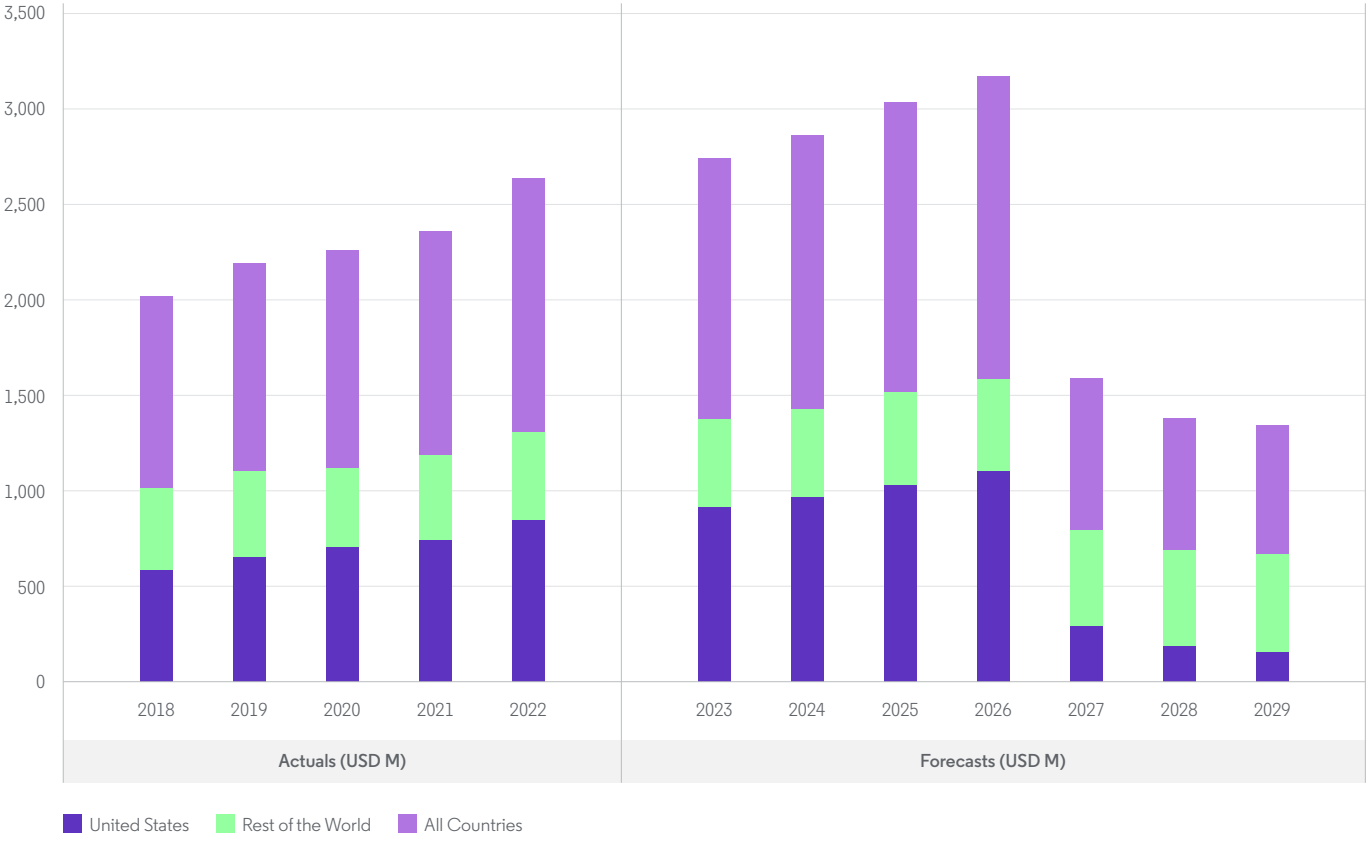
Velcade set the stage for future innovation in proteasome inhibitors, including the second-generation drug KYPROLIS, which has greater potency and a better toxicity/safety profile than Velcade. Proteolix Inc, the original parent company of KYPROLIS, began as an informal conversation between two academics, Ray Deshaies from the California Institute of Technology and Craig Crewes from Yale University, at a meeting in the 1990s. The combination of a years-long collaboration to develop an idea that is now known as PROTACs (an R&D strategy for novel small molecule drugs) and the men's separate academic work with proteasomes inspired them to seek venture capital (VC) funding to start their own company in 2001.

Two years later, they secured $18.2 million in seed funding that allowed them to further development for YU101 (the parent of carfilzomib). However, along the way were multiple rejections from VCs who failed to see the value in their proposition—potentially aided by the team's inability to adequately describe the potential of an, as yet, unproven molecule.

However, six months after establishing Proteolix using this seed funding, the team had a breakthrough—the novel irreversible proteasome inhibitor PR-171 (later carfilzomib and KYPROLIS) was developed from the YU101 scaffold. Prior to its first acquisition, Proteolix also discovered other next-generation proteasome inhibitors, including an oral proteasome inhibitor and a selective immunoproteasome inhibitor, with the potential to significantly impact cancer treatment.

Structurally and mechanistically distinct from Velcade, KYPROLIS achieves longer suppression of proteasomes in multiple myeloma at a more tolerable safety profile, adding another treatment option for this patient population and achieving blockbuster status under Amgen.

Figure 1: At a Glance Drug Sales by Therapy Area in USD (millions)



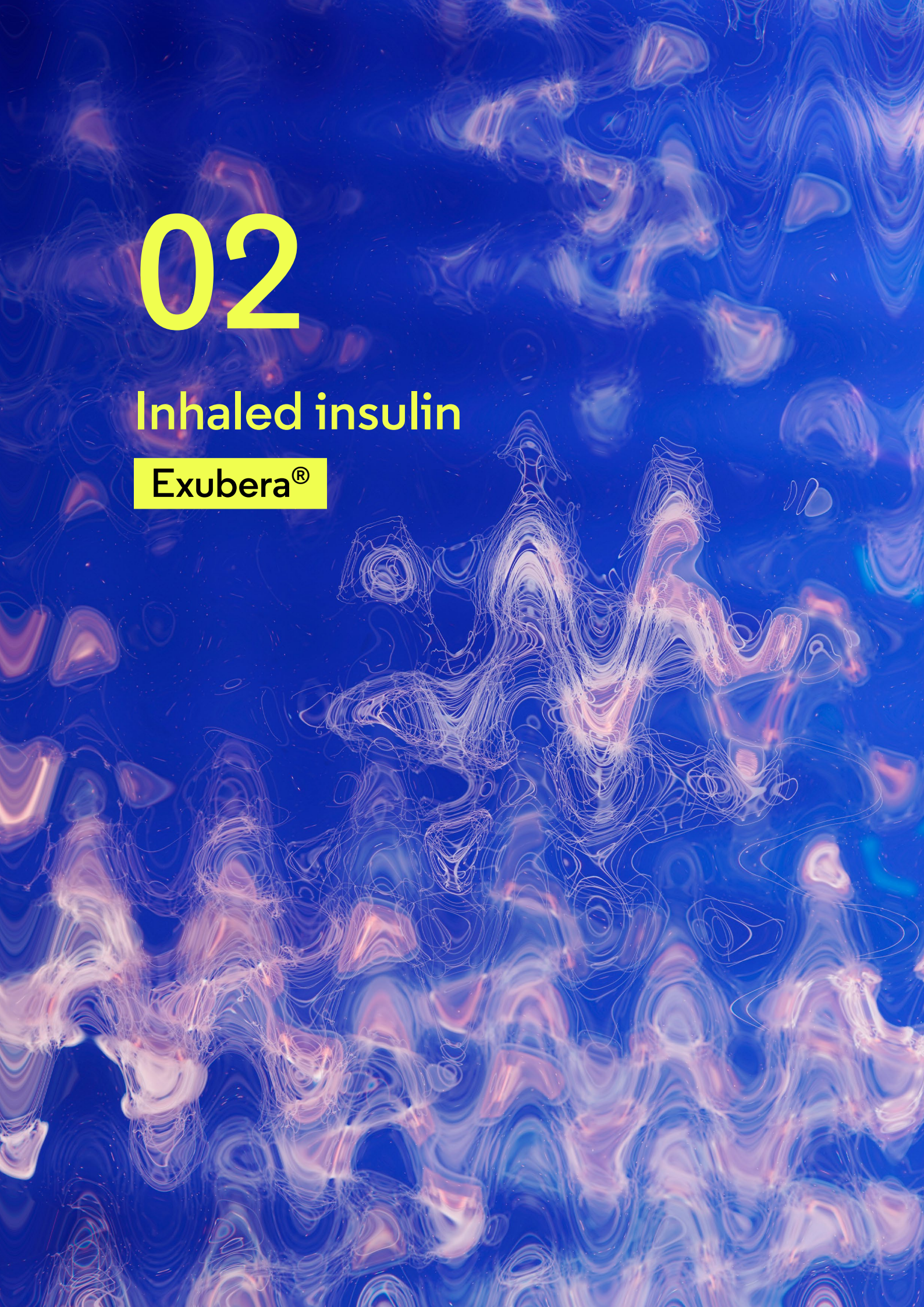
Lessons learned

Patient input can highlight the value of a new drug that is addressing a significant unmet need.

Understanding the funding landscape can guide how to communicate the value of a product to potential investors.

Being able to communicate that value to internal and external stakeholders can be key to sustaining a program that might initially be viewed as having a detrimental risk-to-benefit ratio.

Competitive analysis, including the strengths and weaknesses of existing products within the same class, informs how to differentiate investigational products from funding discussions through development and commercialization. For example, the Clarivate Disease Landscape & Forecast solution helps companies identify and evaluate unmet needs, by providing in-depth, disease-specific insights into clinical and non-clinical attributes that influence treatment decisions and current drug performance against treatment drivers.



02

Inhaled insulin

Exubera®

Scientific success did not guarantee market acceptance

Overview

Producers

Pfizer Inc, Aventis Pharmaceuticals Inc (now Sanofi), Nektar Therapeutics

Type

Insulin

Usage

Inhaled, short-acting, dry insulin powder preparation to treat type 1 and type 2 diabetes

- 1995: Partnership formed to begin development of EXUBERA
- January 2006: Marketing authorization granted by the EMA and approval granted by the FDA for adults requiring insulin therapy
- October 2007: EXUBERA withdrawn from the market

An innovative, highly anticipated delivery method failed to meet patient, physician and payer expectations

Alternatives to burdensome, frequent insulin injections to treat type 1 and type 2 diabetes have long been sought, and inhaled insulin was heralded as a breakthrough that would provide a more convenient, discrete mode of administration that could enhance compliance and thus patient outcomes.

The first inhaled formulation to be approved was EXUBERA, human insulin delivered via powder (stored in blister packs) inhaled from a specially designed handheld inhaler device designed by Nektar Therapeutics. Stabilizing the insulin molecule for bioavailability as a dry powder was a significant technical achievement that took many years of development and testing, contributing to the excitement when it was proven feasible in clinical trials and received regulatory approval.

As a short-acting insulin, patients were to inhale EXUBERA before meals, as part of combination therapy with longer-acting insulin for individuals with type 1 diabetes and either as monotherapy or in combination with other diabetes treatments (insulin or oral antidiabetic agents) for individuals with type 2 diabetes.

Regarding efficacy, HbA1c control was non-inferior compared with injectable insulin in clinical trials.

Stakeholders across the industry felt inhaled insulin offered a much-needed treatment option that patients would prefer. Their hopes for EXUBERA were validated in clinical trials: participants with type 1 or type 2 diabetes preferred this delivery method over injectable subcutaneous insulin (note: pen-injector devices were not yet approved in the U.S.). Satisfaction was high: 85% of the participants who received EXUBERA chose to continue using it over injectable insulin, and 75% of participants switched from injectable insulin to EXUBERA when given the choice (compared with 13% switching from EXUBERA to injected insulin). In addition, EXUBERA resulted in smaller increases in body weight than insulin injections in both type 1 and type 2 diabetes, a particular concern for patients and physicians when starting insulin treatment.

As a result, Pfizer Inc predicted sales of more than $1.5 billion by 2010, but sales were slow out of the gate: $4 million in Q2 2007 and $12 million for the first three quarters of 2007, only 1% of insulin sales overall. The $1.4 billion price tag for Pfizer to acquire EXUBERA from Sanofi, the 10%-20% in sales and royalties paid to Nektar Therapeutics and $300 million to upgrade Pfizer's manufacturing plant for EXUBERA only exacerbated the lackluster sales.

So, what went wrong? A myriad of factors coalesced to impact sales and prompt Pfizer to abandon the drug:

Inability to provide a consistent dose

The blisters contained either 1 mg or 3 mg of insulin, and multiple blisters were used simultaneously to achieve higher doses, which was deemed cumbersome. Clinicians complained of the inability to easily select a specific insulin dose.

Large, bulky inhaler and difficult-to-manage blister packages

The companies went to market with an early inhaler design—a clunky, flashlight-sized device—despite having a smaller device in the works. Although the inhaler design was considered reliable and effective from a scientific point of view (after all, it optimized insulin delivery into the deep lung), the design did not meet expectations for all patients. Discretion is a major desire for individuals with diabetes, and some found it embarrassing to use the bulky inhaler in public. Patients also found inhalation of a higher dose time-consuming: it could take several minutes to insert a series of blisters, activate the air pump in the inhaler and inhale the entire cloud of powder.

