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Sickle Cell Drug Development Gains Momentum Across Disease Spectrum

Transplants An Alternative To Genetic Medicines For Some

by Mandy Jackson

The recent ASH meeting began with US FDA approvals of the first genetic medicines for sickle cell disease, but doctors and biopharma companies still see a need for new oral therapies and other options.

The approval of the first genetic medicines for sickle cell disease (SCD) on the eve of the American Society of Hematology (ASH) annual meeting set off a celebratory feel for the conference, held 9-12 December in San Diego, and drew increased attention to data presented at ASH for multiple novel drug candidates for the disease.

The FDA approved *Vertex Pharmaceuticals Incorporated*/*CRISPR Therapeutics AG*'s CRISPR/Cas9 gene editing medicine Casgevy (exagamglogene-autotemcel, exa-cel) and *bluebird bio inc.*'s viral vector-based gene therapy Lyfgenia (lovotibeglogene autotemcel, lovo-cel) on 8 December for SCD patients aged 12 and older with recurrent vaso-occlusive crises (VOCs) or a history of vaso-occlusive events (VOEs).

Longer-term data from pivotal trials for both approvals were presented at ASH as well as early Phase I/II results for *Editas Medicine Inc.*'s gene editing candidate

Key Takeaways

- The pipeline of new medicines for sickle cell disease is growing rapidly as evidenced by data presented for gene-editing medicines, gene therapy and small molecules at ASH.
- Recent approvals for Casgevy and Lyfgenia provide new options for severe SCD, but leave room for oral drugs that may be more accessible to the broader patient population.

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EDIT-301 (renizgamglogene autogedtemcel, reni-cel) and data from the Phase II portions of ongoing Phase II/III trials for *Pfizer Inc.*'s GBT021601 and *Agios Pharmaceuticals, Inc.*'s Pyrukynd (mitapivat). Also, in a late-breaker session, haploidentical bone marrow transplantation was presented as an effective option for patients with severe SCD.

- Haploidentical bone marrow transplant data at ASH also show that transplant can be expanded beyond HLA-matched donors and offer efficacy competitive with genetic medicines.

"The recent FDA approvals of CRISPR/Vertex Pharmaceutical's Casgevy (exa-cel) and bluebird bio's Lyfgenia (lovo-cel) have been regarded as transformational for the treatment of SCD," William Blair's analysts wrote in a 14 December meeting recap. "However, at ASH there was still excitement and optimism surrounding the potential of small-molecule treatments (Agios's mitapivat and Pfizer's GBT601), particularly for the pediatric SCD population of whom many are too young for gene therapies, and new data on bone marrow transplants as a significantly less expensive curative alternative to gene therapies for older patients with a history of strokes or organ damage."

The approvals of Casgevy and Lyfgenia provided a 50% increase in the number of FDA-approved therapies for SCD, following behind hydroxyurea, the first drug cleared for SCD, back in 1998, and Endari (L-glutamine), approved in 2017. Now owned by Pfizer, *Global Blood Therapeutics, Inc.* won approval for Oxbryta (voxelotor) in 2019. (Also see "*Global Blood Therapeutics' Oxbryta Approved Broadly For Sickle Cell Disease* " - Scrip, 25 Nov, 2019.) *Novartis AG*'s Adakveo (crizanlizumab) was also approved in the US in 2019. (Also see "*FDA Approval For Novartis's Sickle Cell Treatment Adakveo*" - Scrip, 18 Nov, 2019.) However, the p-selectin-targeting monoclonal antibody failed in the Phase III STAND trial at the start of 2023. (Also see "*Pfizer In Pole Position To Benefit From Novartis Sickle Cell Drug Setback*" - Scrip, 30 Jan, 2023.) Now, the European Medicines Agency has recommended revoking its conditional approval and Novartis has said EU patients will no longer be treated with Adakveo. (Also see "*EMA Recommends Revoking EU Approval For Novartis's Sickle Cell Disease Drug*" - Pink

Vertex/CRISPR Nab First-Ever Gene Editing FDA Nod, Overshadow Bluebird's Same-Day Win

By Mandy Jackson

09 Dec 2023

The two first-ever therapies to offer sickle cell disease patients the possibility of lifetime relief from painful vaso-occlusive events or crises are hitting the market, but face tough commercial challenges.

