For almost 30 years, researchers have struggled to develop successful gene therapies. Now five approvals in the field have fueled hopes that the old dream of curing diseases with a single treatment is within our grasp. But the sector is still trying to figure out the business side of things. Cash-strapped health systems are wary of the high cost, and it's likely outcome-based staggered pricing will have to play a role in allocating reimbursement.

Treatments – paying for performance

OUTCOME-BASED PRICING It's not easy to put a price tag on a medical cure, particularly when it comes to gene therapies. To receive what they say is an appropriate return on investment, developers are demanding up to €1.9m per patient for 'one-time' treatments. Payors are sceptical. Outcome-based pricing is one way to compromise. But what payment model would work best?

hen the first gene therapy went into clinical testing in 1990, researchers were wildly optimistic about its potential impact. The chance to cure people with monogenetic defects that caused life-long maladies with a single treatment seemed just around the corner – but proved far from easy. Developers first had to learn how to construct gene vectors that wouldn't be attacked by a patient's immune system or randomly inserted into the genome, potentially causing cancer. The first gene therapy approved for the EU market only arrived in 2012. Priced at €1.1m, uniqure's Glybera promised a cure for lipoprotein lipase deficiency.

But some would say the extraordinarily high price limited patient access to the therapy. One way or the other, the adeno-associated vector carrying the intact copy of the LPL gene wasn't destined to succeed. Uptake was limited, and in 2017, uniqure and its partner Chiesi Pharmaceuticals stopped reporting long-term follow-up data to the European Medicines Agency (EMA), phasing out conditional market approval for the product.

Two years later, four further genuine gene therapies with larger addressable patient populations than Glybera have received market approvals. And with more than 30 gene therapies in registration studies, Big Pharma players are in a stampede to add late-stage gene therapy programmes to pipelines. Among them:

> Roche offered US\$4.3bn to acquire Spark Therapeutics, which has a portfolio that includes the US- and EU-approved retinal dystrophy gene therapy Luxturna and an impressive pipeline of further gene therapy products.

"Price is the Achilles heel of precision medicine"

- > Pfizer announced it was building a US\$500m manufacturing facility to produce AAV-based gene therapies
- > Following the US\$8.7bn takeover of Avexis, in May Swiss Novartis AG

Number of gene therapy clinical



Source: Alliance for Regenerative Medicine

received FDA market approval for Zolgensma, the first and only gene therapy for pediatric patients with spinal muscular atrophy (SMA). The Swiss pharma giant's treatment price makes it the costliest therapeutic delivery treatment ever: €2.125m per patient. It has further stimulated the debate between payors and developers on what lasting one-shot genetic cures should cost.

"It's a single dose which seems to imply life-changing results," says Doug Henderson, Managing Director at the British patient advocacy group SMA UK. If Novartis' promise holds true, that would actually make Zolgensma much cheaper than Biogen's approved first-in-class SMA antisense drug Spinraza, which costs US\$750,000 for the first year of treatment and \$375,000 for each additional one. "If you look 10 years ahead and compare Spinraza versus a one-time gene therapy, it's a no-brainer what will end up being cheaper over time," stresses Henderson. To achieve the break-even point with Spinraza, a single Zolgensma treatment would need to last 3.6 years. Recently announced results from Novartis' ongoing STRIVE study demonstrate that patients treated with Zolgensma at least remained event-free for a median time of 13.6 months.

"No one has ever proven that a gene therapy would last for 10 years. We always see fading effects," says CEO of Centogene Arndt Rolfs. He was involved in one of the very first gene therapy trials. According to him, it's a question of whether payors and governments will decide they want to save the life of one patient with a rare disease at a price that might save 100 patients with more common diseases.

The payors' perspective

A recent survey of 25 health system representatives by pharma consultancy Precision Value & Health identifies three big concerns among decisionmakers on the payor side: the high up-front cost for gene therapies, obtaining coverage, and identification of appropriate patients. According to study authors Jeremy Schafer and Alex Grosvenor, "new models are needed, and [...] most payors and health systems feel that payment models need to evolve toward outcome-based arrangements." In fact, both in the US and in Europe, payors are tending to replace volume-based payment models with outcome-based models, particularly as highcost therapies are increasingly targeting very small patient populations.

In the US, Spark Therapeutics has launched the first-ever outcome-based model for Luxturna, which it initially priced at \$425,000 per eye. That's \$850,000 in total cost for most of the estimated 8,500 to 10,000 patients in the country who are diagnosed with retinal dystrophy every year. In 2018, long-term follow-up analyses demonstrated a threeyear durability for the therapy of the biallelic defect in the RPE65 gene. Per contract, Spark Therapeutics has to measure patient sight improvement at 30 to 90day intervals, as well as after 30 months on therapy. If a Luxturna treatment fails, contractors receive a rebate from Spark. Not long ago, UK watchdog NICE decided to recommend reimbursement of Luxturna, for which Novartis owns the ex-US marketing rights. NICE will receive a confidential rebate on Novartis' list price of £613,3459 (\$762,8796).