Clinicians also faced challenges allocating the time necessary to educate patients about adequate inhaler use, especially within the context of a busy medical practice.

Risk of decreased breathing ability and increased risk of lung cancer

Although early studies showed acceptable tolerability regarding lung function, respiratory adverse effects reported in later results included infection, cough, pharyngitis and rhinitis. Pulmonary function declined more than with placebo and lasted for the full duration of therapy. Monitoring requirements increased as a result of regulatory requirements (spirometry assessment before initiation and at regular intervals throughout treatment), adding to the already lengthy prescribing process.

Seven newly diagnosed cases of lung cancer (six in clinical trials and one in post-marketing) resulted in changes to the safety information in the label and additional concerns about the safety of the product.

Lengthy development process

The deal between Nektar Therapeutics and Pfizer Inc was first signed in 1995, 11 years before the market launch of EXUBERA. Over that time, Pfizer had three CEOs and numerous changes to program priorities. Although the program continued, poor allocation of commercialization resources at launch likely contributed to EXUBERA's poor uptake.

During this time, newer needle delivery systems were developed, such as easy-to-use "pen" devices and pumps that are discrete, effective and acceptable to patients and clinicians alike. Increased competition from these devices diminished the appeal of a bulky inhaler system that had potential safety risks.

Poor marketing and communication with patients, clinicians and payers

In the face of this competition, Pfizer Inc needed to convince patients, clinicians and payers of the value of initiating or switching to EXUBERA. Many felt the marketing at launch was underwhelming:

- "Samples were sparse, the TV ads were late and they were too benign. They did not court the nurses, the certified diabetic educators, who play an even bigger role than physicians in deciding to put patients on insulin." (*Pfizer dumps Exubera* in Nature Biotechnology)—despite reportedly hiring ~900 part-time diabetes educators to explain the product to doctors and patients.

- "A small, non-branded ad campaign for the drug that doesn't mention Exubera by name started recently." (*Inhaled insulin fails to impress doctors* by NBC News)

- "Presentation of the advantages of Exubera and how it could have been of help in insulin therapy was not convincing." (The Failure of Exubera: Are We Beating a Dead Horse? by Lutz Heinemann in the Journal of Diabetes Science and Technology)

- "Talking with the sales representatives at the [diabetes congress] booth quickly revealed that they were trained to sell Exubera like any other drug but had no in-depth understanding of the advantages and disadvantages of this product." (*The Failure of Exubera: Are We Beating a Dead Horse?* by Lutz Heinemann in the Journal of Diabetes Science and Technology)

- "...a direct-to-consumer ad campaign that might have come too late in the game." (*Hard-Pressed Pfizer Dropping Exubera* by Randy Osborne in BioWorld)

At the time, Pfizer Inc had not yet invested in diabetes assets and likely lacked the drive and commercialization expertise to go beyond the typical marketing efforts that had served them well in the past for treatments that had clearer benefits in a less competitive market.

Double the cost of injectable insulin ($5 vs $2-3) and lack of reimbursement

Failing to convince users and payers of the benefits did not bode well when trying to convince them to pay double the price of a well-established, easy-to-use and efficacious option such as injectable insulin. Undoubtedly, the higher cost stemmed from the lengthy development costs of the formulation and inhaler. In addition, the lower bioavailability of inhaled insulin (10%-20% of injectable insulin) meant that a higher amount of insulin was needed to achieve the same metabolic effect. Although this was not viewed as a barrier when development first began, the increasing scrutiny of the cost:benefit ratio by payers and clinicians by the time of EXUBERA's approval certainly played into reimbursement and prescribing decisions.

WellPoint Inc, the largest insurer in the U.S. at the time, either did not cover EXUBERA or placed it in the most restrictive tier that had higher copays. In the U.K., the NHS denied coverage for EXUBERA.

Financial pressure from loss of patent protection

As Pfizer Inc lost patent protection for revenue generators such as NORVASC® for high blood pressure, ZITHROMAX® (antibiotic) and the antidepressant ZOLOFT®, company leadership may have decided to abandon underperforming assets that did not align with the overall company focus.

In the end, Pfizer may have rushed what it thought would be another potential blockbuster into the market, in an attempt to recoup development costs and make up revenue from losing exclusivity of key assets, without doing its due diligence to ensure that it would be accepted and paid for by patients, clinicians and payers.

Lessons learned

Innovative scientific discoveries do not always translate to real-life uptake.

Direct patient and clinician feedback regarding the barriers and facilitators to use can drive successful product development and refinement before launch. For example, in the Clarivate Disease Landscape & Forecast type 2 diabetes, surveyed physicians in the U.S. and Europe reported being less influenced by convenient administration and safety profiles than they are by the efficacy in their prescribing decisions, including when presented with three target product profiles (TPPs) (Figure 2).

Strong sales are not guaranteed by being first to market, particularly if the product or device is novel and must overcome entrenched treatment paradigms.

Pricing strategies need to be carefully considered, including the value the drug provides, competitive landscape and potential impact of pricing on patient access.

Re-evaluating the market throughout a prolonged development timeline could inform go-no-go decisions at different stages or modifications that could enhance uptake at launch.

Providing data that demonstrate more than just a clinical benefit is recommended, especially when a new therapy is entering a complex, crowded treatment environment.

Conducting market research regarding the reimbursement procedures can guide the type of information needed to address the specific payer's requirements.

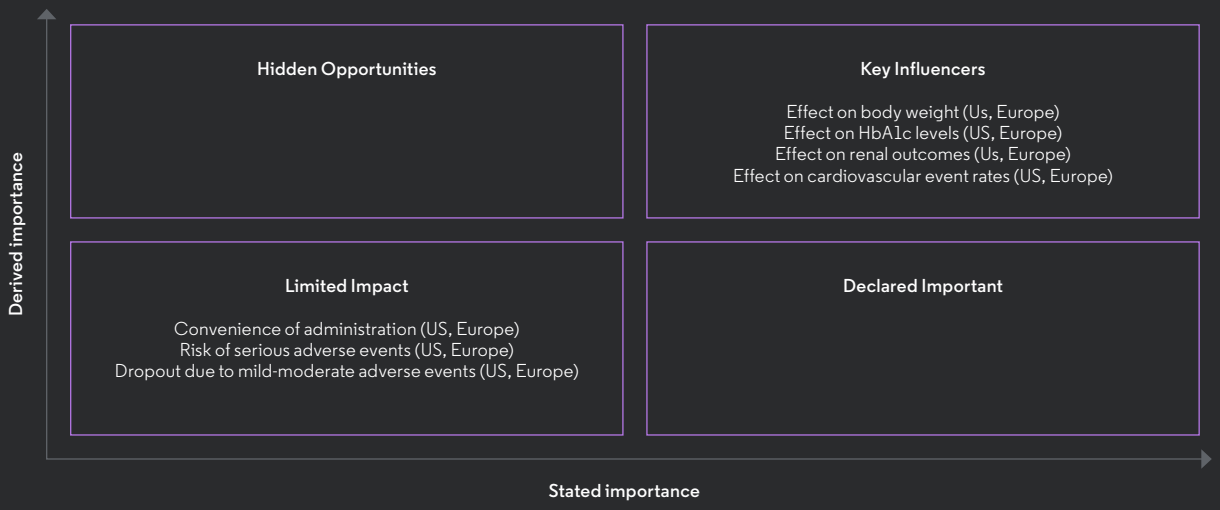
Adoption of novel devices could benefit from strategic pre-launch education and marketing campaigns and outreach.

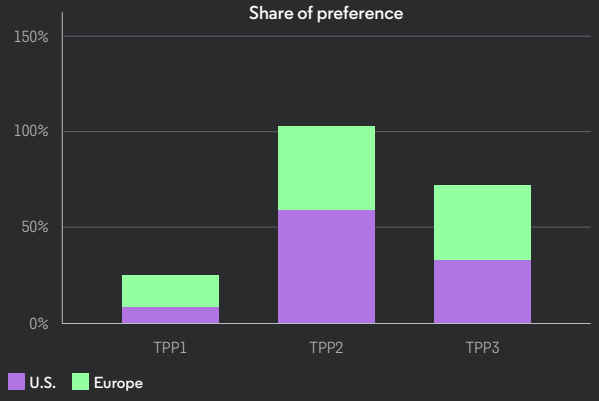
Analyzing and recruiting into trials the type of patient segment who would be the most willing to use a new delivery device could help develop targeted marketing campaigns that encourage adoption before releasing it to the broader patient market. For example, obese patients struggle to achieve optimal insulin therapy with injectables because absorption is delayed by subcutaneous tissue. For these patients, inhaled insulin could be more beneficial and minimize insulin-related weight gain.

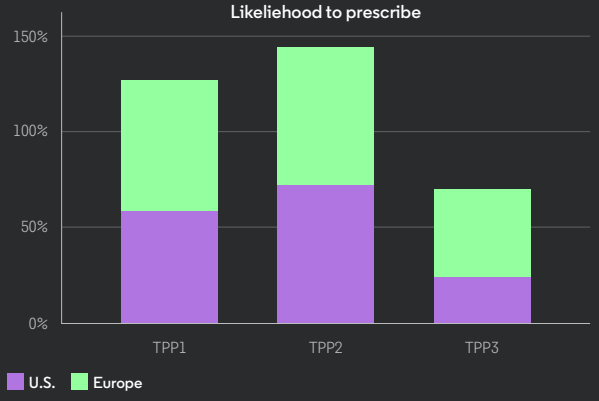
U.S. commercial payers (and even federal programs like Medicare and Medicaid) can be indifferent to benefits to patients and the patient experience, focusing solely on cost.

When needed, information needed to demonstrate an acceptable cost:benefit ratio for payers and how to demonstrate value to patients and prescribers is also key to setting expectations and a successful launch.

Figure 2. Physicians prefer prescribing type 2 diabetes treatments that are more effective over choosing them for convenience.







Drug Attribute	TPP 1 (a hypothetical therapy)	TPP 2 (a hypothetical therapy)	TPP 3 (a hypothetical therapy)
Mean reduction in HbA1c levels from baseline after one year	-2%	-3%	-1.5%
Change in body weight after one year	10% decrease	5% decrease	5% decrease
Reduction in major adverse cardiovascular event (MACE) rates versus placebo	20% reduction	10% reduction	30% reduction
Effect on adverse renal conditions	Moderate improvement in proteinuria	Moderate improvement in proteinuria	Moderate improvement in proteinuria
Dropout $ due to mild-moderate adverse events	3%	3%	3%
Dosing burden	Once daily WITH meal intake restrictions	Once daily WITH meal intake restrictions	Once daily WITH meal intake restrictions
Price per day of therapy	$30/day	$25/day	$50/day

Source: Clarivate Disease Landscape & Forecast

03

Lonapegsomatropin

SKYTROFA®

Sales at launch hindered by lack of robust market insights

Overview

Producers

Ascendis Pharma

Type

Human growth hormone (GH)

Usage

Once-weekly, subcutaneous injection to treat growth failure due to inadequate secretion of endogenous GH

- August 2021: first approval of SKYTROFA to treat pediatric patients 1 year and older with growth failure due to inadequate secretion of endogenous GH
- January 2022: EMA marketing authorization to treat children and adolescents ages 3 to 18 years with growth failure due to insufficient secretion of endogenous GH
- 2022-2023: Impact of lower-than-expected initial uptake on the company's cash runway and financial outlook that required corrective actions

Deprioritized market access planning resulted in slow sales

SKYTROFA was Ascendis Pharma's first drug to be approved in the U.S. and gain marketing approval using its TransCon™ technology. This novel delivery system provided predictable, sustained drug release and therefore enabled once-weekly administration.

When SKYTROFA was launched, daily somatropin injections had been the standard of care for more than 30 years. Daily GH injections result in challenges for treatment adherence, with up to 62% of patients missing at least one dose every month. Switching from daily to weekly injections could result in as much as 86% fewer injection days per year and higher growth rate than the daily therapies.

As the first FDA-approved once-weekly pediatric GH treatment, the SKYTROFA approval also covered an auto-injector and cartridges that can be stored for up to six months at room temperature, another benefit over traditional injections. As a result, the company was confident that patients, parents and prescribers would prefer SKYTROFA as a weekly option despite a higher cost, inflating its expectations for initial market adoption of SKYTROFA at launch.

During a call with investors, CEO Jan Mikkelsen remarked that "premium responsible pricing" would be put in place and promised that a suite of patient support programs would be available. "We have a clear view of where we want to be in pricing, and this is basically part of our current negotiation[s]" with payers.

However, the cost of the drug for end users at launch was:

- ~$219/mg or ~$95,000 annual premium (at the recommended dose for a 35-kg 11-year-old), ~77% more expensive than daily GH, which was priced at ~$123/mg and
- 20%-40% higher at a monthly cost than that of Genotropin® (Pfizer Inc; for a child weighing 30 kg receiving the standard dose).

By the end of the first quarter after FDA approval, most patients had not switched over to a commercial prescription program for SKYTROFA due to a lack of insurance or the lag time between requesting prior authorization and fulfillment of the prescriptions. In addition, the Ascendis Signature Access Program (ASAP) offered the first doses for free, impacting initial sales. Four months after launch, the Ascendis Pharma Market Access team was still actively trying to work with public and private entities to arrange reimbursement for SKYTROFA.