Read the full article here

Sheet, 26 May, 2023.)

Pfizer has its own monoclonal antibody in development targeting p-selectin, inclacumab, with Phase III results due in 2024. If the pivotal trial of inclacumab next year and the Phase III readouts in 2025 for Pfizer's GBT0210601 (GBT601) and Agios's Pyrukynd are positive, that could add another three treatments to the SCD treatment armamentarium by 2026.

"It's phenomenal for patients to have options now," Vertex vice president of hematology clinical development Bill Hobbs told *Scrip*. "Over the last couple of years, the interest in sickle cell disease has grown and I think you're really seeing that now."

Hobbs noted that "it's really difficult to generate interest among physicians and scientists if there is no vision towards what treatment options look like. I think for a long time there were really no really good treatment options and so the field was sort of dim. I think now it's sort of open to a lot of interest and enthusiasm ... and that's only going to benefit patients long-term."

Long Duration Of Efficacy For Genetic Therapies

Casgevy consists of autologous CD34-positive hematopoietic stem cells (HSCs) edited *ex vivo* with CRISPR/Cas9 technology at the erythroid-specific enhancer region of the BCL11A gene with the goal of increasing fetal hemoglobin. The primary endpoint in the pivotal CLIMB-121 study of the gene-editing treatment was the proportion of patients free of severe VOCs for at least 12 consecutive months (VF12), with the proportion of patients free from in-patient hospitalizations for severe VOCs for at least 12 consecutive months (HF12) as a key secondary endpoint.

Haydar Frangoul, a pediatric hematologist/oncologist at the Sarah Cannon Research Institute in Nashville, TN, presented CLIMB-121 results for 44 subjects between the ages of 12 and 35 who were enrolled in the trial and 30 who were treated with Casgevy as of the 14 June cutoff date. The patients all had severe SCD, defined as at least two VOCs per year during the prior two years, but the mean was 4.1 VOCs per year.

Frangoul reported that "29 of 30 patients, or 96.7%, achieved the primary endpoint of VF12" and the VOC-free duration was a mean of 22.4 months, ranging from 15 months to 45 months. He noted that "one patient with complex comorbidities and history of chronic pain did not achieve VF12 but, however, achieved HF12 and remains free from in-patient hospitalization for severe VOCs now over two years." All 30 of the severe SCD patients avoided the hospital, achieving the secondary endpoint of HF12.

Adverse events in CLIMB-121 were consistent with myeloablative busulfan conditioning used in autologous HSC transplants and in the Casgevy treatment regimen, with no serious adverse events or deaths attributed to the gene editing medicine. The efficacy and safety observed in the study show that Casgevy has "the potential to provide a one-time functional cure to patients

with sickle cell disease," Frangoul said.

Vertex head of clinical development Bill Hobbs said the CLIMB-121 update at ASH shows consistent efficacy for Casgevy over time that is having an impact on how SCD patients live their lives, based on patient-reported outcomes (PRO) data collected in the study. With a mean of four severe VOCs per year and three hospitalizations each year prior to treatment, patients in the study had frequent disruption to their lives prior to treatment.

"The thing about those events is that when a VOC happens, it's unpredictable, so a patient does not know when the next one is coming," Hobbs said. "They're always living under the shadow of can I do what I want to do or is it going to get disrupted? So, by having none, they can really live without having the concern of that, without having the disruption of their life, without having the pain and the damage that it's causing in their organs."

Julie Kanter, director of the University of Alabama, Birmingham's Sickle Cell Clinic and associate professor of hematology and oncology, presented data at ASH from up to 60 months of treatment with bluebird's Lyfgenia in group C of the company's Phase I/II HGB-206 study and its Phase III HGB-210 study. In 47 SCD patients as of the 13 February cutoff date, production of anti-sickling adult hemoglobin was stable, while VOEs and severe VOEs were significantly reduced or eliminated, with most adverse events attributable to busulfan conditioning.

