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Submitted via regulations.gov

Administrator Chiquita Brooks-LaSure
Centers for Medicare & Medicaid Services
Department of Health and Human Services
Attention: CMS–1808–P
P.O. Box 8013
Baltimore, MD 21244-1850

RE: Medicare and Medicaid Programs and the Children's Health Insurance Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Policy Changes and Fiscal Year 2025 Rates; Quality Programs Requirements; and Other Policy Changes (CMS-1808-P)

Dear Administrator Brooks-LaSure:

Vertex Pharmaceuticals Incorporated (Vertex) thanks the Centers for Medicare & Medicaid Services (CMS) for this opportunity to comment on the Inpatient Prospective Payment System (IPPS) and Long-Term Care Hospital (LTCH) Prospective Payment System (PPS) Proposed Rule for Fiscal Year (FY) 2025 (Proposed Rule).[1] Vertex is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious and life-threatening diseases. Our goal is to create new possibilities in medicine by combining advances in our understanding of human disease and in the science of therapeutics to dramatically advance human health. Vertex has spent the last 20 years discovering and developing medicines that treat the underlying cause of cystic fibrosis (CF) — a rare, life-threatening genetic disease. With an uncompromising commitment to patients, Vertex has successfully delivered multiple approved medicines that can treat up to 90% of people living with CF. Beyond CF, Vertex has a robust clinical pipeline of investigational therapies across a range of modalities in other serious diseases, including type 1 diabetes, acute and neuropathic pain, APOL1-mediated kidney disease, autosomal dominant polycystic kidney disease, myotonic dystrophy type 1 and alpha-1 antitrypsin deficiency.

Our most recent approval is for CASGEVY® (exagamglogene autotemcel, or exa-cel), the first-ever approved CRISPR-based gene editing therapy for the treatment of sickle cell disease (SCD) with recurrent vaso-occlusive crises and transfusion-dependent beta-thalassemia (TDT) for those aged 12 years and older. CASGEVY is an autologous, hematopoietic stem-cell non-viral therapy modified ex vivo by CRISPR/Cas9 that is administered via a stem cell transplant procedure. The treatment carries life-altering potential by aiming to reduce the chronic and life-threatening health impacts of SCD and TDT, including potentially eliminating painful and debilitating sickle cell crises for eligible people with severe SCD. For patients with TDT, who experience life-threatening anemia that requires regular, lifelong blood transfusions, CASGEVY has been shown to eliminate the need for such transfusions. As a leader in the development of novel gene therapies,

[1] 89 Fed. Reg. 35,935 (May 2, 2023), *available at* https://www.govinfo.gov/content/pkg/FR-2024-05-02/pdf/2024-07567.pdf.

including those targeting rare or under-served medical conditions, such as SCD and TDT, Vertex is excited to make this new therapeutic option available to patients.

In addition to our approved medicines, as mentioned above, Vertex has a robust pipeline of innovative technologies under investigation. Among other technologies, we are developing novel therapeutics that target the underlying cause of pain. In December 2023, Vertex completed our pivotal Phase III clinical trials to study Suzetrigine (previously known as VX-548) in moderate-to-severe acute pain. Vertex has also studied Suzetrigine in chronic pain and plans to complete a Phase II study on lumbosacral radiculopathy and initiate a Phase III study in peripheral neuropathic pain in the second half of 2024. This molecule is investigational, and its safety and effectiveness have not yet been established by any regulatory or health authority.

Suzetrigine is a potent and selective pain signal inhibitor that acts by inhibiting the function of the voltage gated sodium channel NaV1.8. Suzetrigine is anticipated to work by reducing the transmission of pain signals from the periphery to the brain, while leaving other sensations intact. It is the first therapy of its kind intended to specifically target NaV1.8, a sodium ion channel subtype with a role in transmitting nociceptive (i.e., pain perception) signals. Targeting NaV1.8 channels is especially promising because these channels are predominantly located in the peripheral nerves, not the brain, and for that reason are not expected to have the addictive potential of opioids or similar, centrally-acting pain management drugs.

Vertex is excited about the potential for this non-opioid pain management therapy, as pain continues to be among the most significant public health problems in the United States. Pain is one of the most common reasons that people see a doctor. Clinically, pain is typically described as either "acute" (less than 3 months in duration) or "chronic" (more than three months in duration). Recent studies estimate that approximately 80 million people in the United States will experience acute pain annually. Further, treating and managing pain places a heavy burden on the already strained US healthcare system, costing approximately $180 billion annually, with $60 billion attributed to direct health care costs. It also carries a vast human toll on individuals[9] due to disability and in its destruction of quality of life and work productivity. New therapeutic options have the potential to redefine the treatment paradigm for pain, and we must ensure the coverage and reimbursement landscape provides appropriate to these transformative medicines.

The Medicare IPPS has important implications for reimbursement of novel therapies like CASGEVY and future technologies in Vertex's research and development pipeline. Vertex is particularly interested in potential reforms in areas like New Technology Add-on Payments (NTAP), where CMS has put forward notable proposals as part of the FY 2025 rulemaking cycle. Vertex also believes that it is important for CMS to continue to actively work to develop innovative, longer-term solutions within the IPPS's Medicare Severity-Diagnosis Related Group (MS-DRG) framework that facilitate adequate and sustainable reimbursement for cutting-edge gene therapies like CASGEVY.

Vertex emphasizes that it is particularly critical that CMS continue to develop innovative payment policies under the IPPS given the uniquely important role of the IPPS in the payer ecosystem. Even when Medicare is not anticipated to be a predominant payer for a particular therapy, Medicare's reimbursement rules and coverage determinations are highly influential on commercial payers and many state Medicaid programs, often setting the standard for payment rates and patients' ability to access treatment. CMS has long acknowledged the importance of patient access for individuals who have been historically disadvantaged, including Medicare/Medicaid dual eligibles, and Vertex shares this view. We encourage CMS to adopt IPPS policies consistent with CMS and Vertex's shared recognition in the importance of encouraging access to care for beneficiaries, including access to innovative and potentially transformative new gene therapy technologies.

With respect to the Proposed Rule, Vertex writes specifically to comment on the following areas:

I. Vertex's NTAP application for CASGEVY in SCD and TDT
II. CMS's NTAP policy proposals

III. Creative MS-DRG solutions for gene therapy
IV. Vertex Response to TEAM model in regard to pain medication prescribing

I. Vertex's NTAP application for CASGEVY in SCD and TDT

As noted in the Proposed Rule, Vertex has submitted an NTAP application for CASGEVY in both its SCD and TDT indications for consideration in the FY 2025 IPPS rulemaking cycle.

CASGEVY was approved by the Food and Drug Administration (FDA) on December 8, 2023, as a one-time gene editing approach for the treatment of SCD in patients 12 years and older with recurrent VOCs. CASGEVY was also approved on January 16, 2024, as a one-time gene editing approach for the treatment of patients aged 12 years and older with TDT. CASGVEY received several FDA designations for SCD and TDT including Fast Track, Orphan Drug, and Regenerative Medicine Advanced Therapy (RMAT).