Based on internal Clarivate primary market research from the Clarivate Commercial Strategy Consulting team, Ascendis failed to listen to internal U.S.-based subject matter experts who pointed out the considerable market commoditization with other brands, heavy contracting and expected step-therapy approach was unlikely to be adopted by U.S. payers. Few payers were willing to put the product on formulary and noted that the perceived patient convenience of SKTROFA was an insufficient reason for formulary inclusion.

A major strategic error involved expecting that quality-of-life measures as part of the payer formulary review criteria would be viewed in the U.S. in a manner similar to that in E.U. countries.

Patients and physicians were reluctant to switch from the free or relatively inexpensive daily generic somatropin. Some physicians noted that patients and caregivers found it difficult to obtain SKYTROFA due to a lack of insurance coverage. About 40% (8/20) of physicians indicated that reimbursement difficulties with prior authorizations represented a notable hurdle. Although the commercialization strategy targeted 1,400 high-volume daily growth hormone replacement prescribers, by the end of December 2021, only about 10% of them had written a prescription for SKYTROFA.

Based on internal primary market research from the Clarivate Commercial Strategy consulting team, Ascendis failed to listen to internal U.S.-based subject matter experts who pointed out the considerable market commoditization with other brands, heavy contracting and expected step-therapy approach was unlikely to be adopted by U.S. payers.

Market access challenges threatened the success of SKYTROFA and subsequent programs

The TransCon delivery system forms the basis for the development of multiple drugs through 2025 as well as the company's long-term Vision 3x3 strategy. Announced in 2019, the strategy aimed to mitigate the success or failure of any one drug by the release of one of the others. The plan covered the following goals:

01

Attain regulatory approval for the first three drugs using the TransCon delivery system.

02

Increase the covered indications to nine.

03

Gain global market access and awareness.

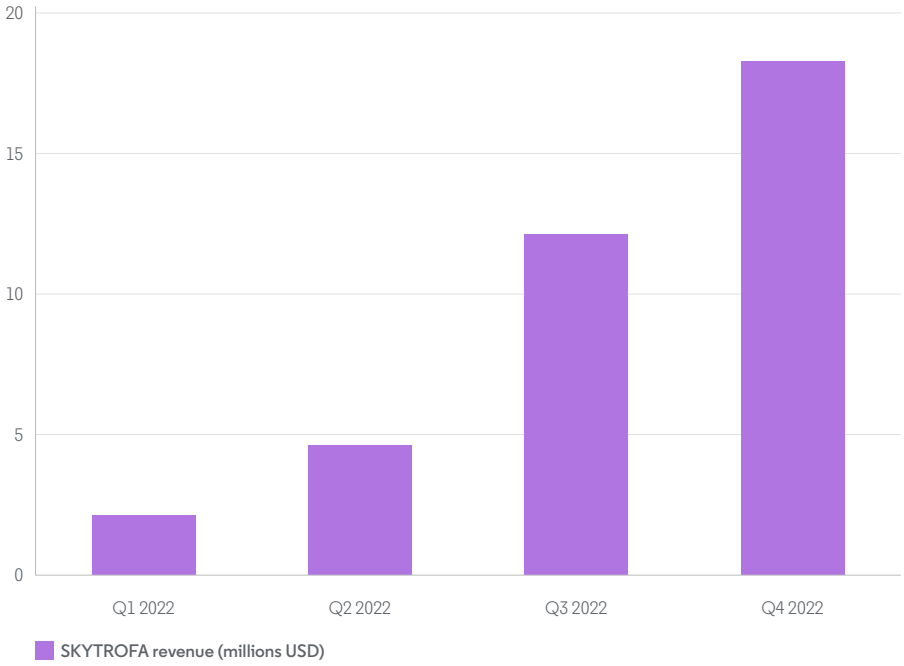
04

Diversify the company into three different specialties: endocrinology, oncology and ophthalmology.

The company's largest misstep during the SKYTROFA launch was prioritizing Steps 1, 2 and 4 in the Vision 3x3 plan before focusing on Step 3 (market access).

SKYTROFA launch sales within the first fiscal year were approximately half of the predicted amount ($1.1 million according to Clarivate data), with initially slow growth in 2022:

Figure 3: SKYTROFA sales picked up in the latter half of 2022, according to quarterly sales.



Source: Ascendis Pharma press release; reported Euro values converted to U.S. dollars using exchange rates from the end of each quarter in 2022

Although delayed SKYTROFA sales had minimal immediate impact on the company's and its shareholders' outlook, the failure of the second drug using the TransCon delivery system (TransCon PTH for parathyroid hormone replacement) to be approved by the FDA in 2023 introduced doubts about the company's financial future and spurred real changes.

In December, just after SKYTROFA was approved, Ascendis Pharma had cash, cash equivalents and marketable securities of €789.6 million. The slow initial SKYTROFA sales and the later FDA rejection of TransCon PTH reduced that number to €399 million by the end of 2023. Losses over the previous five years increased at a rate of 24.8% per year.

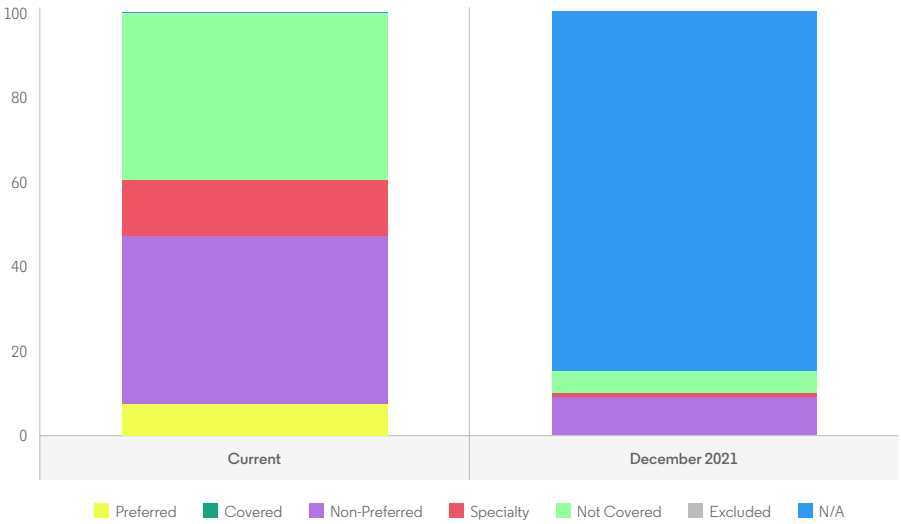
Ascendis Pharma acted in multiple ways to increase market access and sales potential

In addition to streamlining the company structure and processes, the company undertook a multifaceted approach to grow the sales and market reach of SKYTROFA:

Stronger internal team

In May 2022, Ascendis Pharma began investing more resources into SKYTROFA commercialization and market access. The company created new roles to strengthen the marketing team, including Head of U.S. Commercial Endocrinology and Head of Global Commercial Strategy, Endocrinology.

Figure 4. Insurance coverage in the U.S. is ~50% better since December 2021.



Covered Lives	Plans With Coverage	Requires PA	Covered Without Restrictions
60.28%	60.28%	65.55%	5.23%
50.2% more than December 2021	50.2% more than December 2021	55.23% more than December 2021	2.74% more than December 2021

Source: Clarivate Market Access Intelligence

More realistic sales expectations

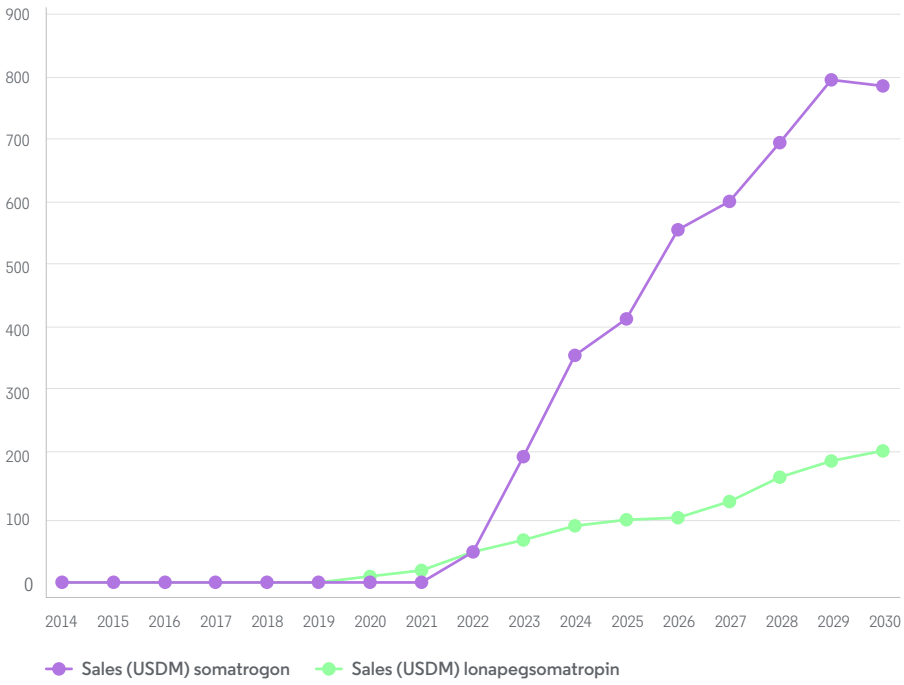
In the U.S., Ascendis Pharma continued to slowly grow the market by adjusting quarterly sales expectations and investing in longer-term success, a strategy that seemed to pay off. Even with the launch of two competitor long-acting GH replacement therapies, sales have continued to grow for SKYTROFA after approval and launches throughout European countries, which led to increased 2023 sales expectations.

These projections were proved correct: in Q3 2023, revenue was 31% higher than in Q2 2023 and 483% higher than in Q3 2022 (Figure 5).

Greater market access

The company announced distribution agreements in late 2023 and early 2024 with several specialty commercialization companies with the aim of increasing market access globally, including in Japan, Singapore, the Middle East and Eastern Europe.

Figure 5. SKYTROFA (lonapegsomatropin) sales are expected to significantly outpace those of competitors such as NGENLA™ (somatrogon).



Source: Cortellis Competitive Intelligence™

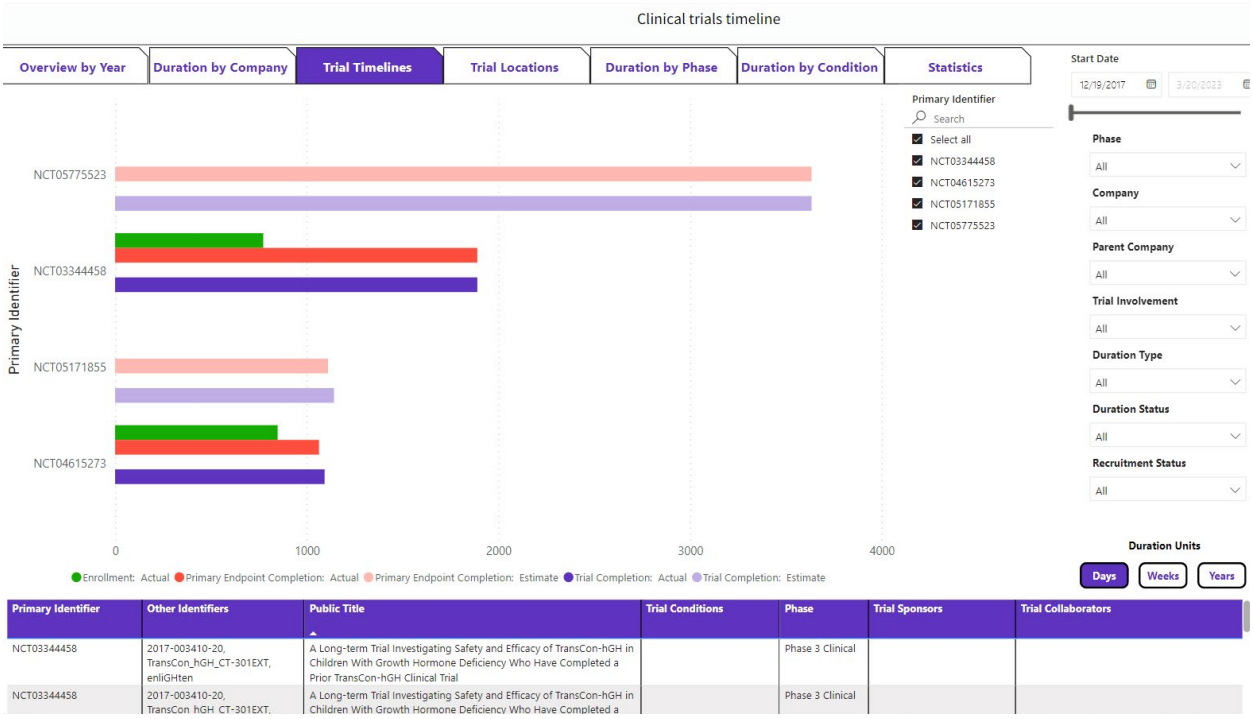
Expanded patient population

Clinical trials are underway to evaluate SKYTROFA to treat adults with GH deficiency and individuals with Turner syndrome (New InsiGHTS Trial) (Figure 6).

Diversified platform use

The company is also seeking approval for other drugs using the TransCon technology platform to treat a variety of conditions, including hypoparathyroidism, wet age-related macular degeneration (AMD) and solid tumors.

Figure 6. Status of clinical trials evaluating SKYTROFA with adults with GH deficiency



Source: Cortellis Clinical Trials Intelligence™

Lessons learned

Strong sales are not guaranteed by being first to market.

