WHITE PAPER

HIGH POINTS AND STUMBLING BLOCKS IN CELL AND GENE THERAPY: EXITING 2022, ENTERING 2023

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Health Advances™

2022 is almost in the rearview mirror and it has been an adventurous year for cell and gene therapies (CGT). The CGT industry continued its eventful journey of disappointing lows and breathtaking highs while persisting in its path forward.

A Challenging Economic Climate

During the pandemic, public attention on healthcare innovation helped promote a tsunami of investment into the biotech sector. In 2022, however, macroeconomic conditions have created significant investment headwinds for the industry, and CGT companies have not been spared. Companies have laid off employees, pivoted pipeline priorities, and redistributed resources in an attempt to remove organizational redundancies, create operational efficiencies, and reduce expenses.

Some players, such as Passage Bio, Solid Biosciences, and Orchard Therapeutics, are trimming preclinical projects to throw support behind more advanced clinical-stage assets. For instance, in November, Passage Bio announced that it would advance ongoing clinical trials in pediatric and adult CNS indications and eliminate almost a quarter of its workforce to decrease expenses.

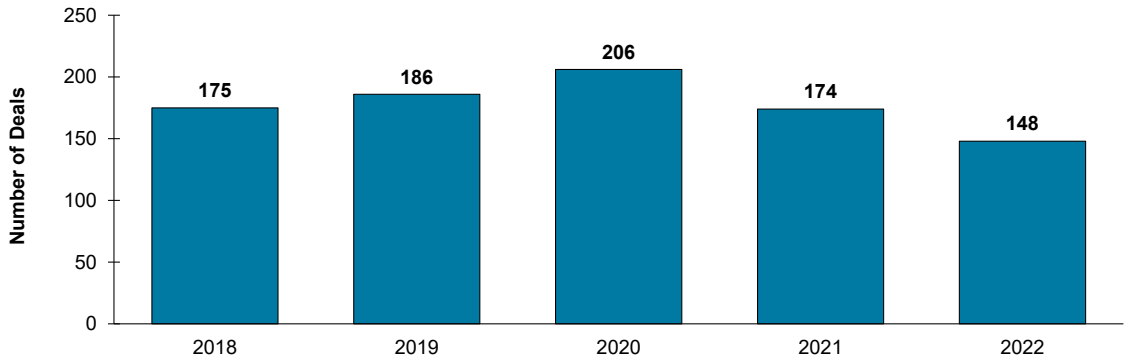
Despite the challenging economic climate and ubiquitous organizational restructuring, notable deals occurred in 2022 (Table 1), continuing the trend of interest and investment in CGTs that has been observed over the last few years (Figure 1). A trend that is proportionately reflected in the significant increase in the number of CGTs in development (Figure 2).

Table 1: Example Deals

Investor	Target	Potential Deal Value	Upfront Fee	Additional Details
Roche	POSEIDA THERAPEUTICS	$6B	$110MM	• (Aug 2022) Collaboration to develop and commercialize multiple allo CAR-T programs including P-BCMA-ALLO1 and P-CD19CD20-ALLO1
GILEAD	ARCELLX	$3.9B	$225MM cash $100MM equity	• (Dec 2022) Collaboration to co-develop and co-commercialize CART-ddBCMA in multiple myeloma • Deal announced after positive data in ASH '22
NOVARTIS	voyager THERAPEUTICS	$1.7B	$54MM	• (Mar 2022) License option agreement for AAV capsids for use with three CNS targets with option for two additional targets
Pfizer	Beam THERAPEUTICS	$1.35B	$300MM	• (Jan 2022) Exclusive four-year research collaboration to develop *in vivo* base editing programs for three targets for rare genetic diseases of the liver, muscle and CNS
Lilly	AKOUOS	$610MM	$487MM	• (Oct 2022) Lilly acquires Akouos to develop gene therapies for hearing loss
AstraZeneca	neogene THERAPEUTICS	$320MM	$200MM	• (Nov 2022) AstraZeneca acquires Neogene to develop TCR-T therapies for multiple indications including solid tumors
IPO	prime medicine	–	$175MM	• (Oct 2022) Prime Medicine raised $175MM on IPO at ~$1.8B valuation – Prime Medicine develops prime editing, a type of gene editing technology • IPO was the 19th in the biotech sector compared to >90 in 2021