In our NTAP application, Vertex submitted evidence and analyses demonstrating that CASGEVY satisfies the newness, cost, and substantial clinical improvement criteria to qualify for NTAP for both SCD and TDT, effective October 1, 2024. In the Proposed Rule, CMS posed a number of questions related to the evidence supporting Vertex's NTAP application for CASGEVY. We address those questions and provide additional evidence below.

a. CASGEVY satisfies the newness criterion for both SCD and TDT, and is not substantially similar to other technologies used in the treatment of SCD and TDT

As noted in Vertex's NTAP submission, CASGEVY represents the first therapy approved to use CRISPR/Cas9 gene editing technology. No other approved technologies use this mechanism of action, and CRISPR/Cas9 technology has never previously been used in humans outside of clinical trials.

CASGEVY is a one-time treatment that uses ex vivo non-viral CRISPR/Cas9 to precisely edit the erythroid-specific enhancer region of BCL11A in CD34+ HSPCs. While other non-gene therapy-based therapeutic approaches impact production of fetal hemoglobin (HbF), no other approved technology has been able to reactivate production of endogenous HbF to levels known to eliminate disease complications (e.g., VOC and transfusion dependence), consistent with individuals with a clinically benign condition called hereditary persistence of fetal hemoglobin (HPFH) who experience no or minimal disease complications from SCD/TDT when they co-inherit both HPFH and SCD/TDT. Therefore, CASGEVY satisfies the "newness" criterion.

In the Proposed Rule, CMS requested public comment on whether CASGEVY should be considered substantially similar to other technologies used in the treatment of SCD or TDT. In its comments, CMS focused on perceived similarities in treatment journey and categorical product characteristics between CASGEVY and certain other technologies, but did not acknowledge material differences in the underlying technology which impact the safety and efficacy profile of these products. No clinical studies exist that compare CASGEVY with other technologies and no comparisons or conclusions of comparable safety or efficacy may be made.

As noted in our original submission, CASGEVY is a nonviral, autologous cell therapy that is designed to reactivate fetal hemoglobin production by means of ex vivo clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 gene editing at the erythroid enhancer region of BCL11A in a patient's own hematopoietic stem and progenitor cells (HSPCs). After CASGEVY infusion, the edited CD34+ cells engraft in the bone marrow and differentiate to erythroid lineage cells with reduced BCL11A expression. This reduced BCL11A expression results in an increase in γ-globin expression and HbF protein production in erythroid cells. In patients with severe SCD, HbF expression reduces intracellular hemoglobin S (HbS) concentration, preventing the red blood cells

from sickling and addressing the underlying cause of disease, thereby eliminating VOCs. In patients with transfusion-dependent β-thalassemia, γ-globin production improves the α-globin to non-α-globin imbalance thereby reducing ineffective erythropoiesis and hemolysis and increasing total hemoglobin levels, addressing the underlying cause of disease, and eliminating the dependence on regular red blood cell (RBC) transfusions.

As such, CASGEVY is not similar to the current standard of care (i.e., bone marrow transplant for SCD and non-curative, lifelong regular blood transfusions for TDT), nor to other technologies used in the treatment of SCD and TDT. CASGEVY relies on a completely different mechanism of action than either of these treatments—none of which rely on CRISPR gene editing to, in SCD patients, reduce intracellular hemoglobin S (HbS) concentration or, in TDT patients, reduce ineffective erythropoiesis and hemolysis and increase total hemoglobin levels, respectively.

Vertex also notes that the gene therapy LYFEGNIA utilizes a separate technology called gene replacement therapy, specifically utilizing a viral-based mechanism to introduce exogenous genetic material into patient's HSPCs. LYFGENIA adds functional copies of a modified βA-globin gene into patients' hematopoietic stem cells (HSCs) through transduction of autologous CD34+ cells with BB305 lentiviral vector (LVV). After LYFGENIA infusion, the transduced CD34+ HSCs engraft in the bone marrow and differentiate to produce red blood cells containing biologically active βA-T87Q-globin that will combine with α-globin to produce functional Hb containing βA-T87Q-globin. βA-T87Q-globin can be distinguished from wildtype βA-globin and from βS-globin through reverse-phase high-performance liquid chromatography (RPHPLC) or ultra-high performance liquid chromatography (UPLC). HbAT87Q has similar oxygen-binding affinity and oxygen hemoglobin dissociation curve to wildtype HbA, reduces intracellular and total hemoglobin S levels, and is designed to sterically inhibit polymerization of hemoglobin S thereby limiting the sickling of red blood cells.

In addition, due to the lentiviral vector (LVV)-based mechanism of action and the semi-random nature of viral integration, there is a potential risk of LVV-mediated insertional oncogenesis after treatment with this other gene therapy technologies used in the treatment of SCD and TDT, as documented in FDA-approved labeling for the respective products. [2]

Importantly, CASGEVY, with its non-viral mechanism of action using CRISPR/Cas9 gene editing, does not employ a viral vector and does not insert a transgene; therefore, insertional oncogenesis cannot occur as a matter of scientific principle. Gene editing approaches, including CRISPR/Cas9, do have the potential to produce off-target edits. The clinical relevance of such potential off-target editing is unknown. In clinical trials to date, CASGEVY's safety profile is generally consistent with complete myeloablative conditioning with busulfan. Off-target editing was evaluated through multiple orthogonal approaches and was not observed in the edited CD34+ cells evaluated from healthy donors and patients, or in clinical trials to date.[3]

Further, while CASGEVY may bear similarities to certain other gene therapy technologies in route of administration via a bone marrow transplantation episode and intended effect of addressing the underlying cause of SCD, CASGEVY uses a unique underlying technology and manufacturing processes, and has distinct product characteristics which differentiate it from other technologies used to treat SCD and TDT. Additionally, were CMS to consider gene replacement therapy and gene editing technologies to be substantially similar, it could set a precedent based on overgeneralization which could deter further innovation in the form of new technologies with distinct benefits, chilling

[2] LYFGENIA® (lovotibeglogene autotemcel) [package insert]. Somerville, Massachusetts: bluebird bio, Inc.; 2023
[3] NEJM 2024 Yen A et al

development in the still nascent but growing field of cell and gene therapy to the detriment of patients.

b. CASGEVY satisfies the NTAP cost criterion for both SCD and TDT

As noted in the Proposed Rule, Vertex submitted multiple analyses demonstrating that CASGEVY exceeds the cost threshold for MS-DRG 016. Cost analyses combined both SCD and TDT cases to account for low case volume, modeled two different cohorts to identify potential cases representing patients that could be eligible for CASGEVY, and, for each cohort, assessed scenarios in which there were no changes to patient drug regiment with the use of CASGEVY and in which no ancillary drugs are used in the treatment of CASGEVY patients. The submitted cost criterion analyses in CASGEVY's NTAP application show final inflated average case-weighted standardized charges of $12,181,526 and $12,086,551, exceeding average case-weighted thresholds of $182,491. These analyses demonstrate that CASGEVY meets the cost criterion.

c. CASGEVY satisfies the Substantial Clinical Improvement for both SCD and TDT

In Vertex s original NTAP application, Vertex submitted evidence to demonstrate that CASGEVY represents a substantial clinical improvement over existing technologies because it expands patient eligibility for potentially curative SCD therapies due to the lack of necessity for human leukocyte antigen (HLA)-matching as an autologous therapy, is the first gene therapy specifically approved for the treatment of SCD in patients 12 years and older with recurrent VOCs, is anticipated to have significantly improved clinical outcomes relative to available therapies as shown by elimination of severe VOCs in those patients, and is expected to avoid certain serious risks or side effects associated with approved viral-based gene therapies for TDT and SCD and other potentially curative treatment options for SCD.