Payment strategies should be in place before commercialization.

Conducting early market research for the target countries, formularies, reimbursement procedures and patient needs is key to setting expectations and a successful launch. For example, Clarivate Market Access Intelligence can help identify the formulary managers, the populations they cover and the current pharmacy coverage to allow targeting of market access efforts at the plans and population that are not currently being served.

To set realistic expectations regarding immediate sales post-launch, "specialty drugs" require a robust understanding of prior authorization and reimbursement processes worldwide.

U.S. commercial payers (and even federal programs like Medicare and Medicaid) can be indifferent to benefits to patients and the patient experience, focusing solely on cost.

04

Olaratumab

LARTRUVO®

Late-phase results failed to show survival benefits, despite promising early-phase results

Overview

Producers

Eli Lilly and Co

Type

Monoclonal antibody (mAb) directed against platelet-derived growth factor receptor alpha

Usage

Infusion to treat soft tissue sarcoma (STS)1 and type 2 diabetes

- February 2016: Accelerated approval by the FDA, in combination with doxorubicin: first new therapy for the first-line treatment of STS in over 40 years.
- November 2016: EMA conditional marketing approval, in combination with doxorubicin
- January 2019: Confirmatory phase 3 trial (ANNOUNCE) failed to show benefit for extension of survival
- April 2019: LARTRUVO withdrawn from the global market by Eli Lilly and Co; EMA conditional marketing approval withdrawn
- September 2019: Official request by Eli Lilly and Co to the FDA to withdraw LARTRUVO
- February 2020: Approval revoked by the FDA to manufacture and market LARTRUVO
- April 2022: Licensing agreement with Telix Pharmaceuticals Ltd to repurpose LARTRUVO

Early-phase results did not translate to later-phase benefits

The prognosis for sarcoma remains poor, and effective, safe treatments remain an unmet need. Surgery, followed by radiation, has long been the first-line treatment for STS, but many patients still develop metastatic disease, for which systemic chemotherapy, particularly doxorubicin, may be used but with varied effectiveness.

LARTRUVO (in combination with doxorubicin) emerged as an innovative treatment that showed potential to change the treatment paradigm and address the significant patient need. With this view, the EMA granted conditional marketing approval, and the FDA granted LARTRUVO fast track designation, breakthrough therapy designation, priority review status, orphan drug designation and accelerated approval.

Approvals in the U.S. and E.U. were granted based on data from a small phase 2 study that included adult patients (n=133) in the U.S. with more than 25 different STS subtypes. The study results showed significant improvement in progression-free survival (PFS), overall survival (OS) and objective response rate (ORR) as well as a tolerable safety profile compared with doxorubicin alone.

Eli Lilly and Co undertook a confirmatory phase 3 (ANNOUNCE) trial with ~500 participants across more than 100 sites in the U.S., Canada, Europe and Asia.

The results, released years after the accelerated approval, failed to show improved survival for patients with advanced or metastatic STS compared with doxorubicin (median OS: 20.4 months vs 19.7 months). Based on these results, the company suspended promotions and new prescriptions of the drug in the global market and ceased further internal development.

Upon review of the ANNOUNCE results, Eli Lilly and Co voluntarily withdrew the drug from the global market and implemented a patient access program to ensure a smooth transition and continued access. No new patients were to receive LARTRUVO outside of ongoing clinical trials.

The phase 1b ANNOUNCE-2 trial comparing olaratumab + gemcitabine + docetaxel with placebo + gemcitabine + docetaxel continued after LARTRUVO was pulled from the market. However, these results also failed to demonstrate a survival benefit with olaratumab.

Figure 7. Comprehensive regulatory timelines for the indication addressed by LARTRUVO

Company	Indication	Country/Territory	Status	Date
Eli Lilly & Co	Gastrointestinal stromal tumor	US	No Development Reported	31-May-2024
Eli Lilly & Co	Gastrointestinal stromal tumor	Europe	No Development Reported	31-May-2014
Eli Lilly & Co	Prostate Tumor	Europe	No Development Reported	30-Apr-2015
Eli Lilly & Co	Ovary Tumor	US	No Development Reported	31-Aug-2015
Eli Lilly & Co	Glioblastoma	US	No Development Reported	31-Mar-2016
Eli Lilly & Co	Metastatic pancreas cancer	Spain	Phase 2 Clinical	30-Oct-2018
Eli Lilly & Co	Metastatic pancreas cancer	US	Phase 2 Clinical	30-Oct-2018
Eli Lilly & Co	Metastatic pancreas cancer	Germany	Phase 2 Clinical	30-Oct-2018
Eli Lilly & Co	Soft tissue sarcoma	Austria	"Withdrawn [Lack of Activity or Efficacy]"	25-Apr-2019
Eli Lilly & Co	Soft tissue sarcoma	Taiwan	"Withdrawn [Lack of Activity or Efficacy]"	25-Apr-2019
Eli Lilly & Co	Soft tissue sarcoma	Brazil	"Withdrawn [Lack of Activity or Efficacy]"	25-Apr-2019
Eli Lilly & Co	Soft tissue sarcoma	South Korea	"Withdrawn [Lack of Activity or Efficacy]"	25-Apr-2019
Eli Lilly & Co	Soft tissue sarcoma	Canada	"Withdrawn [Lack of Activity or Efficacy]"	25-Apr-2019

Source: Cortellis Competitive Intelligence

Delayed confirmatory data impacted the company's bottom line and confidence in regulatory processes

Sales during the first two full years on the market (~$500 million: $203 million in 2017 and $304.7 million in 2018) exceeded estimates ($373.75 million within five years), and predicted sales for 2019 exceeded $374 million, demonstrating its impact on patient care as well as its potential to contribute to the company's revenues. Withdrawing the drug from the market ended those hopes and instead contributed an $84.6 million impairment cost for Eli Lilly and Co in Q1 2019.

Eli Lilly and Co reduced its 2019 sales and earnings estimates as a result of the loss of LARTRUVO revenue; however, this was not considered a significant impact on the company's overall outlook because of other programs currently underway or in the market. It also entered into a licensing agreement with Telix Pharmaceuticals Ltd in a deal worth up to $225 million in April 2022—Telix Pharmaceuticals viewed LARTRUVO's tolerable, well-established safety profile as a valuable opportunity upon which to build its program. With the agreement, Telix Pharmaceuticals gained exclusive global rights to develop and commercialize radiolabeled forms of the antibody to diagnose and treat human cancers, specifically radiopharmaceutical imaging and treatment.

More broadly related to regulatory processes, the termination of LARTRUVO's marketing after more than two years raised concerns about the FDA's accelerated approval process—in fact, as of December 31, 2021, 12% of accelerated approvals have been withdrawn either voluntarily or involuntarily after FDA proceedings. With LARTRUVO, the lag time between approval and confirmatory safety and efficacy data for LARTRUVO was particularly concerning, not only for the impact on patient care but also the cost of drug coverage and reimbursement while it was on the market.

The FDA has since issued guidelines to meet "the substantial evidence standard based on one adequate and well-controlled clinical investigation plus confirmatory evidence" to address submissions that seek approval using the results from a single study.

Figure 8. Overall Eli Lilly and Co sales were impacted throughout the approval lifetime of LARTRUVO.

Source: Cortellis Competitive Intelligence

Lessons learned

A cautious, comprehensive approach to early-phase data analysis can better inform go-no-go decisions to move to larger, more expensive clinical trials.

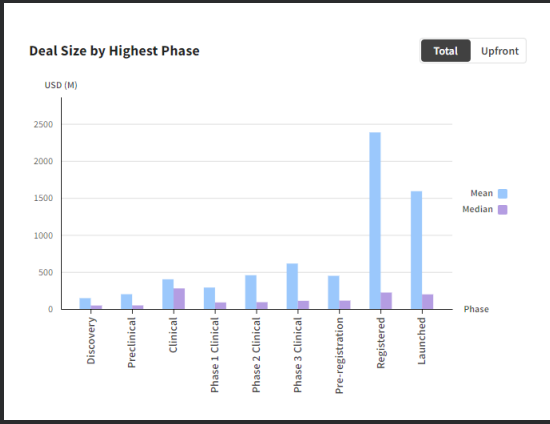
Having insights into disease associations, along with commercial intelligence, could enable pivoting to another, more successful indication (Figure 11).

A deep understanding of the condition being treated down to a molecular level helps identify which disease subtypes a drug will be most effective for.

At early signs that a program will not achieve the expected results, it could be beneficial to seek partnerships with companies that have the necessary technology or capability to repurpose the product—to minimize losses. Deals and competitive intelligence sources help inform the early stages of deal seeking (Figures 9 and 10).

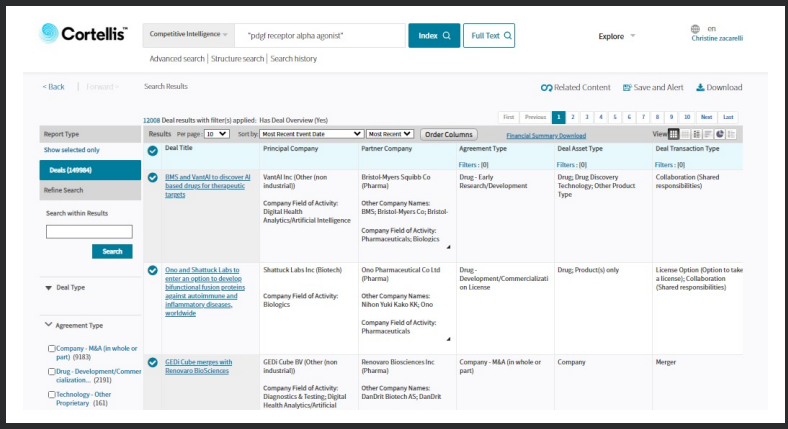
Given the heterogeneity of sarcoma, even slight differences in the phase 2 and phase 3 study populations could have confounded the results, highlighting the importance of rigorous study planning and conduct from the beginning of the program.

Figure 9. Identify potential partners by analyzing past deals and current pipelines: mAb deal size is shown by development stage.



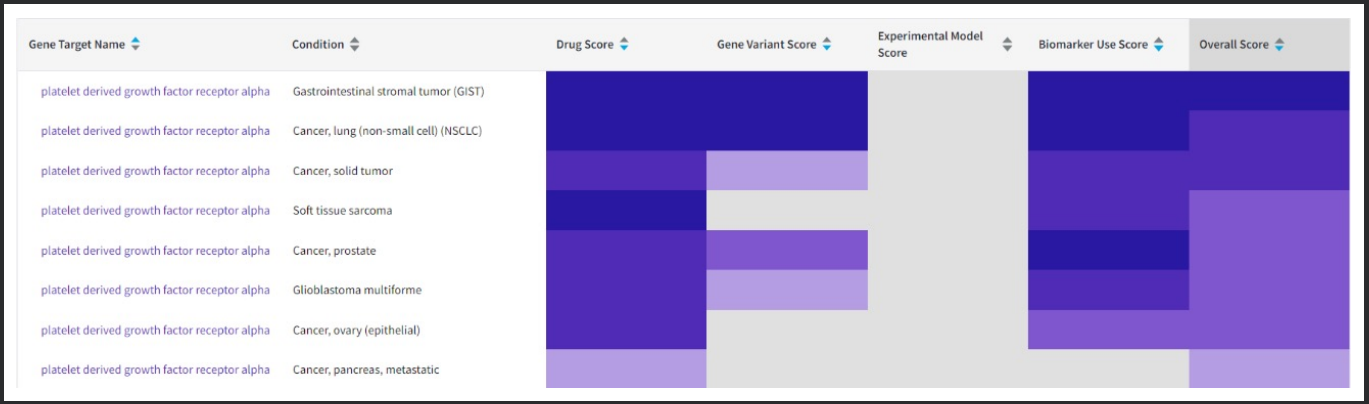
Source: Cortellis Deals Intelligence™

Figure 10. Analyze deals and partnerships between competitors, and identify the companies and areas of research that will be most likely to re-develop a failed drug using the existing data findings.



Source: Cortellis Competitive Intelligence™

Figure 11. Use insights from biological evidence (gene variants, knockout models of disease, biomarkers) and level of competition to identify and prioritize potential new indications.



Source: Cortellis Drug Discovery Intelligence

05

Panitumumab

Vectibix

Prescient data collection allowed for a pivot after initial disappointment

Overview

Producers

Amgen and Takeda Pharmaceutical Co Ltd

Type

Fully human IgG2 mAb EGFR inhibitor

Usage

Infusion every two weeks to treat colorectal cancer (CRC)

- 2002: Acquisition of Immunex Corp (and panitumumab) by Abgenix Inc
- 2002: Partnership between Amgen and Abgenix to develop panitumumab
- July 2005: Fast track designation granted by the FDA
- December 2005: Announcement that Amgen was acquiring Abgenix (and panitumumab) Amgen for $2.2 billion
- September 2006: FDA approval as monotherapy to treat EGFR-expressing metastatic CRC (mCRC) after disease progression with prior standard chemotherapy treatment
- May 2007: Negative decision by the EMA for mCRC after disease progression with prior standard chemotherapy treatment
- December 2007: Conditional marketing authorization by the EMA to treat wild-type KRAS mCRC
- February 2008: Japanese rights to Vectibix (plus 12 other molecules) transferred to Takeda Pharmaceutical Co Ltd for $200 million up front and payment of 60% of ongoing clinical development expenses outside of Japan
- June 2009: FDA permission to submit retrospective biomarker analysis for labeling purposes
- April 2010: Approval in Japan to treat unresectable, advanced or recurrent CRC with wild-type KRAS
- June 2011: EMA marketing authorization for combination first-line treatment with FOLFOX and combination second-line treatment with FOLFIRI for wild-type KRAS mCRC
- May 2014: FDA approval for combination first-line treatment with FOLFOX as first-line treatment of wild-type KRAS mCRC
- January 2015: Full marketing authorization by the EMA for combination first-line treatment with FOLFOX as first-line treatment of wild-type RAS mCRC
- June 2017: FDA approval for a refined indication for patients with wild-type RAS mCRC

Amgen initially struggled to demonstrate the value of Vectibix

Short survival durations characterized mCRC, and panitumumab was the first EGFR inhibitor to show a statistically significant PFS improvement in refractory mCRC, findings that supported the FDA priority review and marketing applications to the EMA and Health Canada and filings in Australia and Switzerland.