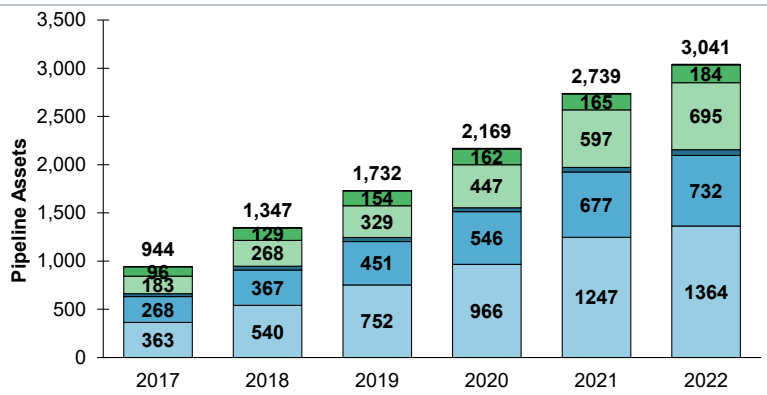
Source: Health Advances analysis, BioPharmadive, company websites.

Figure 1: Deal Activity across CGT by Deal Start Date



Source: Health Advances analysis, Cortellis.

Figure 2: Cell and Gene Therapy Pipeline 2017-2022



		CAGR
Gene Therapy	Launched - Gene Therapy	15%
	Clinical - Gene Therapy	14%
	Preclinical - Gene Therapy	31%
Cell Therapy	Launched - Cell Therapy	14%
	Clinical - Cell Therapy	22%
	Preclinical - Cell Therapy	30%

Source: Health Advances analysis, Cortellis.

Safety Concerns

As clinical activity in the space has risen, so has the occurrence of safety challenges. CGT companies are grappling with a range of adverse events in patients treated with their therapies. Lentiviral-based therapies have encountered issues with genotoxicity and unexpected serious adverse reactions such as myelodysplastic syndrome. Patients treated with AAV gene therapies have succumbed to liver toxicity, liver failure, and in some instances, death. Treatment with CAR-T cell therapy is associated with cytokine release syndrome, which is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction.

The concerns around the safety of cell and gene therapies have rightfully placed them under the microscope of regulatory bodies. BioMarin, Verve, and Beam Therapeutics are among several companies this year that have faced regulatory setbacks due to these concerns. The FDA stopped BioMarin's phenylketonuria BMN 307 gene therapy trial over the presence of tumors in preclinically-treated mice and asked for additional nonclinical studies to further assess the therapy's oncogenic risk in human study participants. In November, regulators requested a three-year data analysis to obtain longer-term efficacy and safety information from BioMarin's phase III GENEr8-1 trial of Roctavian (valoctocogene roxaparvovec). Likewise, the FDA has requested more preclinical data from Verve and Beam, manufacturers of base-editing gene therapy candidates, to demonstrate safety. In August, the FDA placed Beam's CAR T-cell product, BEAM-201, on clinical hold and requested additional control data from genomic rearrangement assessments and analyses of off-target editing experiments. These occurrences reinforce the FDA's mandate to strike the right balance between patient safety and the availability of therapies that effectively treat diseases with high unmet needs.

Clinical holds and regulatory delays can be highly detrimental to early-stage innovators. Whereas large companies are positioned to weather these obstacles, smaller CGT companies with typically only one main platform supported by a short financial runway are placed in a far more precarious position when their data readouts are pushed back. As a result, these companies are left with difficult decisions that often include narrowing their R&D focus and laying off staff to cut costs.