Lyfgenia involves the addition of a functional beta-globin gene to patients' own HSCs. Among 34 evaluable patients, 32 people treated with the gene therapy (94%) had complete resolution of serious VOEs and 30 (88.2%) had complete resolution of all VOEs for a median of 35.8 months; among 10 adolescents, there were no VOEs of any kind during the 12-month enrollment period. The eight patients in bluebird's studies who experienced a VOE at any time after treatment through the long-term follow-up period experienced reduced frequency and severity of VOEs, with the median number of hospital days per year knocked down from 15.75 to 2.2 days.

Kanter also presented PROs for Lyfgenia from 20 patients and noted that there were clinically meaningful improvements in pain intensity, pain interference and fatigue, which improved by 57%, 64% and 64%, respectfully.

"We think, in the long term, one of the advantages we have is we have the longest-term dataset for any gene therapy for sickle cell disease," bluebird chief medical officer Rich Colvin told *Scrip*.

Overall, like Vertex's Hobbs, Colvin said it is an "amazing" time for SCD and noted that the disease has been well understood for much longer than several other rare genetic diseases for which treatments are now available.

"For sickle cell disease, the progress has been slower, and patients are still basically suffering the

way they suffered a lot of time ago," Colvin said, "Yes, there have been some improvements with some meds and certainly hydroxyurea makes a difference. And certainly, the new meds like voxelotor and crizanlizumab are potentially important, but they're not transformative like" genetic medicines.

Editas reported results for 11 SCD patients treated with reni-cel in the ongoing Phase I/II RUBY clinical trial at ASH. All evaluable patients (n=10) are VOC-free since infusion with the therapy, in which CD34-positive HSCs are CRISPR/AsCas12a-edited at the HBG1 and HBG2 gamma globin gene promoters to increase fetal hemoglobin production. Six patients with at least five months of follow-up have achieved and maintained fetal hemoglobin levels of greater than 40%. Safety results are consistent with busulfan conditioning and no serious adverse events have been attributed to reni-cel.

"For reni-cel to be successful, it will need to demonstrate meaningful differentiation, which the company believes could be achieved by targeting the Hemoglobin F promoters HGB 1 and 2 as opposed to the HbF transcriptional regulator BCL11A" targeted by Casgevy, Cantor Fitzgerald analyst Eric Schmidt said in a 13 December note.

"Editas chose to target HBG 1 and 2 based on preclinical data, indicating that disruption of the promoter region might lead to lower levels of hemolysis and higher levels of fetal and total hemoglobin," Schmidt added. "That hypothesis appears to be playing out in the clinic with data from the first handful of patients showing hemoglobin normalization (14-17 g/dL) at ~5 months follow-up. This compares to hemoglobin levels on Casgevy which peak at around ~13g/dL."

Editas announced on 13 December that it entered into an agreement with Vertex related to long-running patent litigation over CRISPR/Cas9 technology. Vertex obtained a non-exclusive license for Editas Medicine's Cas9 gene editing technology for *ex vivo* gene editing medicines targeting the BCL11A gene in SCD and beta thalassemia, including Casgevy. Editas is the exclusive licensee of certain CRISPR patent estates, including a Cas9 patent estate owned and co-owned by *Harvard University*, the *Broad Institute*, the *Massachusetts Institute of Technology* and *Rockefeller University*.

Editas will receive $50m up front under the license agreement, and is eligible to receive another $50m contingent upfront payment and annual license fees of $10m-$40m through 2034. Even after paying a mid-double-digit percentage to the institutions from which Editas licenses the patents, the company expects the license agreement's proceeds to extend its cash runway into 2026.

New Oral Therapies Offer Options For Broader Population

Given the cost and complexity of genetic medicines for sickle cell disease – it takes about six months to complete the Casgevy and Lyfgenia treatment regimens and they will launch at list

prices of $2.2m and $3.1m, respectively – the products are likely to be reserved for the most severe sickle cell patients. Vertex estimates that about 16,000 of the 100,000 people in the US with SCD will be eligible for treatment with Casgevy.