CMS posed several questions related to the evidence provided to support these claims, which we address here.

a. Peer-reviewed literature directly assessing the use of CASGEVY for SCD and TDT provides evidence supporting that CASGEVY satisfies the substantial clinical improvement criterion

In the Proposed Rule, CMS noted that the only assessment of the technology submitted was from conference presentations."[4] When filing and amending the NTAP application by the prescribed regulatory deadlines, Vertex provided the latest and most complete datasets that were available at the time, which were presented at leading hematology meetings in June 2023[5] and December 2023[6] respectively. Following our application submission, additional data were published in the peer-reviewed New England Journal of Medicine for both our SCD and TDT therapies.[7,8] These publications provide further support for why CASGEVY satisfies the substantial clinical improvement criterion, as well as providing further evidence of safety and effectiveness and the transformative potential of CASGEVY to treat SCD and TDT.

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[4] 86 Fed. Reg. at 36,035.

[5] Udeze, C. et al, Mortality and Clinical Complications Among Patients With Sickle Cell Disease With Recurrent Vaso-Occlusive Crises. EHA Meeting 2023, Frankfurt, Germany.

[6] Drahos, J. et al, The Impact of Recent Vaso-Occlusive Crises on Health-Related Quality of Life in Adults With Sickle Cell Disease. ASH Meeting 2023, San Diego, CA.

[7,16] Frangoul H., et al. Exagamglogene Autotemcel for Severe Sickle Cell Disease, New England Journal of Medicine, 390, 18, (1649-1662), (2024). doi/full/10.1056/NEJMoa2309676

[8,17] Locatelli F, et al. Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia, N Eng J Med, 390, 18, (1663-1676), (2024). doi/full/10.1056/NEJMoa2309673

In Frangoul et al. (2024), the authors directly assessed the use of CASGEVY for SCD in a phase 3, single-group, open-label study (CLIMB SCD-121) in patients 12 to 35 years of age with SCD who had at least two severe vaso-occlusive crises in each of the two years before screening. The study was conducted in both the US and EU. As reported by the authors:

> "[A] total of 44 patients received exa-cel, and the median follow-up was 19.3 months (range, 0.8 to 48.1). Neutrophils and platelets engrafted in each patient. Of the 30 patients who had sufficient follow-up to be evaluated, 29 (97%; 95% confidence interval [CI], 83 to 100) were free from vaso-occlusive crises for at least 12 consecutive months, and all 30 (100%; 95% CI, 88 to 100) were free from hospitalizations for vaso-occlusive crises for at least 12 consecutive months (P<0.001 for both comparisons against the null hypothesis of a 50% response). The safety profile of exa-cel was generally consistent with that of myeloablative busulfan conditioning and autologous HSPC transplantation. No cancers occurred."[9]

In Locatelli et al. (2024), the authors directly assessed the use of CASGEVY for TDT in a phase 3, single-group, open-label study (CLIMB THAL-111) in patients 12 to 35 years of age with transfusion-dependent β-thalassemia and a β^0/β^0 , β^0/β^0-like, or non-β^0/β^0-like genotype. The study was conducted in both the US and EU. As reported by the authors:

> "A total of 52 patients with transfusion-dependent β-thalassemia received exa-cel and were included in this prespecified interim analysis; the median follow-up was 20.4 months (range, 2.1 to 48.1). Neutrophils and platelets engrafted in each patient. Among the 35 patients with sufficient follow-up data for evaluation, transfusion independence occurred in 32 (91%; 95% confidence interval, 77 to 98; P<0.001 against the null hypothesis of a 50% response). During transfusion independence, the mean total hemoglobin level was 13.1 g per deciliter and the mean fetal hemoglobin level was 11.9 g per deciliter, and fetal hemoglobin had a pancellular distribution (≥94% of red cells). The safety profile of exa-cel was generally consistent with that of myeloablative busulfan conditioning and autologous HSPC transplantation. No deaths or cancers occurred."[10]

We have included links to the full publications which provide further detail about the clinical trials, endpoints, and data demonstrating the safety and effectiveness of the therapy.

b. The study population from the CLIMB SCD-121 and CLIMB THAL-111 studies are generalizable to the Medicare populations

In the Proposed Rule, CMS requested additional information regarding the generalizability of the submitted clinical trial data to the Medicare population, noting the age range in the enrollment criteria of 12-35 for both the SCD and TDT studies, and CMS' uncertainty about where the studies were conducted.

CASGEVY was studied in trials conducted in the United States and the European Union. Additionally, as noted in the CMS SCD Action Plan[11], 11% of patients with SCD are enrolled in Medicare. CLIMB-121's study population is generalizable as it included patients aged 12-35, reflective of dua Medicare and Medicaid eligible populations. Notably, CMS has previously shared SCD prevalence data, indicating that more than 70% of Medicare FFS beneficiaries with SCD are dual eligibles. Further, more than 80% of these beneficiaries with SCD are covered under Medicare through disability insurance benefits.[12]

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[11] *See* CMS at https://www.cms.gov/files/document/sickle-cell-disease-action-plan.pdf.
[12] See CMS at https://www.cms.gov/about-cms/agency-information/omh/research-and-data/information-products/data-highlights/prevalence-of-sickle-cell-disease-among-medicare-fee-for-service-beneficiaries-in-2016.

We also note that the sample sizes for studies are appropriate. Both SCD and TDT are rare medical conditions: SCD affects an estimated 100,000 Americans,[13] and TDT impacts only an estimated 1,000 to 1,500 Americans.[14] The sample sizes of the studies involving CASGEVY are reflective of the challenges associated with enrolling larger studies for rare conditions, as well as significant challenges in conducting larger studies for an autologous gene therapy that must be individualized to each patient. We believe the study populations are reflective of the patient population for these conditions, including Medicare covered populations who, as noted, will often be dual eligible (and thus often not over age 65).

Therefore, the data from clinical studies of CASGEVY are generalizable to the Medicare population.

c. Peer-reviewed data demonstrates the well-tolerated safety profile of CASGEVY

Peer-reviewed data in the New England Journal of Medicine demonstrates the well-tolerated safety profile of CASGEVY for both SCD and TDT. [15],[16] While patients treated with CASGEVY experienced adverse effects, the adverse effects are consistent with the conditioning regimen, similar to adverse effects in autologous transplant. In the CLIMB SCD-121 trial for SCD, the most common adverse events were stomatitis (55%), febrile neutropenia (48%), platelet count decrease (48%), and appetite decrease (41%).In the CLIMB THAL-111 trial for TDT, the most common adverse events were febrile neutropenia (54%), stomatitis (40%), anemia (38%), platelet count decrease (35%), and thrombocytopenia (35%).[17],[18] Importantly, patients treated with CASGEVY did not have any reported cases of graft-versus-host-disease (GVHD), which is common in allogeneic transplant.

With respect to CMS's question about the length of the follow-up durations being studied, a long-term follow-up study is also continuing to monitor total and fetal hemoglobin levels and safety, including (but not limited to) the potential for secondary cancers, vaso-occlusive events, and markers of end-organ damage in patients who have completed the current study (CLIMB-131; NCT04208529); other studies are being conducted to assess the risk of secondary cancers and off-target effects after genome editing.