Regulatory Tailwinds

Fortunately, however, the FDA appears to be aware of the impact of their pushbacks on CGT developers and has been attempting to compensate with supportive measures. For instance, the FDA drafted guidance for the development of CGT products suggesting additional preclinical testing to evaluate the functionality and safety of genetic modifications, novel accessory molecules, and the overall investigational product. In terms of clinical recommendations, the FDA also recommended staggered treatment intervals to allow time to monitor for any adverse events. Additionally, the FDA worked with industry representatives, healthcare professionals, patient advocates, and other stakeholders to propose enhancements for the Prescription Drug User Fee Act (PDUFA) VII, which will provide much needed funding to support faster FDA review of new drug and biologic license applications. In September, the President of the United States signed the reauthorization of the Act.

CAR-T Therapy Manufacturing Bottlenecks … Brighter Future

Another core challenge for CGT companies that became clear this past year is manufacturing. Due to complex manufacturing and distribution models, cell-based therapies have faced challenges with manufacturing scale-up. To compound matters, the demand for CAR-T therapies continues to outpace supply. During the 2022 ASH Annual Meeting, physician researchers reported that only about 40% of R/R multiple myeloma patients on a waiting

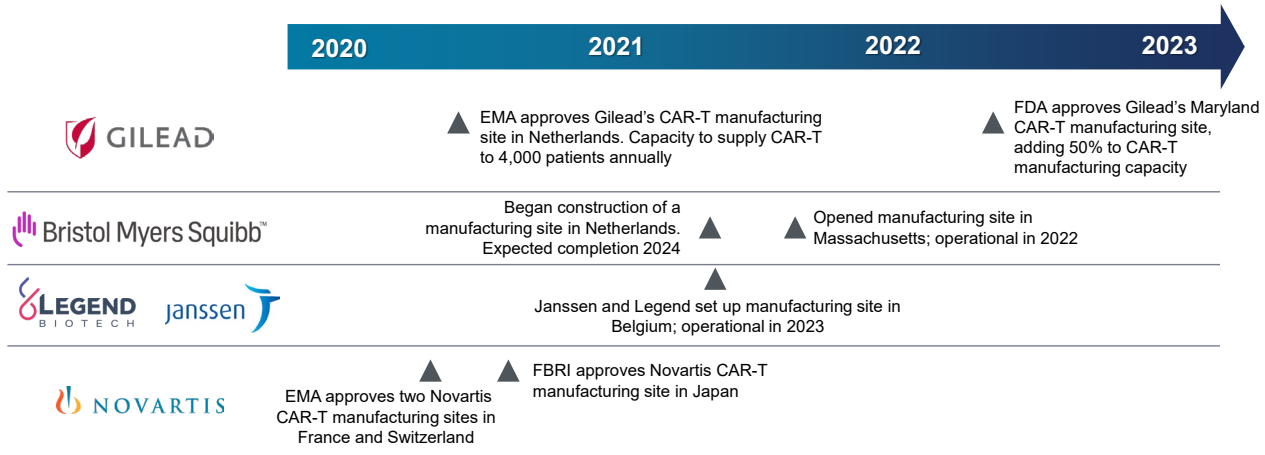
list for Abecma received the CAR-T cell therapy within a year. The study was based on data from two centers, the University of Arkansas for Medical Sciences in Little Rock and the Medical College of Wisconsin in Milwaukee. Unfortunately, about 25% of patients died waiting for the therapy. CGT companies have highlighted limitations in their manufacturing capacity and are making efforts to mitigate the issue.

In July, BMS announced that it would not be able to increase production capacity of its CAR-T treatment Breyanzi until the first quarter of 2023 due to lower-than-expected manufacturing success rates. In September, BMS claimed the manufacturing issues had been addressed but a shortage of lentiviral vector continued to pose challenges. These issues are not unique to BMS or Breyanzi; industry-wide, makers of CAR-T therapies have each run into manufacturing challenges with their respective treatments.

Nevertheless, growing CAR-T sales and efforts to expand production capacity may signal that these manufacturing issues can be overcome. Players like Gilead are proactively expanding their CAR-T cell therapy production capacity (Figure 3). In October, Gilead announced that the FDA had approved its new 100,000-square-foot facility for vector manufacturing. Moreover, the growing sales of many CAR-T therapies are likely indicative of winds of change. Q3 2022 sales of Tecartus reached $81 million up 72% YoY while Yescarta reached $317 million up 81% YoY. Some analyst projections suggest that Tecartus/Yescarta combined sales may exceed $600 million by end of year.