Agios CEO Brian Goff told *Scrip* the company expects its pyruvate kinase (PK) activator Pyrukynd to be applicable to a broad swath of sickle cell patients. It estimates the SCD market size at 120,000-135,000 in the US and top five EU markets, much larger than the 3,000- to 8,000-patient PK deficiency (PKD) market; Pyrukynd was approved to treat hemolytic anemia associated with PKD in 2022. (Also see "*Agios Anticipates PK Deficiency Diagnosis Ramp-Up After Pyrukynd Approval*" - Scrip, 21 Feb, 2022.) Agios will have Phase III data for the drug in alpha- and beta-thalassemia in 2024 that could support approval in 2025, making it available to a population of 18,000-23,000 patients a year ahead of Pyrukynd's potential approval for SCD.

With Sickle Cell Results For Pyrukynd, Agios Enters Increasingly Competitive Market

By Alaric DeArment

26 Jun 2023
The company has significantly built up its pipeline since divesting its oncology business to Servier, with multiple Phase III readouts for Pyrukynd expected in 2024-2025.

Read the full article here

As a PK activator, Pyrukynd reduces 2,3- diphosphoglycerate (DPG), which is associated with red blood cell sickling, and increases adenosine triphosphate (ATP) energy production associated with anemia. In SCD, Agios's goal with its drug is to improve hemoglobin and fatigue while reducing the number of VOCs that patients experience. "If we're able to deliver on that profile, then in every sense, mitapivat could be thought of as foundational therapy for these patients," Goff said.

In the Phase II portion of the Phase II/III RISE UP study, 79 SCD patients took twice-daily 50mg or 100mg doses of Pyrukynd or placebo; about 70%-80% of patients remained on background hydroxyurea therapy. The primary endpoint was hemoglobin response, defined as an increase of at least 1g/dL between weeks 10 and 12 versus baseline. Rates of sickle cell pain crises (SCPCs) in the 12-week treatment period were assessed on an annualized basis as a secondary endpoint.

Hemoglobin response was achieved by 46.2% of patients in the 50mg dose group, 50% in the 100mg group and 3.7% in the placebo group (p=0.0003 and p=0.0001, respectively). Annualized SCPC rates were 0.83 in the 50mg arm of the study, 0.51 in the 100mg arm and 1.71 in the placebo arm.

TD Cowen analyst Marc Frahm said in a 2 November note following the release of ASH abstracts

that Agios investors have expressed concern that the relatively small patient numbers and limited follow-up in RISE UP's Phase II portion mean that the observed SCPC reductions could be statistical noise.

“While this is certainly possible, we are reassured that the independent Utrecht [investigator-sponsored trial (IST)] is observing a very similar 50% VOC reduction (vs. baseline not placebo) at 52 weeks of follow-up,” Frahm said. “Taken together, we and KOLs are growing increasingly optimistic that mitapivat lowers VOCs and is a significant advance in the care of SCD patients.”

Headache, arthralgia, dysmenorrhea, pain, nausea, fatigue and influenza-like illness were the most common treatment-related adverse events associated with Pyrukynd in the Phase II portion of RISE UP. There were no drug discontinuations or deaths.

Goff said there may be potential for Pyrukynd to be administered as part of combination regimens for sickle cell disease, but Agios is focused on single-agent development for now as the company seeks to show that its drug works as a monotherapy in SCD.

“Pyruvate kinase activation is not necessarily a competing mechanism with the other mechanisms available or in pursuit right now, so [combination therapy] is an option, which is great because I think that creates tremendous optionality for patients,” he said. “But the focus for us is [to] establish ourselves as first-in-class, best-in-class and foundational.”

Pfizer’s next oral sickle cell treatment after Oxbryta has the same mechanism of action as the Global Blood-developed drug, but the sickle hemoglobin (HbS) polymerization inhibitor GBT601 is designed to have a better safety and efficacy profile with a lower dose because of its longer half-life.