Pricing drugs for rare conditions

EU In June, bluebird bio gained EU market approval for ZytegloTM, a gene therapy that corrects a defect in the β -globin gene in patients with β -Thalassemia. European Biotechnology spoke with bluebird bio Germany's General Manager Susanne Digel and Medical Lead Steffen Hartrampf.

EuroBiotech_In June, bluebird bio's first gene therapy product, ZyntegloTM, received EU market authorisation. What market does the therapy target, and when and where will you start the European product roll-out?

Digel_bluebird bio received a fast approval within the EU PRIME scheme to treat transfusion-dependent β -thalassemia (TDT) patients 12 years and older. The conditional approval is for patients with a non β^0/β^0 genotype for whom hematopoietic stem cell (HSC) transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available.

Hartrampf_Due to a gene defect, the haemopoietic system of these patients is unable to produce enough healthy hemoglobin from birth. That means they must come to the clinic every three to four weeks for their entire lives to re-



Susanne Digel, General Manager at bluebird bio Germany, has over 20 years of experience in the biopharmaceutical industry. Before she joined the company in March 2018, the pharmacist held various marketing positions at Spark Therapeutics, Alexion Pharmaceuticals, Celgene, Amgen and Baxter. ceive transfusions with red blood cells. Excess iron must be removed afterwards to prevent negative effects, especially on the heart and liver. In our clinical studies, 80% of patients achieved the primary endpoint of transfusion independence with just a single treatment of autologous, CD34-positive blood cells containing an added copy of the βA– T87Q-globin gene.

Digel_bluebird bio expects to treat the first patients in Germany at the end of the year. Currently, we are preparing the enrolment at two or three certified centres in Germany.

EuroBiotech_It's a conditional authorisation, so what additional data did the European Medicines Agency request from bluebird bio?

Hartrampf_The EU conditional market authorisation is based on data from 42 patients who were enrolled in four global registrational trials. However, we are investigating LentiGlobin in children younger than 12 years. We are conducting and planning long-term studies: first, a long-term follow-up study of patients enrolled in our clinical trials, and second, a registry study for patients treated with Zynteglo to generate real-world evidence data. According to an analysis conducted by Wall Street firm Bernstein, a third of the 30 most influential insurers are sceptical about Novartis/Avexis' Zolgensma versus Biogen's Spinraza. Novartis CEO Vasant Narasimhan says the company has actually used "value-based pricing frameworks to price Zolgensma at around 50% less than multiple established benchmarks, including the 10-year current cost of chronic SMA therapy." Concrete rebates depending on outcomes, however, have not yet been published.

Insurance expert Felix Schneuwly from Swiss firm Comparis says the number of expensive one-shot therapies like Zolgensma will only rise, and will burden stretched health systems even further. "Sooner or later we'll have a problem," he says, adding that US prices would be viewed as anchor prices that other manufacturers will use as a guide for new therapies.

The challenge is matching up the potential lifetime value with concerns about whether those benefits are going to be realised

Novartis also currently has some trust issues with payors, with accusations floated that it hid data manipulation in a preclinical trial with Zolgensma conducted by Avexis. In August, it emerged that Novartis had phased out top scientists in its subsidiary who were involved in developing the gene therapy.

The problem with monopolies ...

Pharmaceutical companies have a quasimonopoly on patented treatments, which means they have the power to dictate prices or withhold potentially life-saving treatments from markets that won't accept their asking price.

Unequal access to therapies, however, is not just a problem when it comes gene

Digel_bluebird bio considers such studies to be an important investment in ensuring long-term safety not only of Zynteglo, but also of its entire gene therapy pipeline. Besides gene addition therapies such as Zynteglo, we are active in two other fields of gene therapy: gene editing and CAR-T cell therapies in immuno-oncology. While gene editing is still in the preclinical development stage, we are already conducting Phase III studies with our CAR-T candidate idecabtagene vicleucel (bb2121) in multiple myeloma, for which Celgene has licenced European commercialisation rights.

EuroBiotech_Gene therapies for orphan diseases have their price. You have priced Zynteglo at €1.575m per patient, but with a truly innovative outcomebased pricing model...