Achieving first-in-class status with the FDA approval to treat EGFR-expressing mCRC after disease progression with prior standard chemotherapy treatment, sales were estimated to reach $2 billion annually. However, the drug experienced several setbacks over the next year.

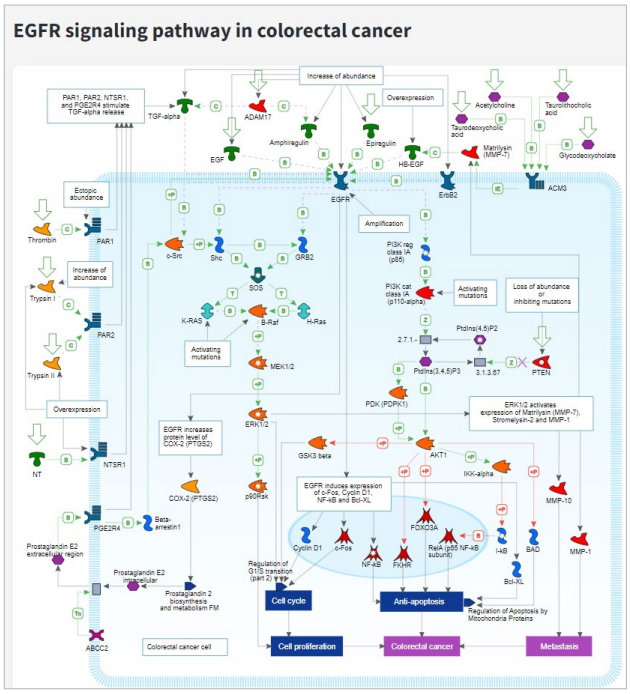
Despite expectations of Vectibix as a first-line competitor to Avastin® (Genentech), in March 2007, Amgen terminated a head-to-head study of Vectibix against Avastin for first-line use because Avastin had superior PFS in the interim results. Then, in May 2007, the European Committee for Medicinal Products for Human Use (CHMP) adopted a negative opinion about Vectibix for patients with mCRC who had failed chemotherapy, raising serious questions about its efficacy. In the study data, EGFR expression alone was not predictive of treatment efficacy, failing to convince authorities that the benefit of Vectibix for these patients outweighed its risks.

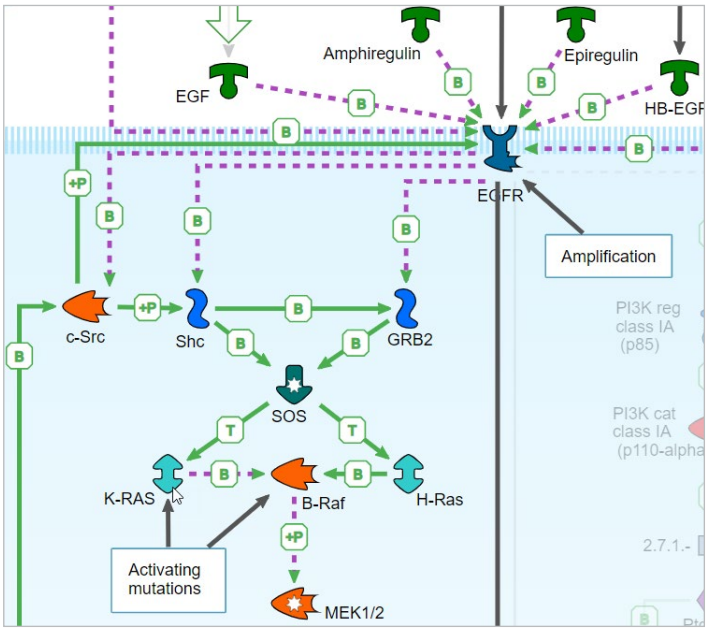
Amgen's interest in biomarkers to define disease and understand drug responses was its saving grace

The company had initiated a biomarker program in the early 2000s with the aim of defining disease types and identifying correlations between drug response and specific disease types within the patient populations it was studying. Because of this program, Amgen collected tumor samples during its pivotal phase 3 study (study 408) of Vectibix. For its own internal purposes, the company ran retrospective analyses based on biomarkers of interest, including KRAS—because EGFR signaling may continue despite anti-EGFR therapy in the presence of KRAS mutations.

Figure 12. This pathway map for EGFR signaling in CRC visually summarizes the current understanding of the signaling cascade from a thorough review of the relevant scientific literature and provides insights into the disease mechanisms.

Activating mutations in KRAS (bottom left) lead to constitutive activation of the RAS signaling pathway, making it ligand-independent and resistant to anti-EGFR treatment. The pink dotted lines indicate signaling cascade components that are enhanced in the disease state.





Source: MetaCore™, a Cortellis™ solution

A breakthrough in understanding the fairly lackluster results with Vectibix in the overall mCRC population came from this KRAS analysis—patients with non-mutant KRAS tumors had significantly better outcomes than patients with mutant KRAS tumors. About 40% of patients with mCRC have KRAS mutations, while the other nearly 60% have the wild-type KRAS gene, and panitumumab became the first mAb to demonstrate the use of KRAS as a predictive biomarker.

Based on this info, Amgen also amended the trial protocols of two ongoing large phase 3 trials of Vectibix to allow primary analysis of the KRAS wild-type population. This shift in strategy gave Amgen an advantage over rival EGFR inhibitor Erbitux (cetuximab; ImClone Systems Inc), by enabling it to generate the first clean clinical data that demonstrated KRAS mutations could impact treatment efficacy.

Laying the foundation for true precision medicine, physicians, for the first time, had a method to predict which patients would be most likely to respond to treatment with Vectibix. However, Vectibix was already approved for a broader mCRC patient population, introducing yet another hurdle of convincing the FDA to incorporate the retrospective biomarker data about patient subsets into the drug labeling. Until KRAS testing was included on the drugs' labeling, the benefit of using the biomarker in treatment decisions for patients with mCRC could not legally be communicated with the medical community.

Predictive biomarkers permeated discussions across the industry in 2009 with the increasing recognition of the potential to personalize cancer treatments, improve outcomes and cut treatment costs. HERCEPTIN® (trastuzumab) was indicated specifically for patients with HER2-positive breast cancer, and Novartis AG's GLEEVEC® (imatinib) was prescribed for chronic myeloid leukemia (CML) and gastrointestinal stromal tumors based on biomarker-based companion diagnostic test results.

In June of that year, the FDA allowed the retrospective biomarker data for Vectibix, introducing a classwide revision for EGFR inhibitors used as monotherapy in mCRC, inviting Vectibix into the exclusive group of biomarker-driven oncology treatments and advancing personalized medicine by allowing other cancer treatments to retrospectively refine their labels based on biomarkers.

Stratified analyses supported future approvals of Vectibix globally, as combination treatment and in different lines, and Amgen reported year-over-year sales increases of 5% for Q4 2023 and 10% for 2023, driven by 5% and 10% volume growth, respectively.

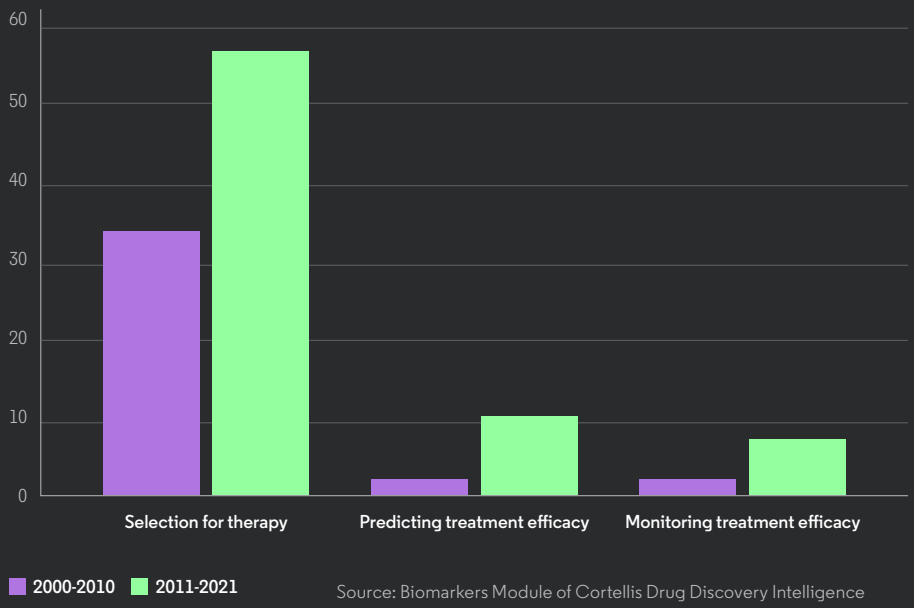
Lessons learned

Identifying patient segments most likely to respond to a drug can help demonstrate clinical efficacy and increase chances of approval.

Having a deep understanding of molecular mechanisms of disease is essential for biomarker identification.

Being prepared to adapt protocols of ongoing clinical trials following setbacks can open up new opportunities.

Figure 13. Efficacy-related biomarker uses in FDA drug approvals



Source: Biomarkers Module of Cortellis Drug Discovery Intelligence

An analysis of efficacy biomarkers specified in FDA approvals shows that "Selection for Therapy" biomarkers almost doubled from 2000-2010 to 2011-2021.

The role of "Selection for Therapy" is applied by Clarivate analysts specifically to biomarkers used in a clinical practice setting for personalizing the treatment of a patient.

06

Ponatinib

ICLUSIG®

Postmarketing safety concerns restricted use and limited the treatable population

Overview

Producers

ARIAD Pharmaceuticals Inc (now Takeda Pharmaceutical Co Ltd)

Type

Tyrosine kinase inhibitor (TKI)

Usage

Oral administration to treat CML and acute lymphoblastic leukemia (ALL)cancer (CRC)

- December 2012: FDA approval as a priority orphan medication
- October 2013: Suspension of the FDA approval; ICLUSIG voluntarily removed from market
- November 2013: EMA approval for a smaller subset of patients than in the FDA approval
- December 2013: Re-approval restricted to the subset of patients as in the E.U.
- May 2016: ARIAD Pharmaceuticals Inc's European operations acquired by Incyte Corporation, as well as a licensing agreement for exclusive development and commercialization rights to ICLUSIG in Europe and other specific countries
- February 2017: ARIAD Pharmaceuticals Inc acquired by Takeda Pharmaceutical Co Ltd
- December 2020: FDA approval for label expansion

Postmarketing safety issues resulted in suspension of the drug

CML and Philadelphia chromosome (Ph)+ALL are both rare diseases. Although first- and second-generation TKIs such as imatinib and dasatinib have been available as the standard of care, resistance to these drugs is the primary cause of treatment failure, resulting in poor disease prognosis. The BCR-ABL gene and its mutations, including the T315I mutation, are often responsible for treatment resistance and are present in up to 20% of patients.

Therefore, ICLUSIG was developed as third-line TKI treatment to block the BCR-ABL gene and its mutations.

Serious safety concerns emerged during continued safety monitoring by the FDA after launch, particularly related to the risk of arterial occlusive events (AOE). The proportion of treated individuals experiencing AOEs such as blood clots and severe blood vessel narrowing was much higher than initially reported, which represented a significant change to the safety profile provided in the regulatory submission. As a result, the FDA requested voluntarily suspension of the drug's marketing and required the following:

- New safety measures to narrow the indication
- Additional warnings and precautions about the AOE risks
- Revised recommendations about dosage and administration
- Updates to the Medication Guide
- A Risk Evaluation and Mitigation Strategy (REMS)
- Postmarket investigations to further characterize the drug's safety and dosing

Loss of revenue impacted the company's ability to operate

In addition to the temporary suspension of the drug's marketing for two months, all participant enrollment into clinical trials of ICLUSIG was paused. Trial enrollment and marketing only resumed after the FDA-recommended changes in the dose and other requests were met.

Restrictions on the drug's use following re-approval reduced the number of patients meeting the treatment criteria by 50% (from 2,500 to 1,300), significantly impacting the drug's commercial success despite its efficacy in some patient populations.