Contract development and manufacturing organizations (CDMOs) like Wuxi, Lonza, and AGC Biologics have also been investing in internal capabilities to improve vector technologies and manufacturing efficiency. For example, WuXi launched TESSA (Tetracycline-Enabled Self-Silencing Adenovirus) which can improve scalability, expedite AAV manufacturing, and significantly reduce costs for manufacturing many CGTs. The combined efforts across stakeholders will support future development of CGTs.

Figure 3: CAR-T Manufacturers Have Added Manufacturing Sites to Increase Production Capacity



Note: Site distribution of key CAR-T manufacturers upon completion of ongoing projects. Gilead has 3 sites (2 in US, 1 in Europe), Novartis 7 sites (2 in US, 3 in Europe, 2 in Asia, and 1 in Australia), BMY 4 sites (3 in US and 1 in Europe), J&J/Legend 4 sites (2 in US, Europe and Asia).

Source: Health Advances analysis, company websites.

Gene Therapy Approvals

We are in the midst of exciting times for gene therapies with recent approvals and promising data releases (Figure 4). These advances are crucial for the gene therapy field and particularly significant for patients affected by genetic diseases with high unmet needs.

This year saw the addition of three first-in-class gene therapies to the US market. Joining Spark Therapeutics' Luxturna approved in 2017 for biallelic RPE65 mutation-associated retinal dystrophy and Novartis' Zolgensma approved in 2019 for pediatric spinal muscular atrophy, bluebird's Zynteglo was approved in August for patients with beta-thalassaemia who require regular blood transfusions, followed shortly thereafter by Skysona which received FDA approval in September for the treatment of cerebral adrenoleukodystrophy, a rare pediatric brain disorder. The November 22nd approval of CSL's Hemgenix, a single-dose gene therapy for adult hemophilia B patients who currently use factor IX prophylaxis therapy, or those who have had life-threatening hemorrhage or repeated spontaneous bleeding episodes, marked its achievement as the first one-time gene therapy for adults with hemophilia B. Lastly, on December 16th, the FDA approved Adstiladrin (nadofaragene firadenovec-vncg), the first gene therapy for bladder cancer.

Similarly, two gene therapies were approved by the European Commission (EC) in 2022. In July, the EC authorized Upstaza, the first gene therapy to treat aromatic L-amino acid decarboxylase deficiency - a rare genetic nervous system disorder. BioMarin's Roctavian also received a nod of approval in August for the treatment of severe hemophilia A (congenital Factor VIII deficiency) in adult patients without a history of Factor VIII inhibitors.

We expect this momentum to continue as CGT companies report directionally positive findings from ongoing clinical trials. Take for example, Sangamo Therapeutics which presented updated preliminary data from its phase I/II Fabry disease clinical trial, demonstrating that ST-920 (isaralgagene civaparvovec)-treated patients had elevated levels of the enzyme, α- galactosidase A even after coming off enzyme replacement therapy which is the current standard of care.