Initial Phase II results from the two lowest once-daily doses tested in the ongoing Phase II/III trial showed that hemoglobin levels increased at 12 weeks in the 100mg dose group by 2.72g/dL for nine patients who were not also taking hydroxyurea and by 2.53g/dL for three patients who were taking hydroxyurea, while in the 150mg group hemoglobin increased 3.27g/dL for five patients without hydroxyurea and by 3.09g/dL for six patients with hydroxyurea.

By contrast, with higher patient numbers

Pfizer’s Growing Hematology Pipeline Matures With New Hemophilia, Sickle Cell Data

By Mandy Jackson

11 Dec 2023
The big pharma is building on its hematology legacy beyond coagulation factors with marstacimab and gene therapies for hemophilia, plus oral and injectable medicines

in the Phase II RISE UP results for Pyrukynd, mean hemoglobin levels increased at 12 weeks by 1.11g/dL in the 50mg group (n=26) and by 1.13g/dL in the 100mg group (n=26) versus 0.05g/dL in the placebo group (n=27), with no breakdown by hydroxyurea use.

for sickle cell disease.

Read the full article here

The annualized VOC rate for Pfizer's GBT601 decreased from 2.3 events at baseline to 1.2 at week 12. Treatment-emergent adverse events were observed in 62.9% of patients treated with the drug, but none of the grade 3-5 events were deemed treatment-related. A patient who died from cerebrovascular accident (CVA) had a history of CVA. Sickle cell anemia with crisis, headache, upper respiratory tract infection, diarrhea and arthralgia were the most common treatment-emergent adverse events.

"VOC reduction with '601 was ~50% at week 12, marked improvement from the ~26% seen with Oxbryta," Jefferies analyst Akash Tewari said in a 2 November note. "Overall safety and tolerability also look better than Oxbryta."

Haploidentical Bone Marrow Transplant As A Non-Drug Alternative

While patients in the gene therapy and gene-editing therapy clinical trials had severe SCD with many VOCs and hospitalization annually, some of the sickest patients were excluded from those studies, including individuals with multiple organ impairment from multiple VOEs. New data in these patients shows BMT could be a commercial challenge for the gene therapies, with similar efficacy at lower cost, albeit with different risks.

Adetola Kassim, associate professor at *Vanderbilt University*, presented the late-breaking results of a Blood and Marrow Transplant Clinical Trials Network multi-center, single-arm Phase II prospective clinical trial of haploidentical bone marrow transplant (BMT) with post-transplant cyclophosphamide (PTCy) to estimate event-free survival (EFS) at two years in adults with severe SCD. Reduced intensity human leukocyte antigen (HLA)-haploidentical BMT was explored to increase the pool of available donors relative to allogeneic HSC transplants with cells from HLA-matched siblings. Allogeneic HSC transplants can be curative, but less than 15% of sickle cell patients have HLA-matched donors. However, haploidentical BMT comes with a risk of graft versus host disease (GvHD).

The overall survival rate at two years for 42 patients in the BMT CTN study was 95% with an 88% estimated two-year EFS rate. Two patients died in the first year of the study, but the deaths were due to COVID-19 complications and not related to bone marrow transplantation.

At day 100, 26.2% of patients had grade 2-4 acute GvHD, including 4.8% with grade 3 and no

grade 4 acute GvHD. Three patients had severe chronic GvHD and the cumulative two-year chronic GvHD estimate was 22.4%, but at two years only one patient was still on immunosuppressive therapy for GvHD. The post-transplant PTCy regimen was administered to reduce GvHD.

“Haplo BMT is as effective as gene therapy and gene editing in improving donor engraftment and hemoglobin level at one-fifth the cost,” Kassim concluded, comparing BMT’s $200,000-$400,000 cost with the $2.2m and $3.1m list prices for Casgevy and Lyfgenia, respectively.

“These results support haploidentical bone marrow transplant with post-transplant PTCy as a suitable and tolerable curative therapy for adults with sickle cell disease and severe end organ toxicity, such as stroke and pulmonary hypertension, a population typically excluded from participating in myeloablative gene therapy and gene editing trials,” he said.