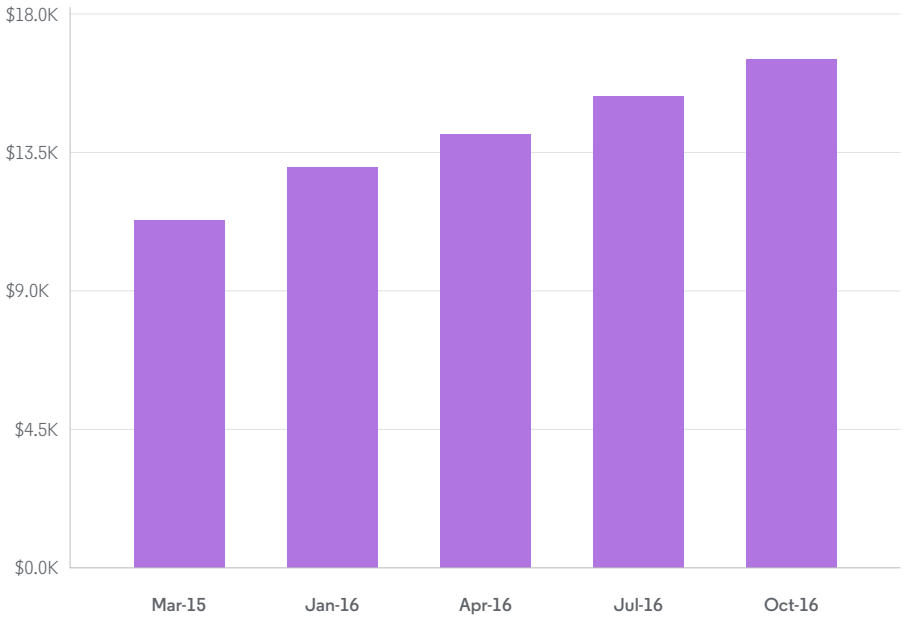
Banking on the desperation of patients with CML or ALL, ARIAD Pharmaceuticals Inc aimed to increase revenue by increasing the annual price of the drug by 75%, from $114,960 in 2012 to $198,732 in 2016. Initially, the company reduced the number of pills in each prescription without reducing the price, resulting in a significant stealth increase in the annual price, followed by incremental price increases (Figure 14).

According to the company, the price increases were justified because the drug addresses a significant unmet need for an orphan patient population. However, the high prices considerably impacted patient access to the drug.

To further address the resulting loss of revenue and company valuation, the company:

- laid off 160 employees,
- suspended plans for a new company headquarters,
- began selling off parts of the business, such as the European operations to Incyte Corporation in 2016 and
- was acquired by Takeda Pharmaceutical Co Ltd in 2017.

Figure 14. The price of ICLUSIG was incrementally increased to help address slow revenue.



Source: How Ariad Pharma Used a Safety Problem to Jack Up a Cancer Drug's Price

The company instituted immediate actions to address the safety concerns

Within the ongoing development program, participants continued receiving ICLUSIG but with monitored reductions in the dose. The exclusion criteria for all ICLUSIG clinical trials were extended to individuals who had experienced prior arterial thrombosis resulting in heart attack or stroke.

Results from a dose-finding trial (OPTIC trial) to find the lowest effective dose informed the supplemental new drug application (sNDA), and the label was updated to reflect the new dosing recommendations. Updates to the safety information included the possibility of blood clots.

The FDA-recommended restrictions to the indication were accepted, meaning the following individuals were eligible for treatment:

- Adult patients with T315I-positive CML (chronic, accelerated or blast phase) or T315I-positive Ph+ ALL
- Adult patients with chronic, accelerated or blast phase CML or Ph+ ALL for whom no other TKI therapy is indicated

Lessons learned

Potential safety issues can be identified and addressed via thorough preclinical and clinical trials, helping to establish the safety profile.

A better understanding of which patients stood to benefit most from the drug might have helped to rein in overbroad labeling and indications.

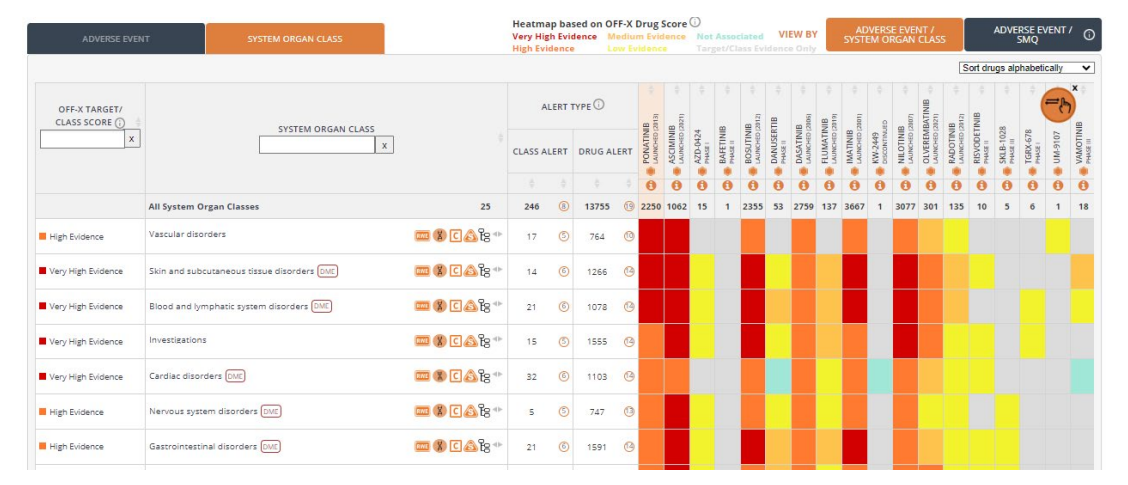
In addition to continuous monitoring of a drug's safety profile post-launch, companies must also have mechanisms in place to communicate promptly with healthcare providers and patients if safety concerns arise.

Review of safety concerns within the drug class could guide identification and monitoring of issues during development and post-launch (Figures 15 & 16).

Robust post-marketing surveillance is needed to detect and respond to safety concerns that might not be apparent in earlier stages of drug development.

Pricing strategies need to be carefully considered, including the value the drug provides, competitive landscape and potential impact of pricing on patient access.

Figure 15. Adverse events of drugs within the same class can highlight safety concerns early in development



Source: OFF-X™

Figure 16. Adverse events for the specific drug can also help identify those of greatest concern, by frequency of reporting.

Source: OFF-X™

07

Rucaparib

RUBRACA®

Poorly designed trials, funding woes and fierce competition bedeviled this PARP inhibitor

Overview

Producers

Clovis Oncology
(licensed from Pfizer Inc)

Type

Poly ADP-ribose polymerase (PARP) inhibitor

Usage

Oral administration to treat epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer

- May 2009: $145 million raised by Clovis Oncology in start-up financing
- June 2011: RUBRACA licensed from Pfizer Inc by Clovis Oncology; single-agent trial for BRCA1/2-positive ovarian cancer initiated
- December 2016: Accelerated approval by the FDA for BRCA-mutated ovarian cancer (including Foundation Medicine's FoundationFocus™ CDxBRCA companion diagnostic)
- April 2018: FDA approval for maintenance treatment of recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer regardless of BRCA status
- May 2018: Conditional approved granted by the EMA for maintenance treatment of recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer
- May 2020: FDA approval for BRCA-mutated, metastatic, castration-resistant prostate cancer (mCRPC)
- June 2022: Voluntarily withdrawal of the indication for third-line treatment of BRCA-mutated ovarian cancer in the United States and Europe
- July 2022: Recommendation by the EMA to restrict use of RUBRACA from third-line treatment to maintenance treatment of partially or completely cleared recurring cancer
- December 2022: Bankruptcy filing by Clovis Oncology
- April 2023: pharma and Pharma& Schweiz GmbH highest bidder to acquire RUBRACA

Delay to market and an inability to pivot placed RUBRACA at a disadvantage from the start

The introduction of PARP inhibitors, including RUBRACA, represented a significant change to the treatment armamentarium for multiple cancers. The promise of RUBRACA in this space was recognized by the FDA, which granted the drug breakthrough therapy designation, priority review status, orphan drug designation and accelerated approval, and Clovis Oncology emerged as one of the pioneers evaluating PARP inhibitors for oncology treatment.

Results from the pivotal phase 2, single-arm ARIEL2 trial and the single-arm "Study 10" safety and dose-finding trial supported the FDA decision. Based on discussions with the FDA, the review of efficacy was limited to a combined sample of 106 participants from both trials, and the safety evaluation was based on data from 377 participants from both trials. Primary endpoints were PFS and ORR, and the secondary endpoint was OS. Median PFS was significantly higher with RUBRACA in the trials.

The subsequent approval by the FDA for maintenance treatment of recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer (with complete or partial response to platinum-based chemotherapy) was based on the placebo-controlled ARIEL3 trial with 561 participants. The primary endpoint again was PFS, which was significantly greater with RUBRACA than placebo (10.8 months vs 5.4 months).

Despite these approvals, several factors converged to negatively influence further success of RUBRACA:

A rapidly competitive space

Clovis Oncology struggled to best its competitors from the very beginning. AstraZeneca's LYNPARZA® (olaparib) was first to market for later treatment lines in BRCA-mutated advanced ovarian cancer, followed by RUBRACA approximately two years later.

TESARO Inc (now GSK) entered the market not long after (March 2017) with an approval for a PARP inhibitor (niraparib/ZEJULA) for maintenance treatment of recurrent ovarian cancer regardless of BRCA mutation status, beating both LYNPARZA (August 2017) and RUBRACA (April 2018) to that indication. Being first-to-market guaranteed a competitive advantage, nabbing ZEJULA almost double the sales as maintenance treatment in only nine months than RUBRACA earned as third-line treatment in all of 2017. As the standard of care for advanced ovarian cancer shifted toward maintenance treatment, the lag in market entry for RUBRACA set it at a clear disadvantage, as did the lack of a competitive dataset from its early trials (single-arm evaluations with immature OS data).

Although RUBRACA won the first-to-market race for third-line treatment of BRCA-mutated CRPC (again, with single-arm trial data), LYNPARZA quickly followed suit with an approval just five days later for earlier second-line use with a broader population and more robust data.

With yet another missed opportunity for unimpeded market share and improved brand recognition from prolonged first-to-market status, RUBRACA continued to be used later and in fewer patients than its competitors. To top it off, in its rush to be first to market for prostate cancer, the company sacrificed effectiveness for the potential of exclusive sales, granting LYNPARZA an additional advantage.

Evolving regulatory requirements

RUBRACA's competitors benefited from more robust trial designs, including comparator arms across the entire program and reporting of OS. The FDA and EMA increasingly require OS data for PARP inhibitors, and in the U.S., submissions with only PFS data now require FDA Oncologic Drugs Advisory Committee (ODAC) discussion. Although an ODAC vote is non-binding, a negative conclusion can negatively affect the outcome.

Unfortunately, Clovis Oncology came up short in its OS data in the follow-up studies. Final findings from the ARIEL3 study, presented to the FDA in 2022 as follow-up data for the 2018 approval as maintenance therapy, did not demonstrate improved OS as second-line maintenance treatment of ovarian cancer, compared with placebo: 45.9 months for those with BRCA mutation vs 47.8 months with placebo; 40.5 months for those with homologous recombination deficiency (HRD) vs 47.8 months with placebo.

In addition, the ARIEL4 study, conducted to confirm the ARIEL2 findings, showed lower OS with RUBRACA (19.4 months) than with chemotherapy (25.4 months). Based on these collective findings, the EMA restricted RUBRACA use to maintenance therapy following chemotherapy for cancers of the ovary, fallopian tubes or peritoneum. In addition, the indication in the U.S. was restricted to cancers with BRCA mutations.

Much of Clovis Oncology's hopes for survival were pinned on approval as first-line maintenance therapy for ovarian cancer, which would have allowed it to be more competitive with LYNPARZA and ZEJULA. Although the ATHENA-MONO trial for this indication met its PFS primary endpoint, the FDA advised in May 2022 that the company should not file until it had OS data that was at least 50% mature. At the time, the OS data were only 25% mature, and Clovis Oncology estimated it would take another two years to meet the FDA's expectations.

Clovis Oncology was not the only company to be impacted by the shifting regulatory framework to a focus on mature OS data for PARP inhibitors, especially for drugs previously approved based on PFS. Because of this requirement, ZEJULA and LYNPARZA were also withdrawn from third-line or later treatment for BRCA-mutated ovarian cancer. However, the earlier financial successes of ZEJULA and LYNPARZA, along with the companies' diversified portfolios, enabled them to weather this storm.

Poorly coordinated go-to-market plan

To control costs, several members of the sales organization were laid off, and the commercial team took an omnichannel marketing approach, primarily leveraging an outside tech company to augment share of voice with a digital marketing campaign. This email campaign failed to drive sufficient use of RUBRACA to offset the loss of the sales team who had relationships with healthcare providers (HCPs). Before engaging in this dramatic strategic marketing change, no research was conducted to ensure prescriber communication preference or potential loss of market share due to the switch.

The launch of RUBRACA's indication to treat BRCA-associated mCRPC after taxane treatment was poorly coordinated and lacked an understanding of the urology market segment treating most of the metastatic prostate cancer patients. Again, little pre-launch research was conducted to determine value messaging, market size or HCPs' willingness to partner with an oncologist for chemotherapy administration. The lack of pre-launch planning dramatically impacted the success of the product. An earlier co-marketing partner may have helped drive sales for this therapeutic indication.