In response to CMS' concern regarding oncogenesis with gene therapy, we note that the two primary potential mechanisms for oncogenesis post-treatment include a late effect of alkylating chemotherapy or oncogene activation from off-target editing or insertional oncogenesis, as seen in other technologies used in treatment of SCD and TDT. In newly published peer-reviewed research in New England Journal of Medicine no off-target editing was found through multiple orthogonal approaches. Alkylating agents, however, generally require five to seven years before secondary malignancies occur.[19] In the most recent data published in New England Journal of Medicine earlier this year, the longest follow-up in both the CLIMB SCD-121 and CLIMB THAL-111 trials has surpassed four years, and Vertex will continue to follow study patients for up to 15 years.

d. The autologous, non-viral mechanism of CASGEVY is de facto evidence of the absence of the risk of insertional oncogenesis in other technologies

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[13] Nat'l Library of Medicine, Sickle cell disease, https://medlineplus.gov/genetics/condition/sickle-cell-disease/#frequency.

[14] ICER, Report at a Glance: Beta Thalassemia (July 2022).

[15, 21, 23] Frangoul et al, "Exagamglogene Autotemcel for Severe Sickle Cell Disease." *N Engl J Med*. Online April 24, 2024. DOI: 10.1056/NEJMoa2309676.

[17] Locatelli F, et al. Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia, N Eng J Med, **390**, 18, (1663-1676), (2024). doi/full/10.1056/NEJMoa2309673

used in the treatment of SCD and TDT, and the risk of GVHD or graft rejection associated with allogenic transplants

In its discussion of the claim that CASGEVY is expected to avoid potential risk associated with other technologies used in treatment of SCD and TDT and allogenic bone marrow transplant procedures for SCD and TDT, CMS questions whether variations in clinical trial conditions allows for adequate comparison of adverse event rates between clinical trials.

As noted in the previously referenced peer-reviewed publications (which supplemented evidence available at the time of Vertex's original NTAP application submission), the adverse event profile for CASGEVY in SCD and TDT is consistent with busulfan myeloablative conditioning and HSPC transplant. In addition, the CASGEVY mechanism of action does not employ a viral vector and does not insert a transgene. Therefore, insertional oncogenesis, a documented risk other technologies used in the treatment of SCD and TDT, by definition, cannot occur.

Although off-target genome editing was not observed in the edited CD34+ cells evaluated from healthy donors and patients, the risk of unintended, off-target editing in an individual's CD34+ cells cannot be ruled out due to genetic variants. The clinical significance of potential off-target editing is unknown.

Similarly, as an autologous therapy, which is manufactured from the patient's own HSPCs, which are modified with CRISPR/Cas9 gene editing technology and administered to the patient, there is no risk of GVHD or graft rejection, nor a need for immunosuppressive drugs, because the drug product is based on the patient's own cells. This has been supported by clinical data generated to date in the CLIMB SCD-121 and CLIMB THAL-111 studies, in which no GVHD or graft rejection/failure were observed.[20]

Vertex greatly appreciates CMS' careful review of our NTAP application for CASGEVY for both SCD and TDT. Taken together, Vertex believes that the original NTAP application, the additional peer-reviewed literature detailed above, and clarifying information clearly demonstrates that CASGEVY satisfies the newness, cost, and substantial clinical improvement criteria to qualify for NTAP for both SCD and TDT, effective October 1, 2024.

Furthermore, Vertex believes that (i) the clock on the newness period should begin at the date of first administration; that (ii) CMS should adopt a three-year NTAP for *all* autologous gene and cell therapies; and that (iii) CMS should use its exceptions and adjustments authority to adopt a new add-on payment adjustment that further extends NTAP effectiveness for an additional two years for these technologies for the policy rationales set forth in section II(d) of these comments.

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II. NTAP policy proposals

(a) Proposal to increase NTAP percentage to 75% from 65% for Gene Therapies for SCD

Vertex acknowledges and thanks CMS for its continued partnership in developing potential ways to improve patient access to gene therapies for SCD—including CMS's proposal to increase the NTAP payment percentage from 65% to 75%. We are appreciative of CMS's efforts to improve adequacy of

[20] Frangoul H., et al. Exagamglogene Autotemcel for Severe Sickle Cell Disease, New England Journal of Medicine, 390, 18, (1649-1662), (2024). doi/full/10.1056/NEJMoa2309676; Locatelli F, et al. Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia, N Eng J Med, 390, 18, (1663-1676), (2024). doi/full/10.1056/NEJMoa2309673

NTAP reimbursement for gene therapies for SCD, but also believe further refinements are essential to ensure appropriate reimbursement and adequate access to these important technologies. Furthermore, as we discuss in subsection II(b), Vertex believes it is essential that these efforts recognize the broader need and similar policy rationale beyond gene therapies for SCD, and would extend the same policies to ensure access to gene therapies for TDT, as well as other inpatient gene therapies meeting the NTAP eligibility criteria.

CMS's proposal to enhance NTAP reimbursement for these technologies is encouraging, as it recognizes the value of SCD gene therapy to Medicare beneficiaries. As CMS knows, SCD patients have long experienced great disparities in accessing care and the quality of care they receive. While medical advancements such as newborn screening and therapeutics have transitioned SCD from a fatal childhood disease to a chronic condition, patients with SCD still have a significantly shorter life expectancy – more than 20 years shorter than the general population.[21] Additionally, many serious, long-term health complications – including stroke, acute chest syndrome, heart failure, kidney disease, and chronic end-organ damage persist throughout the life of an individual with SCD. [22]

That said, while proposing to increase the NTAP percentage by 10% is noteworthy, it would not adequately address the underlying problem of insufficient total reimbursement for SCD gene therapies (nor for TDT and conceivably other inpatient cell and gene therapies). Rather, hospitals would continue to have significant shortfalls in reimbursement for these technologies. Vertex urges CMS to implement a more significant increase to the NTAP reimbursement percentage for SCD gene therapies. We believe this is a critical step to incentivize access to such innovative technologies for the small but critically important and historically undeserved population of beneficiaries with SCD, and to reduce losses for hospitals furnishing these therapies.

To further demonstrate the impact of the current reimbursement methodology to hospitals and the impact of different potential NTAP reimbursement percentage amounts, Vertex conducted data modeling simulating potential reimbursement scenarios for a SCD gene therapy like CASGEVY. FY 2023 MedPAR data was used to perform the analysis. Claims in MS-DRG 016 were selected and further limited to claims that hospitals that have expressed interest in providing SCD gene therapy, with an assumption that these hospitals would be purchasing the treatment directly, and not through a specialty pharmacy. The estimated charges of CASGEVY were added in by taking the price point of $2.2M and dividing by the national standardized pharmacy cost to charge ratio (CCR) of 0.182. These claims were then mapped to MS-DRG 016, and the estimated FY 2025 payments were calculated using the Proposed Rule's relative weights, standardized amounts, and hospital specific adjustments. In Table 1, we summarize the simulated NTAP reimbursement amounts at 65%, 75%, 85% and 100%.[23]

Table 1. Estimated Mean NTAP at Increasing Percentages

NTAP Percent	Mean NTAP Reimbursement Amounts	FY 2025 Proposed MS-DRG Base Rate	Mean Hospital Loss
65% (current)	$ 1,237,893	$43,059	$919,048
75% (proposed)	$ 1,428,338	$43,059	$728,603
85%	$ 1,618,783	$43,059	$538,158
100%	$ 1,904,450	$43,059	$252,491

[21] Estimated Life Expectancy and Income of Patients with Sickle Cell Disease Compared with Those without Sickle Cell Disease, 2019. Accessed March 13, 2024, at: 10.1001/jamanetworkopen.2019.15374
[22] Udeze c, et al. Projected lifetime economic burden of severe sickle cell disease in the United States. Accepted for EHA, 2022.
[23] CMS MedPAR Data FY 2023 from IPPS Proposed Rule.