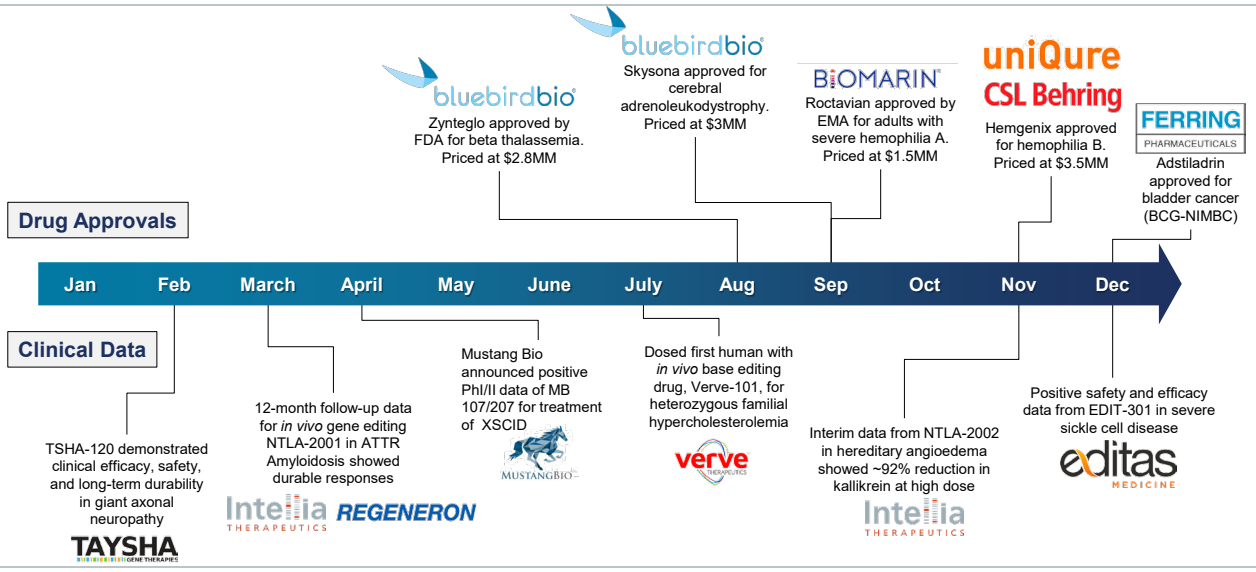
CAR-Ts are Moving On Up

Similarly, breakthroughs have occurred in the cell therapy space. Within the last decade, about half a dozen CAR-T cell therapies for treatment of leukemia, lymphoma, and multiple myeloma have been launched on the US and EU markets. As companies continue to develop CAR-T assets, clinical studies are being conducted to champion their use earlier in the treatment algorithm.

In 2022, two CAR-T therapies, Yescarta and Breyanzi, received approval as earlier-line treatments (Figure 5). Gilead's Yescarta was authorized as a second line treatment by the FDA for R/R large B-cell lymphoma and as a second-line treatment by the EC for R/R follicular lymphoma. Bristol-Myers Squibb's (BMS) Breyanzi scored FDA approval as a second line treatment for R/R large B-cell lymphoma and is under review in Europe as a second-line treatment.

Other CAR-Ts are also being evaluated for use in earlier lines. For instance, BMS is trying to move another one of its assets, Abecma, up the treatment sequence for multiple myeloma (MM). Based on interim analysis of the KarMMa-3 study, Abecma outperformed standard of care in relapsed/refractory MM patients who failed two to four prior lines of therapy by significantly prolonging the time to tumor progression or death. Positive results in the final readout of the KarMMa-3 trial may secure FDA approval of Abecma as a third-line myeloma treatment, progressing up from its current use in the fifth line.