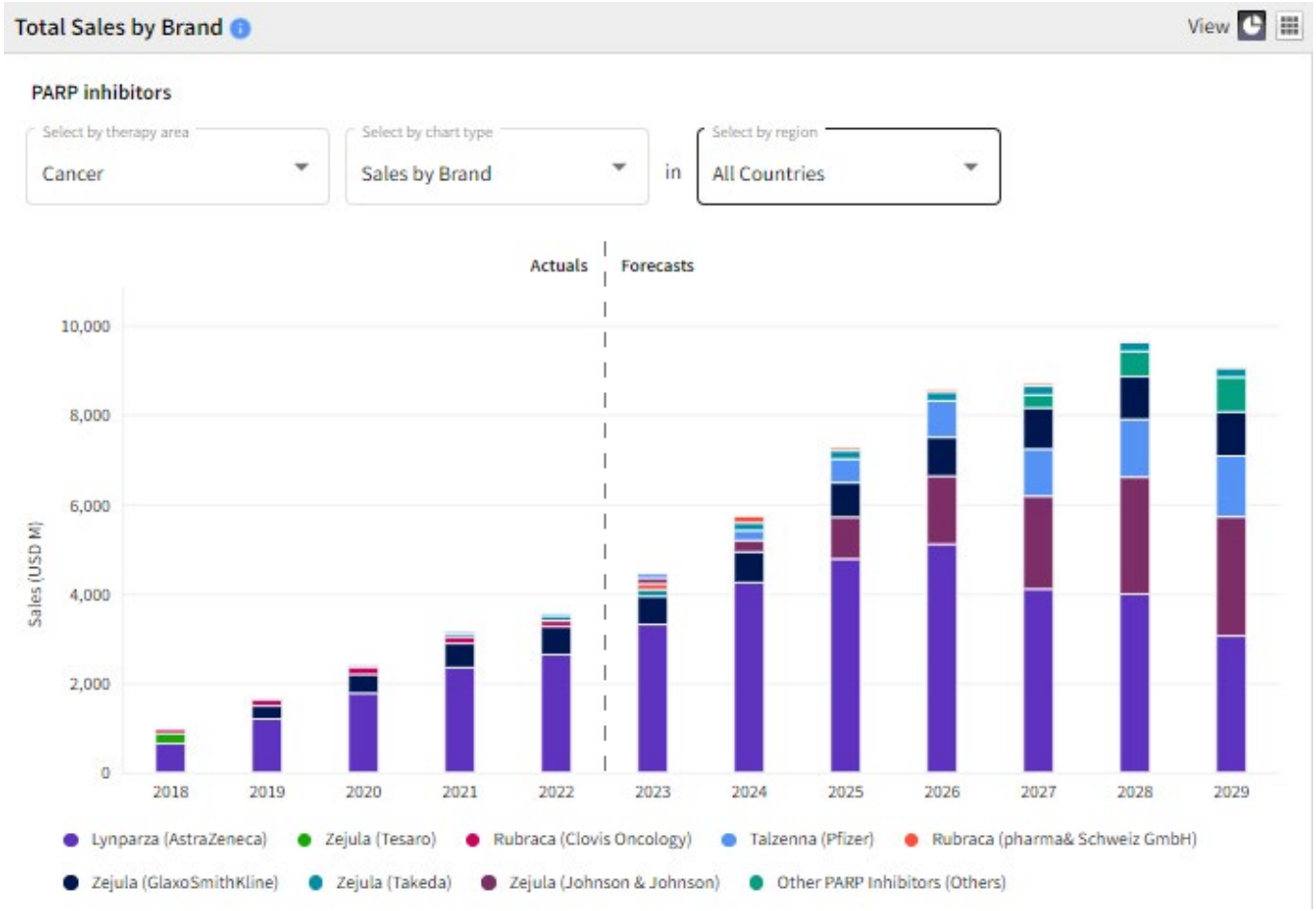
Failing to meet revenue estimates

Sales faltered from the first launch of RUBRACA. As its only commercial product, Clovis Oncology suffered large money losses from RUBRACA. By the first half of 2021, only $74.9 million in sales were recorded, compared with the $1.13 billion brought in by LYNPARZA during the same period.

Revenues from RUBRACA further dropped to nearly $38 million in Q3 2021 and again to just under $31 million in Q3 2022 (Figure 17).

These sales dealt the company another financial blow after the failure of rociletinib, its first developed drug, at the late pre-registration stage. Clovis Oncology was even fined by the SEC for misleading investors regarding rociletinib's efficacy: actual 28% efficacy compared with the 60% reported in investor presentations, press releases and SEC filings. In May 2016, the company ceased development of rociletinib just as it was preparing to launch RUBRACA.

Figure 17. Competition among the PARP inhibitors for oncology favored LYNPARZA.



Source: Cortellis Competitive Intelligence

Insufficient funds in a competitive landscape resulted in company failure

Despite the loss in revenue with RUBRACA, the company continued to forge ahead with clinical trials for RUBRACA in other indications, such as first-line maintenance therapy for ovarian cancer, to salvage the program and remain competitive. However, in the end, the cumulative effect of the more successful competition, stricter regulatory requirements and lack of finances was its undoing.

The company's Q3 2022 filing showed an accumulated deficit of more than $3 billion, resulting in insufficient funds to continue operating beyond January 2023. Unfavorable market conditions, especially for biopharma, meant funds couldn't be raised via equity, shareholders had not granted permission to issue stocks and only a small number of unissued shares remained. To top it off, when company leadership warned of potential bankruptcy, shares decreased more than 71%.

In an attempt to continue operating, the company:

- laid off 115 of its ~400 employees for a savings of $29 million per year;
- reduced selling, general, administrative and R&D expenses;
- explored other options including sub-licensing RUBRACA outside the United States or selling the radiopharmaceutical FAP-2286 co-developed with 3B Pharmaceuticals GmbH ($12 million deal in September 2019);
- asked creditors for the option to defer payments until a decision was made about approval for RUBRACA as first-line treatment for ovarian cancer;
- eventually deferred a $1.9 million interest payment on its debt;
- negotiated with Pfizer Inc to delay RUBRACA-related royalty payments; and
- finally filed for bankruptcy in December 2022.

Clovis Oncology rallied until the end

To continue operating, Clovis Oncology secured a $75 million loan and sold all rights to its FAP-2286 cancer candidate to Novartis for $50 million up front, up to $333.75 million in development and regulatory milestones and up to $297 in sales milestones.

In a bid to compete with LYNPARZA, Clovis Oncology attempted to fulfill the FDA's approval requirements in its later-stage trials and continued trials to expand the indication, such as the phase 3 TRITON3 trial (second-line mCRPC with HRR mutations), phase 3 ATHENA-MONO trial (first-line ovarian cancer maintenance) despite the advice from the FDA that more mature OS data were needed and ATHENA-COMBO trial (front-line maintenance treatment ovarian cancer setting evaluating RUBRACA plus OPDIVO® [nivolumab]).

The FDA issued a complete response letter (CRL) for the sNDA for RUBRACA as first-line maintenance treatment for ovarian cancer six months after the company filed for bankruptcy, shattering its last hope for revenues from RUBRACA. Survival data from a phase 3 trial were needed for the FDA to consider the application.

However, after acquiring RUBRACA in early 2023, pharma& Schweiz GmbH announced approvals for RUBRACA by the EC (November 2023), and the U.K. Medicines and Healthcare products Regulatory Agency (MHRA; February 2024) as first-line maintenance treatment in advanced ovarian cancer based on the results from the Phase 3 ATHENA-MONO trial.

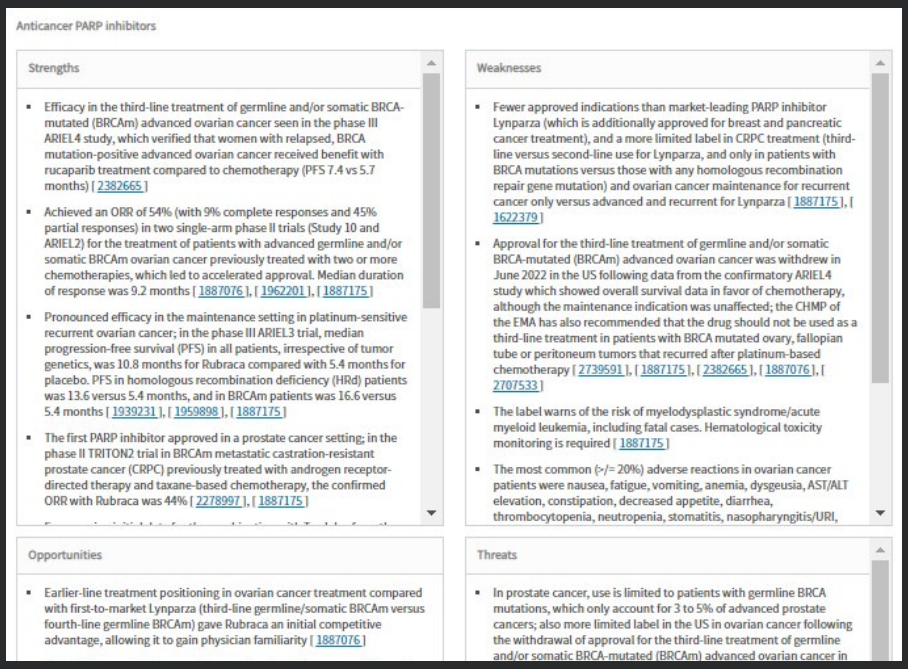
Lessons learned

Awareness of competitors' clinical development plans and clinical trial designs can identify strengths and weaknesses of internal strategies and inform go-no-go decisions and further development (Figure 18).

It can be beneficial to evaluate, early in development, whether the financial wherewithal exists to execute plans for a program and develop contingency plans for delayed regulatory approval: GSK had the ability to stay afloat when the FDA implemented stricter requirements, while Clovis Oncology did not (Figure 19).

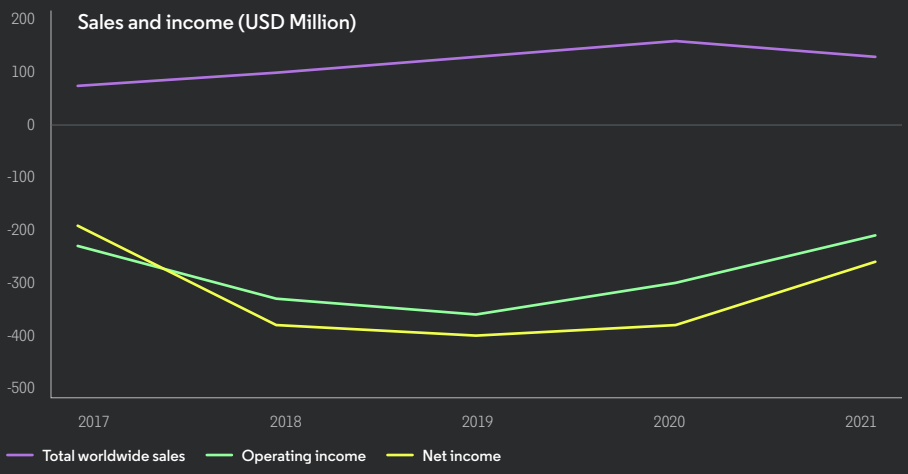
Diversified portfolios and assets can offset losses from one program.

Figure 18. SWOT analysis detailing RUBRACA's weaknesses and threats



Source: Cortellis Competitive Intelligence

Figure 19. Financial standing of Clovis Oncology



Balance sheet – Assets (USD M)	2017	2018	2019	2020	2021
Current assets - total	626.94	572.299	366.468	310.829	198.087
Property, plant, and equipment- net	4.007	26.524	43.428	42.523	25.663
Total assets	735.23	863.56	669.604	605.554	472.833
Inventories - total	27.508	27.072	26.519	30.714	13.688
Other assets - total	104.283	264.737	259.708	252.202	249.083

Source: Cortellis Competitive Intelligence

08

Sintilimab

TYVYT®

Single-country data from Mainland China deemed insufficient for the diverse U.S. population

Overview

Producers

Innovent Biologics Inc and Eli Lilly and Co

Type

Anti-PD-1 monoclonal antibody

Usage

Injection to treat Hodgkin's lymphoma, non-small cell lung cancer (NSCLC) and hepatocellular carcinoma (HCC)

- December 2018: first approval by Mainland China National Medical Products Administration (NMPA) for R/R classic Hodgkin's lymphoma after at least two lines of systemic chemotherapy, followed by expansions in Mainland China as first-line treatment for non-squamous NSCLC, squamous NSCLC, HCC, esophageal squamous cell carcinoma (ESCC), gastric or gastroesophageal junction adenocarcinoma as well as combination therapy for EGFR-mutated non-squamous NSCLC
- May 2021: Biologics license application (BLA) accepted for review by the FDA for sintilimab injection in combination with pemetrexed and platinum chemotherapy for first-line treatment of non-squamous NSCLC
- March 2022: CRL issued by the FDA recommending an additional clinical trial
- No further submissions made to the FDA; unlikely that additional approvals in the U.S. will be pursued

Lack of regulatory input during development created hurdles at submission

Sintilimab is a novel PD-1 inhibitor collaboratively developed and commercialized since 2015 by Innovent Biologics Inc and Eli Lilly and Co, one of the first Chinese-multinational pharmaceutical collaborations. Developed solely for the Chinese population, sintilimab (TYVYT) received marketing approval for multiple indications in Mainland China, is currently the only anti-PD-1 antibody included in China's National Reimbursement Drug List (NRDL) and is in the 2019 Guidelines of the Chinese Society of Clinical Oncology for Lymphoid Malignancies. Submission to the FDA was a secondary priority.