As the analysis demonstrates, NTAP reimbursement amounts at or under the proposed 75% amount would still leave hospitals severely under-reimbursed for the product and patient care costs. At the 75% NTAP level, and assuming assignment under MS-DRG 016 with its proposed FY 2025 base reimbursement rate of $43,059, hospitals stand to lose over seven hundred thousand dollars with each case, which risks jeopardizing patient access to SCD gene therapy. Hospitals cannot reasonably be expected to sustain losses of that magnitude – and such sizeable shortfalls create vast barriers to utilization of a therapy, no matter the clinical benefit. Even at 100% NTAP, some hospitals would still not be made whole for the product cost and would lose over $250,000, and for those that are reluctant to mark up their charges (as discussed below), loses will amount to much more.

As noted above, this analysis assumes that hospitals set charges for the SCD gene therapy in line with the national average drug CCR of 0.182, (although we know that in reality hospitals are more likely to mark up in line with CCRs CMS uses in NTAP and outlier formulas). In other words, it assumes that hospitals would mark up a $2.2m gene therapy to more than five times their cost. In reality, hospitals often do not markup higher cost drugs by the same ratio as lower cost drugs, and this is especially common for gene therapies. If hospitals set charges for SCD gene therapies with a 50 % markup (e.g., charge $3.3m for a $2.2m drug, reflecting a CCR of 0.666), but CMS applies a much lower CCR to that charge, CMS would drastically underestimate the cost of the drug. For example, applying the CCR of 0.182 to the $3.3m charge would result in an estimated cost of $600,600, only 27% of the actual cost of the SCD gene therapy. That calculation, combined with the determination of the NTAP as the lesser of the 75% of cost of the drug or 75% of the amount by which costs of the case exceed the standard DRG payment, would mean that hospitals would receive much smaller NTAP amounts than are shown in this analysis. We urge CMS to consider these dynamics as it implements the NTAP for SCD gene therapies.

In addition, Vertex emphasizes the importance of CMS continuing to actively work to develop longer-term solutions to facilitate reimbursement adequacy for novel gene and cell therapies that are not reliant on temporary add-on payments like NTAP. Section C of this comment letter offers additional data-driven, creative MS-DRG solutions for gene therapy to address the Medicare beneficiary access barriers that exist in today's IPPS reimbursement construct.

(b) Recommended increase of NTAP percentage for Gene Therapies for TDT

Vertex urges CMS to also extend the proposed increase in the NTAP payment amount to gene therapies when used in the treatment of TDT, as well as other inpatient gene therapies which satisfy the NTAP eligibility criteria. This would allow for the enhanced NTAP to apply consistently for gene therapies like CASGEVY regardless of whether the therapy is used for its SCD or TDT indication.

Vertex believes the same public policy concerns that warrant CMS's proposal to enhance NTAP for gene therapies used in the treatment of SCD would apply with equal force when those same gene therapies are used in the treatment of TDT. Like SCD, TDT is a serious genetic condition that extends across the patient's lifespan and is often life-threatening. Also like SCD, historical treatment options for TDT also carry numerous limitations resulting in significantly under-served patient populations.

As noted above, historically, "blood transfusion [has been] the mainstay treatment to prolong survival" for individuals with TDT, with patients requiring "blood transfusion[s] at more than 100 ml/kg annually and iron-chelating therapy (ICT) to prevent iron overload (IOL)."[24] Life expectancy for individuals with TDT is also well below the general population. Even with access to non-gene-therapy treatments, from 2011 to 2021 the median age of death for a person in the US with TDT was

[24] A. Shafie et al., Economic burden in the management of transfusion-dependent thalassaemia patients in Malaysia from a societal perspective, 16 Orphanet J Rare Dis 2 (2021).

37—and patients have also historically reported significant decreases in their quality of life due to the severe impacts of the condition, which can require transfusions as often as every weeks.[25]

In addition, enhancing NTAP is vital to ensuring individuals with TDT have appropriate access to potentially transformative treatment options. The same reimbursement adequacy issues described above with respect to the gene therapy NTAP enhancement for SCD apply with the same force regardless of when the therapy is used in the treatment of patients with TDT. In both cases, enhanced NTAP is needed to ensure reimbursement adequacy consistent with the modeling and analysis summarized in Section (B)(a). Vertex also notes that extending enhanced NTAP to gene therapies used for TDT is likely to have a minimal impact to the IPPS from a budget neutrality perspective. There are only an estimated 1,000 to 1,500 individuals in the US living with TDT, and the proportion of Medicare eligible individuals with TDT is far smaller.

(c) Elimination of "Lesser of" Methodology

CMS should also eliminate the "lesser of" NTAP methodology for gene therapies targeting SCD. Under the lesser of methodology, CMS reimburses NTAP based on the lesser of a percentage of a drug's costs or a percentage of the difference between the amount by which the costs of the case exceed the standard DRG payment, as determined by application of the agency's CCR methodology.[26] Rather than having hospitals artificially inflate their charges in order to obtain appropriate reimbursement, a more principled approach would be for CMS to eliminate the lesser of methodology entirely for NTAPs targeting gene and cell therapies for SCD (and TDT). CMS should instead look to the *actual* costs of such therapies when determining the NTAP reimbursement amount—i.e., base the NTAP reimbursement amount on a percentage of wholesale acquisition costs (WAC) or the hospital's actual acquisition cost, as reported on the claim form.

In practice, the costs associated with inpatient stays involving gene therapies tend to overwhelmingly be driven by the costs of the associated gene therapy, and the WAC of these products is readily determinable from third party databases. Accordingly, there is no need to look at individual hospital charging practices to determine the costs of these technologies. Rather, reliance on the "lesser of" methodology and CCRs introduces unnecessary distortion in the NTAP reimbursement formula—relative to basing the NTAP reimbursement formula on WAC (or another data point grounded in actual acquisition costs, rather than charges). Alternatively, CMS could instruct hospitals to report their acquisition cost, without a markup, on their claims using value code 90.

(d) Proposal on NTAP Effective Duration

In addition to enhanced NTAP payment amounts, Vertex continues to stress the importance of other reforms that aim to increase the availability of add-on payments for novel technologies. While Vertex appreciates CMS's proposal to change the April 1 cutoff to October 1 for NTAP newness determinations, we ask that CMS take additional steps to ensure a more adequate data collection period for autologous gene and cell therapies, as these technologies have unique characteristics that warrant an extended add-on payment and data collection period.

We encourage CMS to adopt the below policies to better tailor the agency's approaches to the unique needs of autologous gene and cell therapies, including the following two reforms:

- First, given the unique patient timelines and manufacturing dynamics of autologous gene and cell therapies, **Vertex asks that CMS start the clock on newness following the first administration**. This administrative change will allow for maximum data collection to benefit patient access, provider reimbursement and future CMS rate-setting.

[25] *See* D. Farmakis, 2021 Thalassaemia International Federation Guidelines for the Management of Transfusion-dependent Thalassemia, 6 Hemasphere e731 (2022).
[26] 42 C.F.R. § 412.88(a)(2)(ii).