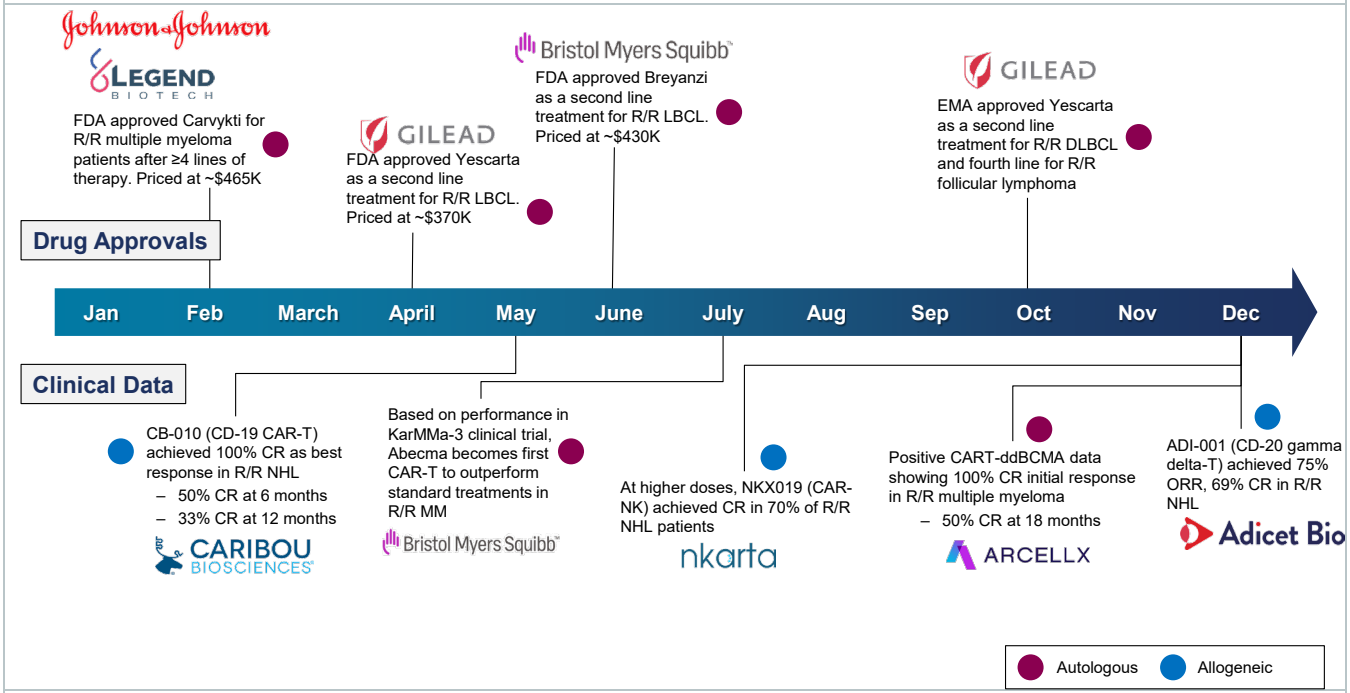
Figure 4. Gene Therapy Readouts in 2022



Note: XSCID = X-linked severe combined immunodeficiency, BCG = Bacillus Calmette-Guérin, NMIBC = non-muscle-invasive bladder cancer.

Source: Health Advances analysis, analyst reports, company websites.

Figure 5. Cell Therapy Readouts in 2022



Note: ORR = overall response rate, CR = complete response.

Source: Health Advances analysis, analyst reports, company websites

Allogeneic CAR-Ts as Complementary to Autologous CAR-Ts

Despite the demonstrated efficacy of autologous CAR-T therapies (auto-Ts), the appeal of treating larger patient populations with readily available cell therapies persists. Allogeneic CAR-Ts (allo-Ts) provide an off-the-shelf solution that addresses the availability (insufficient T-cell yields from patients), logistical challenges, and variable product quality of auto-Ts. However, whereas auto-Ts continue to show long-term efficacy, early clinical readouts for allo-Ts have been somewhat disappointing. Allo-Ts including ALLO-501 (Allogene Therapeutics), CTX110 (Crispr Therapeutics), and CB-010 (Caribou Biosciences) have failed to achieve the same durability of response as auto-Ts. These data suggest that allo-Ts are unlikely to displace auto-Ts in the near term, but in the future, their wider availability may provide an option to patients with access limitations associated with auto-Ts.

CRISPR-Based Therapies

We recently published an article titled "What Do the Next 10 Years Hold for CRISPR?" with reflections on the biomedical applications of CRISPR for the next 10 years. Of note is the remarkable speed at which this therapeutic class has demonstrated initial genome editing in in human cells to first-in-human clinical trials of CRISPR genome editing therapies.

Importantly, we may be less than a year away from a potential FDA approval of the first CRISPR therapy. CTX001, developed by CRISPR Therapeutics and Vertex Pharmaceuticals, is an autologous, ex vivo gene-edited cell therapy to treat sickle cell disease (SCD). CTX001 has shown consistent and sustained responses from at least 22 patients following treatment.