Digel_For us, it is important that the price reflects the value of a therapy. The value of Zynteglo is that it can achieve transfusion independence in a chronic progressive disease – which otherwise would require lifelong treatment with hundreds of transfusions – with a one-time treatment. We proposed a model to payors that couples reimbursement with the period of transfusion independence achieved in reality. The first charge of €315,000 is to be



Dr. med. Steffen Hartrampf, Medical Lead Germany, is a pediatrician with broad clinical expertise in pediatric hemato-oncology from LMU Munich and Memorial-Sloan Kettering Cancer Center. He recently joined bluebird bio from Bristol-Myers Squibb, where he started his industry career in medical affairs.

paid after the doctor has selected and treated the patient with Zynteglo. The other four payments over four consecutive years are payable only if the patient remains transfusion-free. Thus, 80% of the price is outcome-based.

EuroBiotech_What feedback did you receive from payors?

Digel_Currently, we have feedback from relevant stakeholders that the doors are wide open for outcome-based pricing. However, some challenges remain concerning the documentation of therapy success, as well as the staggered reimbursement.

EuroBiotech_What kind of challenges? **Digel_**Therapy outcome must be documented appropriately, but this is not completely in our hands. To document the outcome in a registry, we need long-term informed consent from the patient. We also need to share outcome data with payors in order to get reimbursed. Both are not fully in our responsibility, because according to European data protection rules, patients have the right to reject their consent. Because of that, documentation can become incomplete without any responsibility from our side.

EuroBiotech_bluebird bio has about 1,000 staff members globally. How do you manage the imminent risk of pricing that depends up to 80% on an outcome?

Digel_We rely on a solid pipeline of gene therapies, particularly in oncology, that will arrive on the market in the coming years.



therapies, but also to conventional highpriced drugs like Biogen's Spinraza. According to Rolfs, doctors in Germany can prescribe Spinraza without having to go through committees – making the country a lucrative market for the therapy. In the rest of Europe, says Kacper Rucinski, large numbers of citizens still have no access to the treatment. The board member at patient advocacy group SMA Europe adds that countries with small healthcare budgets like Bulgaria, Estonia, Ireland or Latvia have not agreed to make the therapy available.

US gene therapy player bluebird bio has taken a different approach to the problem. It's discussing the projected cost of its β -thalassemia gene therapy with multiple stakeholders before market approval, and has piloted a payment model that offers an alternative to huge upfront payments. Zynteglo received the EU stamp of approval this summer, and will file for a BLA this year (see interview, p. 14). β -thalassemia is an orphan disease that affects fewer than 100 patients in Germany, and approximately 200,000 people globally.

Taking risk for promise

The company's risk-sharing approach with payors couples five annual payments of €315,000 to the outcome. If a second administration of the gene therapy is necessary to keep patients transfusion-free, there is to be no additional payment. In effect, this means 80% of all payments for Zynteglo will depend on outcome. A smart approach, as EU fast-track approval was based on data from just 20 patients. While the concept appears simple, it faces practical hurdles. Healthcare experts told EUROPEAN BIOTECHNOLOGY that in Germany, where bluebird bio will enroll the first patients, there is no mechanism for reimbursing one-time-treatments like Zynteglo, as the German Health Fund always couples its annual assignments to treatments. It's set up to address permanent, ongoing medication – not for cures that are applied only once.

Besides risk-sharing like that proposed by bluebird bio, mechanisms must be in place to assure patient access to gene therapies by limiting cost-sharing to what is affordable – particularly in the US. There Spark has offered to pay all costsharing bills for patients treated with Luxturna, but will other companies follow that example? They might be forced into it. By November, the US Senate is set to decide on the "Lower Drug Costs Now Act". In its current draft, drugmakers that refuse to negotiate on fair price measures would be penalized dramatically.

Estimated sales for market-approved and selected late-stage gene therapies (Source: Evaluate Pharma)

Product	Company	Indication	Development Stage	Annual Sales Forecast (m\$)		
				2020	2022	2024
> Zynteglo	bluebird bio	β-thalassemia/ sickle cell anemia	EU approval 6/2019/ Phase II/III	105	735	1,890
> Zolgensma (AVXS-101)	Novartis/Axevis	Spinal muscular atrophy	FDA approval 5/2019 under EMA review	105	735	1,890
> Vyondys 53 (golodirsen)	Sarepta Therapeutics	Duchenne muscular dystrophy	FDA approval rejected 8/2019	-	723	1,591
> Luxturna	Spark Therapeutics/ Novartis	Inherited retinal dystrophy	FDA approval 12/2017, EU approval 11/2018	n.A	n.A	n.A
> Valoctocogene roxaparvovec	Biomarin Pharmaceuticals	Haemophilia A	Phase III	18	423	1,219
> AMT-061	Uniqure NV	Haemophilia B	Phase III	-	354	771
> SPK-8011	Spark Therapeutics	Haemophilia A	Phase III	-	122	458