Q. In the case studies, you presented the situation for Glybera in Germany and France and it wasn’t very promising. The centre of expertise for Strimvelis is in Italy. Can you comment on whether the Italian market was better prepared than the French and German? Is it easier to launch gene therapies in some markets than in others?

The key learning from the Glybera and Strimvelis case studies is that the manufacturer or commercialising company needs to understand the environmental constraints (e.g. access barriers) and customer (regulator, payer, provider and patient) uncertainties around the product (and accompanying data package). They then need to work with customers to find solutions that address their underlying uncertainties to drive reimbursed access and utilisation.

The constraints may vary across countries. My view is that within the EU5 there is no market that is overall better suited for launching gene therapies than the others. For example, if I were to launch a gene therapy product in Germany, I would likely face lower willingness among payers to enter into performance-based contracting or annuity-based payment models due to Germany’s fragmented payer system (multiple sick funds with patients moving from one sick fund to another). However, this fragmented insurer system is counterbalanced by an opportunity as Germany usually supports the highest net price in the EU for ultra-orphan therapies.

However, the US may offer some regulatory challenges for launching a gene therapy, such as more stringent data requirements than EMA. To date, the Center for Biologics Evaluation & Research (CBER), which falls under the FDA, does not have specific pathways for gene therapies. This is in contrast to the EMA, which has specific guidance for ATMPs. However, this situation may change in the near future, as a few FDA Working Committees are investigating specific guidance for (human) gene therapy regulation and regulatory approvals that may align data requirements for the US with Europe.

Q: Is there any update on gene therapy for cystic fibrosis and sickle cell disease? At least for these diseases the size of the patient population does not present a challenge.

Although the patient population is relatively for these diseases, gene therapies tend to be targeted at a narrow and well-defined population target. Current gene therapy trials usually target a monogenic manifestation of the disease. This is the case in ongoing sickle cell and beta thalassemia trials that have exclusion-inclusion criteria that imply targeted sub-populations within the disease. Additionally, as ongoing improvements in hematopoietic stem cell transplantation (HSCT) are improving both mortality and remission rates, the patient populations targeted by gene therapies are usually those who are ineligible for HSCT (where this is an alternative treatment option).

Another driver for seeking well-defined and narrow patient populations is the high cost of these therapies. For therapies with a higher target price, the likelihood of reimbursement greatly increases if the therapies target narrow populations with high unmet needs. Overall, our view is that the trend to seek ultra-orphan-like patient populations for gene therapy products is likely to continue – although these populations may well be larger than the target populations of Glybera (approximately 150 – 200 in the EU per year) and Strimvelis (10-15 in the EU per year).
Q: You highlight that GSK is adopting a ‘platform approach’ to ROI on gene therapy. Given many companies in this space are SMEs, how realistic is this as a ROI model? What’s the alternative?

There are two parts to the answer:

1. Do we believe that platform approaches to ROI are going to be the new norm for gene therapy pricing and access? GSK’s approach with Strimvelis and early market noise around Novartis’ CAR-T strategy seem to suggest that these early big pharma entrants are driving a platform ROI approach. Whether payers will expect this from other gene and cell therapies entering the market remains to be seen. However, initial indicators, at least those from Europe, suggest payers are resetting their price expectations for gene therapy after GSK’s Strimvelis case.

2. If we believe that a platform ROI approach will become the new norm, then SMEs/biotechs may need to consider an alternative product development, investment and commercialisation model:
   a. Product development: Are there opportunities for SMEs to leverage partnerships with big pharma, academic centres, and gene therapy specialist manufacturing companies so that they can to some extent de-risk the product research and development process? Additionally, can SMEs leverage government-led initiatives (e.g. the CATAPULT group in the UK) that offer opportunities to reduce some of the costs around product development?
   b. Investment and commercialisation model: The innovative annuity and performance-based approach that Strimvelis has pursued has cash flow implications, which could affect the financial viability of SMEs in this space. This effect, coupled with a platform approach to pricing (and hence ROI), is already affecting venture capital funding investment in this area. One approach where we are providing support is for some early cell and gene therapy biotechs to identify alternative, novel models to commercialisation. Additionally, these companies are investigating novel approaches to raising capital to drive development and commercialisation of these therapies.
Q: High-price oncology therapies can cost $100,000: does a price on this level represent a tipping point in access? For example, would treatments costing $150,000 for cell & gene therapies have much lower barriers?

For gene therapies, in common with all other drugs, the supporting evidence package, the value proposition the product offers, KOL endorsement, as well as the competitor value propositions and price are all key determinants of willingness to pay and access. However, for gene therapies, cost density is an additional consideration. In our experience, therapies with a one-off cost exceeding $500,000 in the US and $300,000 in the EU face access barriers such as individual funding requests with stringent requirements to prove medical need, and/or additional access pathway hurdles (e.g. stop-loss insurance in the US).

Q: Yesterday there was an Advisory committee meeting for Novartis’s CAR-T therapy, and it seems to be progressing towards approval. Can you comment on potential gene therapy approval in the US?

Although CAR-T is strictly speaking a cell therapy, we do expect a few gene therapy approvals in the US in the coming year (including an ATMP from Spark Therapeutics, expected to be FDA approved next year). However, the challenges around commercialisation, including the ability to identify the right patient subgroups, concerns around supporting short- and long-term safety and efficacy, and financial considerations (e.g. potential for a high cost density and affordability considerations) are also likely to play a role in the pricing and access for these transformative therapies. These challenges will be further exacerbated by burdensome reimbursement pathways (e.g. stop-loss-insurance) for therapies that are high priced. An appreciation of these challenges will be critical and manufacturers will need to work with policy makers, payers, providers and patient support groups to co-create solutions to address these challenges (e.g. innovative contracting approaches, access and claim processing services etc.)
Q: Do you expect that as more therapies come to market, HTA agencies will develop specific pathways and guidance with specific cost thresholds and endpoint/comparator restrictions, or that access pathways will be developed on a case-by-case basis?

The access challenges for gene therapy fall into two categories:

1. Uncertainties regarding the product and the supporting data package (e.g. long-term safety and efficacy data, patient-relevant outcomes and comparators). Payer and HTA needs are already well defined, although they are changing over time (e.g. AMNOG 2.0). A key first step is to engage with payers to understand their uncertainties around the product and data package. Once these are understood, we can design solutions such as innovative contracting approaches, phase 4 studies, registries and RWE initiatives to bridge the gap between the promise of value that a particular gene therapy offers and the evidence supporting the promise.

2. Healthcare system challenges. Examples include insufficient transplant centre capacity and expertise in a country for autologous ex-vivo gene therapy, insufficient ring-fenced funding for certain diseases to cover novel gene therapies, burdensome reimbursement pathways for cross-border funding of planned treatments in another country, and others. Industry will have to work with payers to find solutions for these challenges.

While working with some early stage biotechnology companies, I have observed an expectation that some of these healthcare system challenges (e.g. funding pathways for reimbursed treatment in another country/region) will be addressed by early entrant gene therapy technologies. However, companies also appreciate that some system challenges are disease/indication-specific (such as a lack of guidelines around gene therapy for the disease and insufficient ring-fenced funding of diseases to cover gene therapies). In these cases, the first entrant gene therapy for the specific indication/disease will have to take the onus of addressing these barriers so that they avoid a situation like Glybera where a promising therapy was withdrawn due to lack of reimbursed demand.
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