In vivo CRISPR therapies have also demonstrated promising advancements with the field eagerly awaiting clinical readouts from companies like Intellia. Intellia has two in vivo CRISPR-based genome editing candidates (NTLA-2002 and NTLA-2001) in clinical trials. Interim results from the Phase I/II study of NTLA-2002, a therapy being developed for the treatment of hereditary angioedema (HAE) showed that a single dose of NTLA-2002 significantly reduced the mean plasma kallikrein. Uncontrolled kallikrein activity causes overproduction of bradykinin, which leads to the recurrent and potentially fatal swelling attacks that occur in people living with HAE. Likewise, in its Phase I trial, NTLA-2001, a therapy targeted at heart-related issues in transthyretin amyloidosis, caused serum transthyretin levels to decline with mean reductions of 93% and 92% at two different doses. With these promising advances, we expect that CRISPR will continue to revolutionize gene therapy by delivering results that could lead to approved medicines.

To further highlight progress in this space, next-gen CRISPR technologies are already being tested in humans. CRISPR 2.0 companies including Verve Therapeutics and Beam Therapeutics have started clinical trials with base-editing technologies. Base editing is a newer, more targeted technology that builds on CRISPR, adapting it to make single base changes in a gene without breaking both strands of the DNA double helix. In July, Verve dosed its first patient with VERVE-101, a base-editing treatment for a form of heart disease known as hereditary familial hypercholesterolemia. In November, Beam enrolled its first patient in the BEACON clinical trial of BEAM-101, a base editing treatment for sickle cell disease.

Conclusions

Through the collective learnings from early R&D, clinical trials, manufacturing, and regulatory evaluations, we are hopeful about the future of CGTs. As we move toward 2023, we spotlight a few activities to keep an eye on (Table 2). For example, on the regulatory side, we await the FDA's stance on Biomarin's hemophilia A treatment, Roctavian, which has been approved in the EU but has faced additional data requests from the FDA. With regard to clinical readouts, we look forward to interim data from Verve's base-editing candidate to provide a glimpse into the performance of next-gen gene-editing technologies. Finally, we acknowledge that CGT is younger than other modalities and therefore still going through its growing pains, but we remain optimistic about the advent of transformative therapies.

Table 2: Regulatory and Clinical Readouts Expected in 2023

Events	Company	Technology	Estimated Date	Additional Details
Regulatory Updates	BIOMARIN	Gene therapy	March 2023	• FDA in Oct '22 accepted resubmitted BLA for Roctavian to treat severe hemophilia A with March 31, 2023 PDUFA date
	Bristol Myers Squibb	Auto CAR-T	N/A	• BMS seeking approval of Abecma in 2023 as third line treatment for multiple myeloma • Based on the positive KarMMa-2 and KarMMa-3 studies, Abecma will likely be approved for earlier line treatment but probably in 2024
	CRISPR THERAPEUTICS VERTEX	Gene therapy	2H 2023	• Vertex/Crispr will submit BLA applications for exa-cel for sickle cell disease and beta thalassemia to FDA and EMA for rolling review
	SAREPTA THERAPEUTICS	Gene therapy	May 2023	• FDA accepted and granted priority review for SRP-9001 BLA for the treatment of Duchenne Muscular Dystrophy with May 29, 2023 PDUFA date
	bluebirdbio	Gene therapy	2H 2023	• Bluebird plans to submit BLA for Lovo-cel for sickle cell disease in Q1 2023
Clinical Data Readouts	verve THERAPEUTICS	Base editing	2H 2023	• Interim safety and efficacy data on VERVE-101 based on ongoing study in New Zealand and UK • Study currently placed on hold by the FDA
	CARIBOU BIOSCIENCES	Allo CAR-T	2H 2023	• Caribou will initiate enrollment in early 2023 for CB-011 in R/R MM – CB-011 incorporates TRAC, B2M KO and B2M-HLA-E insertion to improve efficacy and durability
	Intellia THERAPEUTICS	Gene therapy	N/A	• Intellia plans to begin human studies to evaluate NTLA-3001, an *in vivo* targeted gene insertion of SERPINA1, for treatment of alpha-1 antitrypsin deficiency

Source: Health Advances analysis, company websites.

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