

ONE-SHOT CURATIVE TREATMENTS: A PHARMA AND PAYER REVOLUTION

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In the last few years, the number of gene and cell therapy products being developed across therapeutic areas has increased rapidly. The hope that these will become one-time curative treatments has spurred unprecedented interest and investment. As of early 2019, sponsors have filed more than 800 active cell or gene therapy INDs with the FDA, with the Agency predicting the approval of 10-20 such therapies each year by 2025. While the scientific and medical excitement for these new approaches is high, companies developing them are faced with new commercial challenges.

Revenue Diversification & Portfolio Strategy

The Challenge: One of the most striking challenges for developers of one-shot therapies is building a sustainable revenue model. With a high penetration in the clinic, these treatments will 'cure' the prevalent pool of existing patients so that new treatment initiations will be purely incidence based. This can become particularly challenging in the case of therapies for rare and

ultra-rare diseases where very few new cases are diagnosed every year.

How can developers of one-shot curative treatments ensure a sustainable revenue stream over time?

Consideration 1: Prioritize development in indications with high incidence rates, such as hemophilia (estimated at ~1 in 4,000 males) or spinal muscular atrophy (estimated to affect ~1 in 10,000 newborns) where the pool of addressable patients will be quickly renewed over time. Looking at incidence rates thus becomes particularly important in the early commercial assessments for gene and cell therapies.

Consideration 2: Diversify the revenue through life-cycle management of the product, including geographic expansion. In orphan indications in particular, it is critical to think beyond the US alone and establish a global commercial vision for the product, which includes an aggressive ex-US product launch sequence (*Figure 1*). Later launch markets can

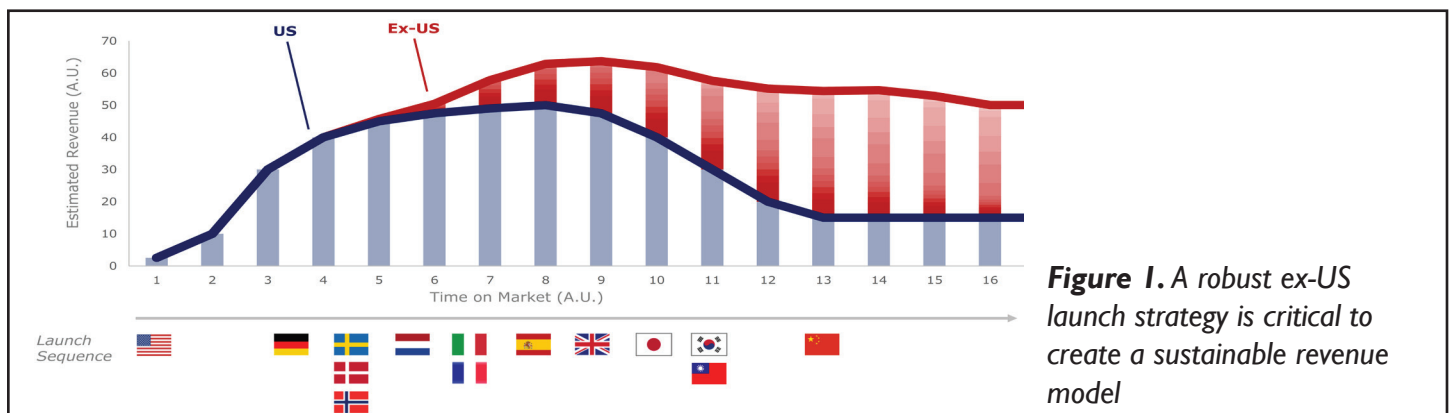


Figure 1. A robust ex-US launch strategy is critical to create a sustainable revenue model

help smooth the revenue curve and make up for decreasing sales in earlier territories.

Consideration 3: Build a robust, diversified portfolio of products that will contribute to the company's future revenue stream.

Often, this can be done by promoting organic growth via development of in-house platforms and optimization of R&D efforts, with a critical look at other areas to prioritize. Careful screening and evaluation of outside assets may also allow for faster expansion into new areas through licensing and M&A agreements or partnerships. Further, expansion to new areas should take into account opportunities for providing complementary solutions for the current indication, to potentially bolster and promote the effects of the therapy or to address previously undetectable phenotypes (for example, in case of a therapy with localized delivery that cures the primary organ but not secondary organs).