- Second, we ask CMS to adopt a three-year NTAP for *all* autologous gene and cell therapies (consistent with the statutory maximum for the NTAP period), regardless of when the three-year anniversary date of U.S. market entry falls in a given year. In addition, we ask that CMS use its exceptions and adjustments authority to adopt a new add-on payment adjustment that further extends NTAP effectiveness for an additional two years for these technologies.[27] This would **effectively create a <u>five-year period</u> where an add-on payment is available for autologous gene and cell therapy products that qualify for NTAP**.

  Vertex acknowledges that extending the availability of an add-on payment for autologous gene and cell therapies qualifying for NTAP beyond the normal maximum of three years would be a significant step. However, there are uniquely compelling policy reasons for CMS take this action, given the characteristics and data collection needs of these technologies—which warrant CMS establishing a longer effective NTAP period to develop the data needed for appropriate MS-DRG rate-setting.

Below, Vertex highlights the unique policy imperatives that support these requested policy changes for autologous gene and cell therapies.

Unique manufacturing requirements of autologous gene and cell therapies – CMS's standard approach to calculating the NTAP period uniquely disadvantages autologous gene and cell therapies.

Specifically, CMS determines the NTAP newness period start date by reference to the date of market availability and uses the date of FDA approval or clearance as its default start date.[28] Using the date of FDA approval or clearance as the default start date is highly problematic for autologous gene and cell therapies—because these technologies are individualized medicines, meaning that each dose of a given gene or cell therapy must be manufactured and tailored to the unique patient. These therapies are created from a patient's own body to create a personalized therapy, which is accompanied by a complex and time-consuming manufacturing process. As a result, there is a manufacturing period of multiple months between FDA approval date and the date that an autologous gene or cell therapy is first administered to a patient, and therefore can first be reflected in the inpatient claims data.

Under the circumstances, it is appropriate for CMS to consider ways to extend the available NTAP period relative to the agency's default policies. Otherwise, autologous gene and cell therapies face an artificially shortened NTAP period when CMS applies its default policy of using the FDA approval date to start the NTAP "newness" period—because of the significant delay between the date of approval and the date that any inpatient claims will actually be submitted.

The significant time lag between approval and administration warrants CMS considering ways to extend the effective time period when an add-on payment is available for autologous gene and cell therapies. At minimum, these technologies should have a default newness period start date of the date of first administration or infusion, or date of first claim received by CMS for the treatment. Relative to the current newness start date, it is important to consider that the process to manufacturer autologous gene and cell therapies has phases to establish eligibility, obtain medical clearance, undergo myeloablative conditioning, and collection – meaning many months of lead time for the first administration.

In addition, the delay period associated with autologous gene and cell therapies warrants extending the effective add-on payment period to five years—because the delays between manufacturing and

[27] The new add-on payment amount would be set at an amount equivalent to the NTAP reimbursement amount.
[28] *See* 87 Fed. Reg 48,911. In cases of documented delay, CMS policy does permit the agency to exercise discretion to define an alternative date of U.S. market entry (rather than to rely on the default FDA approval date). However, CMS has not established clear and specific guidelines detailing what constitutes a documented delay warranting such a departure from the agency's default of using the FDA approval date. *See, e.g.*, *id.* at 48,911 (using the date of approval for a CAR T-cell therapy and declining to consider evidence of a subsequent date of first sale as evidence of a product having a later date of U.S. market entry).

administration will occur for *each* administration of an autologous gene or cell therapy. As such, providers won't be able to take advantage of the full NTAP period because there will always be unusually significant time lags due to the unique manufacturing processes associated with this class of technologies. Absent a policy change altering how the add-on payment duration works for autologous gene and cell therapies, there is a serious risk that the NTAP period will not be sufficient to support access to these therapies and collection of adequate cost and utilization data for future rate setting.

Limited claims data of autologous gene and cell therapies – Establishing a five-year add-on payment period for autologous gene and cell therapies with NTAP would also better allow the agency to develop claims data related to these technologies given the unusually low claims volume associated with individualized gene and cell therapies.

Congress's purpose in authorizing the NTAP was to facilitate data collection for novel technologies by allowing CMS to use the add-on payment to encourage utilization during the NTAP period. The data collected during this period is then intended to be used to inform appropriate rate-setting under the IPPS's standard MS-DRG-based system.[29] Because there is a two-year lag between the claims data used in each rulemaking cycle and the implementation of new payment rates based on that data, CMS has only two years of data to use to set rates by the time a three-year NTAP period ends. In many cases, the first year's data reflect lower utilization than later years due to gradual adoption of a new technology. As noted, however, it takes an unusually prolonged period of time to develop adequate data for autologous gene and cell therapies because each administration is uniquely tailored to an individual patient through a multi-month manufacturing process and the total volume of utilization is anticipated to be very low relative to other, non-individualized technologies. As such, extending the newness period is especially important for autologous gene and cell therapies.

The risk of inadequate data collection is especially high for therapies targeting disease states where there are very few patients who are Medicare beneficiaries, like SCD.[30] For these technologies, there is an especially high risk that very limited Medicare data could be collected during a three-year NTAP period. Other limitations on eligible patient populations will likely only further reduce claims volumes. For example, for CASGEVY, the treatment not only targets a rare disease with limited Medicare patient volume, but the pool of eligible patients will be significantly further restricted—because many patients will have co-morbidities or complications (e.g., organ or tissue damage) that renders them ineligible.

Given that low claims volume is an unusually acute problem with gene and cell therapies, it is vitally important that the NTAP period be extended for a sufficiently long period to maximize the data that can be collected.

Precedent for Expanding Data Collection Period for Add-on Payments - There is also precedent for an extension of the data collection period associated with add-on payments. Vertex's request would be analogous to steps CMS has previously taken in the Calendar Year (CY) 2022 Hospital Outpatient Prospective Payment System Final Rule, where the agency extended an additional four quarters of separate payment for 27 drugs and biologicals (and one device) whose pass-through status was set to expire between December 31, 2021 and September 30, 2022, and thereby effectively extended the reimbursement benefits of pass-through status beyond the normal three-year maximum period.[31]

Impact to providers and patient access - Most importantly, abbreviating the effective NTAP period risks chilling beneficiary access to an important and potentially transformative class of medicines.

[29] *See* SSA § 1886(d)(5)(k).
[30] In 2019, CMS estimated only 11,790 Medicare fee-for-service beneficiaries had SCD, a prevalence rate per 1,000 beneficiaries of only 0.2. *See* CMS, Prevalence of Sickle Cell Disease among Medicare Fee-for-Service Beneficiaries, Age 18-75 Years 4 (2019).
[31] 86 Fed. Reg. 63,458, 63.621 (Nov 16, 2021).

NTAP plays a pivotal role in encouraging adoption of novel gene and cell therapies, and therefore plays a key role in helping Medicare beneficiaries gain access to groundbreaking new technologies with life-altering treatment potential. The resource intensity and low utilization volume of these transformational medicines often makes providers reluctant to provide access to them absent NTAP, especially before there is adequate claims data to better ensure that the resource use associated with these technologies is factored into the base MS-DRG payment rates. In addition, a lack of available NTAP reimbursement at date of treatment administration increases rate volatility for providers of gene and cell therapies, further disincentivizing providers to offer otherwise potentially life-altering access to novel transformative therapies.