Based on the success of the drug in Mainland China, Eli Lilly and Co aimed to use the cost savings from the less expensive trials in Mainland China and single-study approval to introduce a more competitive consumer cost in the U.S. If the FDA approved TYVYT, the company reported the wholesale acquisition would be a ~40% discount of PD-1s already available in the U.S.

At the time of sintilimab submission, the FDA had already approved seven other PD-L1 inhibitors, many of which were based on limited evidence submitted via the accelerated approval program and were found deficient in follow-up studies. Narrowing of their indications after approval occurred for at least two of these drugs (KEYTRUDA® and TECENTRIQ®). Therefore, the FDA may have been more cautious about approving more PD-L1 inhibitors with very limited data, especially since sintilimab was entering an already crowded market and not fulfilling an unmet need in the U.S. Moreover, the company did not consult the FDA during drug development,

the study was not conducted under an investigational new drug application (IND) and the FDA had not conducted site inspections prior to submission.

The initial FDA submission was supported by data from the pivotal Phase 3 ORIENT-11 trial, which was conducted exclusively with 397 patients in Mainland China and had a primary endpoint of PFS. The companies did meet with the FDA in August 2020 to discuss the acceptability of the data from ORIENT-11 to support their BLA submission. At the time, the FDA advised that the impact of intrinsic and extrinsic factors on exposure, efficacy and safety should be addressed in the BLA submission.

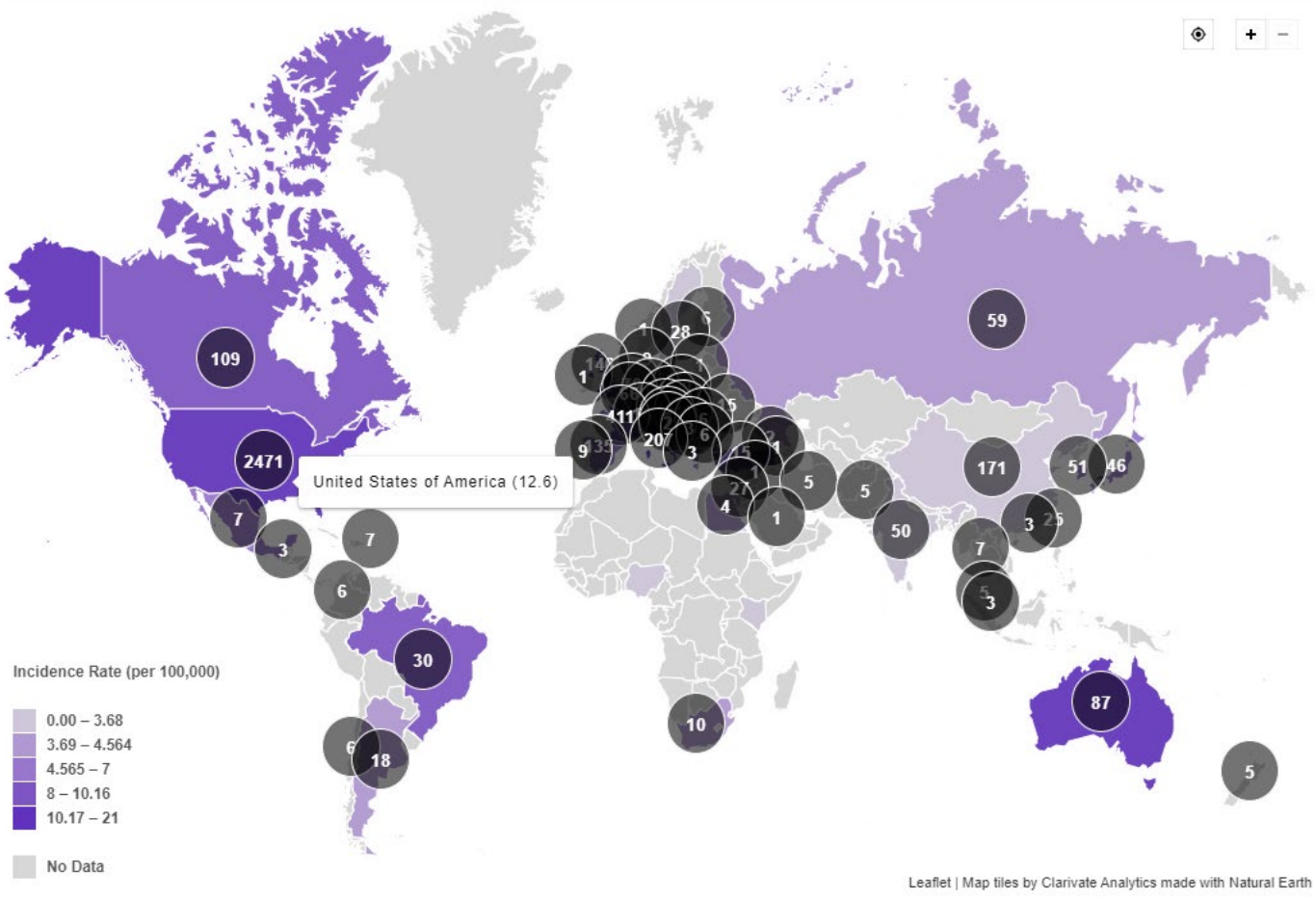
The CRL issued by the FDA in March 2022 followed the vote by the ODAC that additional clinical trial(s) should be required before a final regulatory decision.

The FDA required data showing that the trial's results applied to the U.S. population and U.S. medical practice. In its decision, the FDA noted that "there is no impetus for regulatory flexibility to accept foreign data based on an endpoint with less clinical significance (i.e., PFS)" and a lack of unmet need in this patient population.

As a result, the CRL recommended the following for the additional study:

- Multiple regions
- Comparing standard of care therapy for first-line metastatic NSCLC (instead of placebo plus chemotherapy) against sintilimab plus chemotherapy
- Non-inferiority design
- Primary endpoint of OS

Figure 20. Use epidemiology intelligence to identify trial site locations to reach the target population



Source: Clarivate Epidemiology Intelligence™

The overall impression of FDA reviewers was that the study design itself was flawed and outdated for multiple reasons:

Lack of criteria for foreign data as the sole basis for marketing approval

The study did not meet the criteria outlined in Section 21 CFR 314.106(b):

- Not applicable to the U.S. population and medical practice based on the selected endpoint and control arm
- Studies not been performed by clinical investigators of recognized competence:
- Although prior participation of study investigators in multiregional clinical trials (MRCTs) may have increased the FDA's confidence in the study conduct, the ORIENT-11 investigators had limited interactions with the FDA.
- FDA not able to validate the data through an onsite inspection or other appropriate means:

Although clinical site inspections have since been initiated, they cannot fully capture the heterogeneity of data quality and study conduct across numerous clinical sites.

Outdated clinical trial principles to assess treatment effects

ORIENT-11 followed the older ICH E5 and was not consistent with the principles outlined in the newer ICH E17 (General Principles for Planning and Design of Multi-regional Clinical Trials):

- Did not allow an evaluation of the consistency of treatment effects across geographic regions and subpopulations
- Recommendation in ICH E17: after recording preliminary pharmacokinetic (PK) and general safety data, clinical studies BEGIN as MRCTs, then determine applicability to specific regions/ populations in single-center studies
- Recommendation in ICH E5: the reverse of the above

Inadequate PK data

The PK data did not support conclusions regarding the ability to apply the findings to a diverse U.S. population. Additional PK data representative of the U.S. patient population were needed to support efficacy and safety. Compared with U.S. patients with NSCLC, ORIENT-11 patients were:

- Younger
- Predominantly male
- Less likely to smoke

Inappropriate endpoints

- OS was not included as a primary endpoint when it is the standard endpoint for first-line treatment of NSCLC with immune checkpoint inhibitors.
- PFS is an acceptable clinical endpoint but is less clinically meaningful.
- The NSCLC treatment landscape includes many front-line immunotherapy options with advantages for OS, and approval based on a different endpoint "risks loss of gains in survival for U.S. patients."

Inappropriate standard of care

Enrollment in ORIENT-11 began three days after pembrolizumab was approved as the first PD-L1 inhibitor for first-line treatment of NSCLC. However, pembrolizumab was not included as the standard of care within the study. In addition, the informed consent in ORIENT-11 was not updated to reflect the changing standard of care (i.e., pembrolizumab), which is required to follow Good Clinical Practice (GCP).

The FDA decision impacted the company's global marketing efforts

In the short term, the FDA's decision affected the company's bottom line, while far-reaching implications included changes to FDA requirements for data from more diverse populations.

- Innovent Biologics Inc share price decreased 10% following the FDA's decision.
- The companies had to factor in the considerable cost and time (an estimated seven years) to design, plan and conduct clinical trials if they wanted to generate the evidence needed to support the FDA requirements.
- If sintilimab was approved in the U.S., it faced a shorter time on the market with less competition. At the time of initial filing, pembrolizumab was the only PD-1 inhibitor approved in combination with pemetrexed plus platinum-based chemotherapy, but that was anticipated to change.
- Eli Lilly and Co terminated its agreement with Innovent Biologics Inc to commercialize sintilimab outside of Mainland China because of the prohibitive costs and considerable delays of the required MRCTs. The rights outside of Mainland China were transferred to Innovent Biologics Inc.
- More broadly, the FDA decision contributed to the 2023 Consolidated Appropriations Act in the U.S., requiring the FDA to begin the process of decentralizing clinical trials to better reflect the more diverse U.S. population these drugs target.
- Continued development for marketing in the U.S. is unlikely, and no MCRTs have been initiated since the FDA's decision.

The companies' defense did not meet the FDA requirements

In their materials prepared for the ODAC meeting, the companies defended the ability to apply the PK data to U.S. patients, by outlining the similarities between the Chinese and U.S. populations. They also proposed conducting an additional study in Mainland China, the U.S. and the E.U. to compare two doses of sintilimab in 150 patients. The primary endpoint would be ORR in 100 patients planned to receive the sintilimab 200 mg dose every 3 weeks. However, the FDA noted that this study design would not address the concerns about endpoint selection and that sintilimab should be compared with an approved immune checkpoint inhibitor in an MRCT.

Lessons learned

Identifying the target countries and regions for marketing early in development is key for proactive, appropriate clinical trial, analysis, regulatory and market access planning.

Data from trials outside the U.S. may not be acceptable as the single study to support application approval, especially if the population is not representative of the diverse U.S. population.

"This application reflects an increasing number of oncology development programs based solely or predominantly on clinical data from China, with over 25 applications in drug development phases, planned to be submitted, or currently under review."
FDA response to the BLA

Seeking regulatory guidance during drug development could establish a clearer path to major market approval and help address any potential regulatory roadblocks.

Determination of standard endpoint measures for the condition being treated should be undertaken before the start of clinical trials. In this case, the use of PFS, instead of OS, as a primary endpoint for NSCLC may not support product approval based on data from a single study.

For certain oncologic conditions, sponsors should consider using a comparator treatment instead of chemotherapy (if available) to ensure patients have access to efficacy and safety that is, at least, on par with currently approved therapies.

Although the companies noted that "sintilimab is largely eliminated by catabolism since it is an IgG mAb and therefore sintilimab PK is not expected to be affected by drug-drug interactions and other extrinsic factors," the FDA still requires additional PK data that are representative of the U.S. patient population.

Each study must independently demonstrate efficacy and safety for the specific drug rather than relying on a class effect.

Key takeaways

Failing on the public stage risks a company's reputation and ability to operate. Learning from prior missteps is essential for future proofing assets in an industry littered with abandoned developments. Across the examples presented here and others documented over the years, a common theme is evident: earlier awareness of potential hurdles could have minimized or even prevented the impact of a roadblock—and the cost and time associated with attempting to right the ship later in the development lifecycle. It is well past the era of being able to develop medical products in a vacuum and hope for the best. Companies that succeed in today's environment are those that gather needed insights during the planning phase and iterate early.

Data from a number of sources, including discovery platforms, safety data, competitive analysis of clinical development, historic and pending regulatory actions and market analysis, are key to understanding the product strengths and weaknesses, disease characteristics and information needed to support decisions by a range of stakeholders (investors, clinicians, regulatory agencies, payers). Discussions with patients, clinicians, regulatory agencies and payers inform how to take a product from the lab to the market in a way that is acceptable, beneficial and valuable, contributing to increased uptake and therefore a greater treated population and revenues.

Given the fast-changing regulatory landscape, with the IRA scrambling strategic plans for the U.S. and fresh pharma regulatory reforms on the way in the E.U., it is imperative that companies have a thorough grounding in regulatory intelligence and expertise, as well as a regional focus, even at the research stage. Some of the IRA provisions aim to influence drug prices, which could in turn affect drug development strategies and have begun to shift R&D priorities as companies re-evaluate the expected ROI for their new assets. The ability for the U.S. government to begin negotiating Medicare-covered drugs has some companies favoring the development of biologics over small molecules due to the longer allowable time on the market before prices can be negotiated. In addition, more evidence might be required at launch, and a tactical approach to IRA compliance should include evidence sourced from the literature, real world evidence, internal analytics and consultations with subject matter experts—ready to support IRS-driven pricing negotiations and inform Centers for Medicare & Medicaid Services (CMS) reference-based pricing. Therefore, life science companies at all stages of asset development must adapt to these changing regulations and optimize their approaches to drug pricing and innovation from early R&D through asset commercialization.

"Success is not final, failure is not fatal: It is the courage to continue that counts."

Winston Churchill

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