Pricing and Reimbursement

The Challenge: Over the past year, developers have spent a good deal of time focusing on the challenges of pricing one-shot curative therapies to ensure broad access and reimbursement. While they want to capture the full value of their assets, growing payer budget constraints and the limited ability to assess the long-term benefits of the one-shot cures can create additional hurdles to a successful pricing and reimbursement (P&R) process.

In orphan and ultra-orphan indications, costs of goods sold per patient can be very high given the low manufacturing volumes. This increases the need for high price levels to make a product launch

feasible at all. It is essential for companies developing one-shot curative therapies to discuss reimbursement with payers early on and collect their input on affordability and ability to pay. In addition, new models to evaluate a drug's cost effectiveness are under investigation.

Potential Models: As only a small number of gene and cell therapies have launched on the market, the framework around P&R of these therapies is limited. So far, developers have proposed four payment modalities:

An upfront one-time payment, as with Uniqure's Glybera, a treatment for lipoprotein lipase deficiency priced at about 1.1M€ (~\$1.4M) for an average person, with the final total price tied to a patient's body weight. (Uniqure has now withdrawn this therapy from the market due to limited demand.)

A one-time payment with performance contingencies, as is the case with Strimvelis, GSK's one-time gene therapy for the treatment of severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID) priced at 594,000€ (about \$665,000). The drug comes with a "money-back guaran-

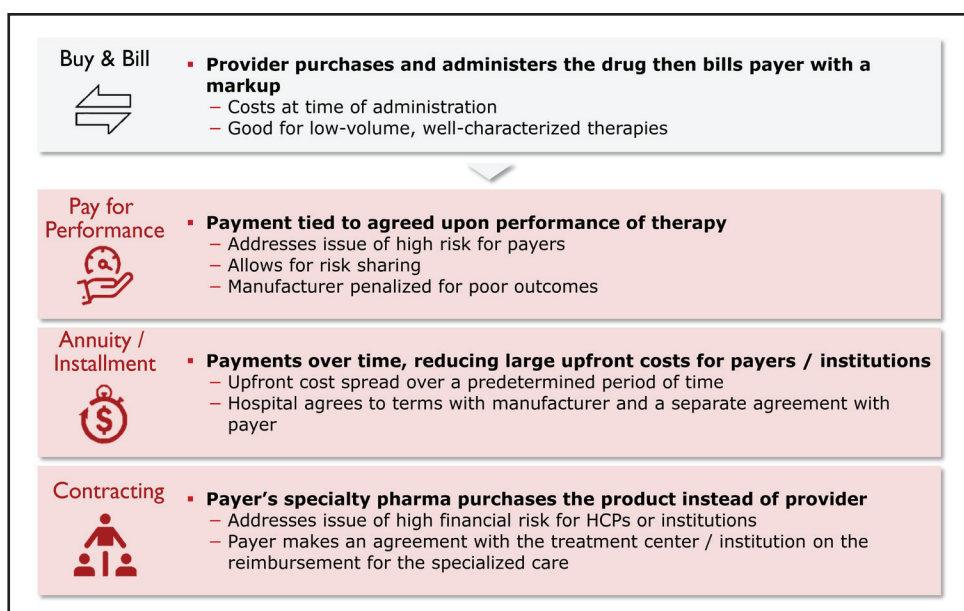


Figure 2. Innovative reimbursement models (red) being brought forward as alternatives to the classic "buy and bill" model (gray)

tee” where the company will refund some of the costs if a patient needs to go back onto a different therapy down the line. Similarly, with Kymriah, Novartis’ \$475,000 CAR-T treatment for some leukemias, reimbursement allows full payment only for patients that respond to the therapy by the end of the first month after the treatment.

An outcome-based rebate arrangement, such as with Spark’s Luxturna, an \$850,000 treatment for an inherited, rare form of blindness, that links payment to both short-term efficacy as well as long-term durability of treatment (up to 30 months). In addition, Spark has developed an alternative to the traditional “buy-and-bill” reimbursement model by contracting directly with payers or their specialty pharmacies, which would purchase the drug instead of the treatment center.

An installment plan/annuity model, which Bluebird bio has proposed for its LentiGlobin treatment for beta-thalassemia that would allow spreading payment over a number of years (as many as 5). LentiGlobin is not yet on the market, but Leerink estimates its price at about \$1.2M.

As developers of one-shot therapies explore payment modalities (*Figure 2*), they should keep in mind that different laws govern in different countries, and that not all payment modalities may be allowed in all countries. This is especially important when thinking about EU entry, where a company will need to work out an EU-wide model that can be refined to match country specifics.