(e) NTAP start date for CASGEVY

With respect to the pending NTAP application for CASGEVY, Vertex also asks that CMS use the date of market entry for CASGEVY as the starting point for NTAP. In the Proposed Rule, CMS proposes to use the ZYNTEGLO market entry date as the start of the NTAP period because the agency proposes to treat the two technologies as substantially similar.[32] Yet this would not be logical, as ZYNTEGLO *did not seek or previously obtain NTAP*. If the NTAP eligibility time period is curtailed or severely shortened, it would run counter to the spirit of the program in decreasing patient access and available claims data.

As discussed above, the purpose of the NTAP is to provide an add-on payment that encourages the collection of adequate inpatient Medicare data to allow for new and innovative technologies to be accounted for in the default MS-DRG rate-setting process.[33] Using the ZYNTEGLO market entry date would run directly counter to this objective, as there would be no add-on payment to incentivize Medicare inpatient utilization for a technology that was not previously granted NTAP. Rather, it would be far more consistent with Congress's purpose in establishing NTAP if CMS were to use the CASGEVY market entry data, as this would maximize the data collection period associated with the add-on payment.

CMS would also not be required to modify its regulations to adopt this interpretation. The agency's regulations do not specifically address how to calculate the NTAP start date for a technology that is substantially similar to another technology.[34] Further, while in preamble guidance CMS has sometimes addressed how it calculates the NTAP start date for a technology that is substantially similar to another technology *previously granted NTAP (or seeking NTAP in the same rulemaking cycle)*[35]—we are not aware of CMS specifically adopting a policy for how to determine the NTAP start date where the agency believes a technology is substantially similar to another technology that did not seek or previously receive NTAP.

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III. MS-DRG Solutions for Gene Therapy

Consistent with CMS's proposals to expand access to novel gene therapies through reforms to pathways like NTAP, Vertex would like to reinforce the importance of ongoing CMS efforts and partnership in continuously evolving the MS-DRG system to fit newly approved gene and cell therapies that have the power to change the lives of Medicare beneficiaries. We sincerely appreciate CMS's noteworthy proposals targeting NTAP reform for certain gene therapies. That said, the temporary nature of NTAP means that evolution of the larger MS-DRG system is the critical next step to ensuring sustainable, long-term reimbursement for pathbreaking gene therapies.

[32] 89 Fed. Reg. at 36,037.
[33] *See* SSA § 1886(d)(5)(k).
[34] 42 C.F.R. §§ 412.87, 412.88.
[35] *See, e.g.*, 66 Fed. Reg. 46,902, 46,915 (Sept. 7, 2011)

(a) Recommended development of a novel pre-Major Diagnostic Category (MDC) MS-DRG for certain gene therapies

Vertex specifically highlights the need for CMS to begin actively considering new MS-DRG solutions for the gene therapy CASGEVY in the near future. In the absence of a new and unique, pre-MDC MS-DRG implemented on or before the expiration of NTAP (if granted), we have concerns about reimbursement adequacy and beneficiary access to this critical technology.

CMS's long-standing approach for determining appropriate MS-DRG groupings also strongly counsels in favor of the creation of new and unique MS-DRG. As part of considering MS-DRG design and placement, CMS considers a combination of clinical and resource comparability factors.[36] CASGEVY is currently mapped to MS-DRGs 016/017, autologous bone marrow transplant—as this appears to be the most clinically comparable available grouping under the current MS-DRG system. That said, CASGEVY still has substantial clinical *and* resource intensity distinctions from the other treatments mapped to these MS-DRGs. We provide more details bearing on resource utilization and reimbursement adequacy in the data-modeling scenarios in the subsection immediately below.

(b) Data modeling of pre-MDC MS-DRG scenarios

To illustrate how the creation of a novel MS-DRG could more sustainably facilitate access to CASGEVY for beneficiaries with SCD and/or TDT, we provide the following data-modelling scenarios comparing the anticipated effect of the creation of a new MS-DRG:

- **Scenario A (Hematopoietic Stem Cell Gene Therapy DRG)**: Adding new cases to a newly created MS-DRG that would include both SCD gene therapy products and TDT products, modeling both 5 and 10 SCD gene therapy cases
- **Scenario B (Continued Mapping to MS-DRG 016)**: Modeling the impact of adding new CASGEVY cases to existing MS-DRG 016 (autologous hematopoietic stem cell transplant), modeling both 5 and 10 SCD gene therapy cases.

To develop these scenarios, SCD and TDT gene therapy products were modeled using the MEDPAR FY 2025 IPPS Proposed Rule data (i.e., claims data from FY 2023).[37] We identified claims in MS-DRG 014 (allogeneic bone marrow transplant) with SCD diagnoses and selected 10 cases which were duplicated in the modeling. The cases were then assigned to have either CASGEVY charges or LYFGENIA charges added to the claims. For each case, the product's cost (e.g., $2.2M for CASGEVY; $3.1M for LYFGENIA) was divided by the IPPS FY 2025 national standardized pharmacy CCR of 0.182. The additional modeled cases were then added to the MEDPAR file and used in calculating MS-DRG weights based on CMS posted methodology with the IPPS FY 2025 Proposed Rule.

Table: Modeling MS-DRG Reimbursement by Scenario:

	Projected Relative Weight	**Projected Base Reimbursement**
Scenario A: SCD + TDT Gene Therapy MS-DRG	220.5282	$1,583,968

[36] *See* CMS, Design and development of the Diagnosis Related Group (DRG), https://www.cms.gov/icd10m/version37-fullcode-cms/fullcode_cms/Design_and_development_of_the_Diagnosis_Related_Group_(DRGs).pdf.

[37] Our model included CASGEVY, one other SCD gene therapy technology, and (for Scenario B) one other TDT gene therapy technology, all of which are administered through hematopoietic stem cell transplant procedures. We believe these are the only currently approved hematopoietic stem cell transplant gene therapy procedures relevant to these clinical disease states of potential interest, and thus the only clinically coherent technologies that should be incorporated into the contemplated new MS-DRG.

Scenario B: Adding SCD Gene Therapy to MS-DRG 016	7.535	$54,118

The analysis demonstrates the critical importance of a new MS-DRG targeting gene therapies like CASGEVY.

Although the creation of a new MS-DRG (Scenario A) would not necessarily fully reimburse providers for the acquisition cost of autologous gene therapies, it would significantly mitigate the scale of reimbursement shortfalls. By only grouping gene therapy products within the new MS-DRG, CMS would also better ensure resource comparability and prevent non-gene-therapy inpatient cases from artificially deflating reimbursement rates. This is especially important given that autologous gene therapies are anticipated to have exponentially lower volumes of utilization than most other procedures—which means that such gene therapies are at heightened risk for being disproportionately under-reflected in the rate-setting process if grouped with non-autologous gene therapy technologies.

The analysis also demonstrates why ongoing mapping of SCD gene therapy cases to MS-DRG 016 would result in significant distortions to that MS-DRG.

While CASGEVY is currently mapped to MS-DRG 016, our modeling projects that the addition of SCD gene therapy cases to MS-DRG 016 (Scenario B) will result in a 11-23% increase in base payment. As a practical matter, this would mean that non-gene therapy cases would see over-reimbursement of approximately $11,000 per case—while gene therapies like CASGEVY would continue to be vastly under-reimbursed at less than 25% of the technology's WAC alone (even before accounting for other potential costs associated with the inpatient stay).