With the high number of one-shot cures expected to enter the market over the coming years, some of the current payer systems may have to evolve. The challenge companies are currently facing is that no one knows what exactly this evolution will look like. This makes early commercial planning more important and more difficult. Developers should engage with payers early on in an active dialog, leading to a process of co-creation.

Key Steps to Site Readiness

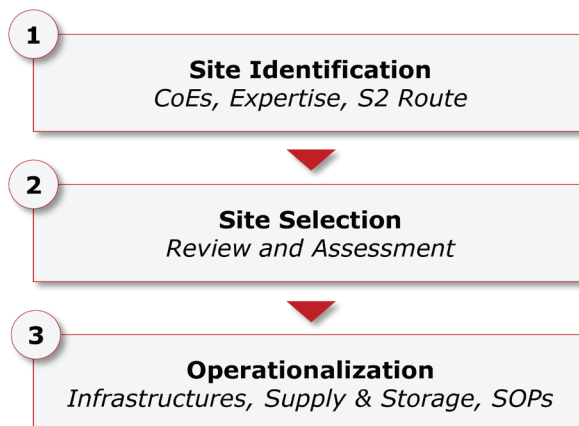


Figure 3. Ensuring administration site readiness is critical for gene / cell / tissue products

Site Readiness

The Challenge: The administration of a gene or patient-specific cell therapy product will likely be restricted to a limited number of centers. This can create several operational challenges, such as the need to fly patients in, accommodate them, etc. In addition, preparation, storage, and administration of the therapy might require special infrastructure and/or training for patient safety. Manufacturers of first-generation autologous cell and tissue therapies have already faced some of these challenges. In the case of the more complex preparations for one-shot therapies, the potential costs and training required are more extensive. Timely site readiness is a critical success factor to ensure patient safety, product uptake, and commercial success (*Figure 3*). Ideally, this process should start during clinical trials.

Site Identification: It is paramount for the developer of a one-shot therapy to understand how and where care for the targeted disease is delivered today, and how this will change as the new therapy becomes available. Given the potential costs and training requirements of gene therapies, administration is likely to

be restricted to very few centers per country. These are most likely going to be existing Centers of Excellence. Identifying these early is a first step in ensuring site readiness.

Payers can also play a role in this context and should be engaged early on:

- In some countries, payers may have specific requirements to ensure adequate national access to and coverage for patients.
- Regulators may also endorse provisions that support the efficient distribution of one-shot therapies to patients. The EU has implemented the S2 route of therapy coverage, with potential implications for ultra-orphan diseases with high technical complexities. The S2 route is a cross-border healthcare provision that allows patients from one EU country to access healthcare in a different EU country with the home country covering the treatment costs. GSK, for example, decided to make Strimvelis available at a single center across Europe (in Milan, Italy; ADA-SCID affects an estimated 15 children per year in Europe).

Site Selection: Once manufacturers have identified potential treatment sites, it will be important to profile them along key criteria (storing capabilities, trained personnel, influence, etc.) and determine which ones to prioritize. In-person site visits will be important.

Selecting treatment sites early on can be beneficial to involve them in clinical trials, as a way to share expertise and knowledge on the technology and treatment. If a site is not included in clinical trials, additional time and resources will need to be devoted to the training and education of staff – physicians, nurses, and other personnel – ahead of launch to ensure the readiness of the site to receive the first patients.

Implementation: Ensuring site readiness will require working out a number of operational complexities such as infrastructure set up, arranging for adequate supply and storage of the therapy, optimizing patient and clinic work flows, and standardizing operating procedures. Manufacturers of one-step therapies need to proactively work with each site to drive these processes during the later stages of clinical development.

As more gene and cell therapies are developed, companies will have to make important decisions to ensure their commercial success and viability. Addressing challenges such as revenue sustainability, pricing and reimbursement, patient access, and commercial readiness will be of paramount importance to be able to develop a robust and favorable corporate growth strategy.

How can Bionest Help?

Bionest Partners is a healthcare-focused strategy consulting company based in New York, Paris, and Basel. We help build and grow innovative companies, supporting them as they transition from clinical development to commercial success. We have developed deep expertise assisting companies tackle challenging questions across markets and stages of development, and have worked with several companies in the area of cell and gene therapy. For more information, please visit our website at www.bionest.com

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