Consistent with our earlier discussion about the need to extend the NTAP duration and to find new avenues for gene therapy reimbursement that are outside traditional transplant-based reimbursement, these analyses reveal that current MS-DRG mappings are simply inadequate given the unique characteristics and needs of autologous gene therapies. It would not benefit the Medicare program or beneficiaries for CMS to over-reimburse non-gene-therapy cases, while vastly under-reimbursing autologous gene therapies. To the contrary, such a result would simply heighten inequities—resulting in artificially inflated reimbursement for certain cases, while deflating reimbursement for gene therapies so significantly as to risk substantially chilling Medicare beneficiary access to a potentially life-transforming class of innovative new gene therapies.

Vertex also emphasizes that the creation of a new MS-DRG targeted gene therapies like CASGEVY would have minimal impact to other MS-DRGs and the IPPS as a whole. In our modeling, we analyzed the impact to relative weights of other MS-DRGs as a result of the creation of a new MS-DRG for gene therapies. Importantly, our data analysis shows that there would be *minimal impact* to other MS-DRGs with the addition of a new MS-DRG for gene therapy. Specifically, there would only be a maximum decrease in MS-DRG weight of -0.018%. Although access to these therapies is critically important to the small but underserved population of beneficiaries that need these autologous therapies, the low volume of overall utilization minimizes the risk of any distortion to other MS-DRGs if CMS moves forward with the creation of a new gene therapy MS-DRG targeted at technologies like CASGEVY.

(c) Additional considerations for the development of a novel Pre-MDC MS-DRG solution

If CMS begins active work and development on a new MS-DRG that could account for the unique needs of autologous gene therapies like CASGEVY, CMS also will need to consider a number of technical considerations bearing on MS-DRG development. When CMS created MS-DRG 018 to

facilitate appropriate reimbursement for Chimeric Antigen Receptor (CAR) T-cell therapy, CMS was forced to tackle a number of challenging implementation questions and developed novel technical solutions, such as its clinical trial adjustment. The creation of a new gene therapy MS-DRG will undoubtedly raise equally significant questions of implementation.

Among other potential considerations, Vertex highlights the following areas of potential importance if CMS moves forward with development of a gene therapy related MS-DRG:

- **Wage Index**. IPPS payment rates are calculated by multiplying the MS-DRGs' relative weight, which reflects the total costs associated with the MS-DRG, by standardized amounts for labor and non-labor operating costs. A wage index adjustment is applied to the labor portion of this calculation to account for differences in the average wages of hospitals operating in different geographic regions. The proposed labor standardized amount accounts range from 62 to 67.6 % of total costs.[38] Thus, the rate calculation assumes a constant ratio of labor and non-labor costs, prior to application of the wage index.

  Of course, the actual ratio of labor to non-labor costs associated with an MS-DRG, including drugs and other technologies, can vary considerably. If CMS were to create a SCD and TDT gene therapy MS-DRG, as discussed above, the actual labor portion would be far less than 62% of total costs for the MS-DRG's costs because the gene therapy would account for most of the discharge's cost. But, under the standard methodology, the wage index would be applied to the labor standard amount of 62 to 67.6% of total cost. As a result, the calculation would assume that the labor portion of the MS-DRG's costs are much higher than the non-labor costs, including the gene therapy's costs. For example, if an MS-DRG has a relative weigh of 240.8780, the labor portion would account for nearly $1 million of the total payment (labor standardized amount multiplied by the MS-DRG's relative weight) and the non-labor portion would account for a little more than $600,000 of the payment, even though the gene therapy cost is a non-labor expense. ***If a hospital has a 0.75 wage index, the hospital would see a nearly $250,000 reduction in its payment rate, although it would have the same gene therapy cost as a hospital in a higher wage index area.***

  The structure of the wage index methodology creates significant health equity concerns in the context of a MS-DRG intended to reimburse high resource intensity gene therapy technologies. The acquisition costs of these technologies do not vary by geography, and the impact of the wage index multiplier can result in significant regional differences in reimbursement, with low wage index hospitals seeing disproportionate reductions in their total reimbursement that are not commensurate with the overall costs of furnishing a gene therapy. These disparities could be especially concerning in the context of CASGEVY because many SCD patients reside in lower wage index states.

  As such, CMS should begin consideration of mechanisms to mitigate the inequities that could result from the wage index for a new gene therapy MS-DRG. Among other things, CMS could consider re-interpreting and reducing the proportion of costs that it deems attributable to "wages and wage-related costs" subject to the wage index in order to reduce wage index distortion for gene and cell therapies.[39] Alternatively, if CMS believes it is necessary, it could consider using the agency's exceptions and adjustment authority to alter how (if at all) the wage index is implemented for such an MS-DRG.

- **Cost to Charge Ratio (CCR)**. The IPPS methodology sets reimbursement rates by reference to a CCR methodology under which costs are estimated from hospital charges to set Medicare reimbursement rates. The methodology requires providers to significantly mark-up their charges to sustain adequate reimbursement.

[38] 89 Fed. Reg. at 36,576.
[39] *See* SSA 1886(d)(3)(E).

As CMS knows, however, in practice, providers are reluctant to mark-up charges of higher cost technologies at ratios necessary to sustain reimbursement adequacy—i.e., the proportional cost-to-charge difference is lower for higher cost technologies have higher CCRs compared to lower cost technologies, resulting in systematic under-reimbursement of higher cost technologies under the CCR methodology. Further, this practice of this "charge compression" has persisted for years, even notwithstanding extensive efforts on the part of provider groups as well as guidance from CMS expressly clarifying that "hospitals are not precluded from setting their charges consistent with their CCRs and the existing administrative mechanisms for hospitals to request CCR changes consistent with lower charges."[40]

The risk of charge related distortion to the rate-setting process could be especially acute for novel gene and cell therapies, given their heightened acquisition costs relative to other therapies. This warrants CMS considering ways to reduce the distortion created by CCRs for an MS-DRG targeting this class of therapies, potentially including eliminating the role of CCRs for this MS-DRG or otherwise developing a new gene therapy cost center to seek to encourage appropriate charging practices and collect accurate cost data that reduce distortions in the rate-setting methodology.

We urge CMS to consider these and other MS-DRG implementation dynamics in the FY 2026 IPPS rulemaking cycle. In advance of such rulemaking cycle, CMS also should consider convening stakeholder listening sessions, townhall meetings, or other avenues to facilitate collaboration and feedback on implementation of a potential new gene therapy focused MS-DRG.

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IV. Vertex Response on TEAM model in Regard to Pain Medication Prescribing

a. CMS Should Ensure the Transforming Episode Accountability Model (TEAM) Does Not Create Unintended Consequences in Opioid Prescribing

As discussed in the Proposed Rule,[46] TEAM would test whether an episode-based alternative payment model linked with quality measure performance for select acute care hospitals can reduce Medicare program expenditures while preserving or improving the quality of care for Medicare beneficiaries who initiate certain episode categories (e.g., certain surgical procedures in a hospital). We write to recommend certain modifications to the model's proposed design to reduce the risk that the model could encourage unnecessary opioid prescriptions and thereby risk increasing opioid misuse among Medicare beneficiaries who receive inpatient surgical care from TEAM participants. In particular, we recommend that CMS:

- Modify the model's quality measures set to create incentives for appropriate pain medication prescribing to be consistent with the Centers for Disease Control's (CDC) 2022 Clinical Practice Guideline for Prescribing Opioids for Pain, which encourage approaches that reduce the risk of opioid pain therapy.[47]
- Establish a separate payment for non-opioid pain medications furnished in the inpatient setting to ensure that the shift to the episode-based payment model does not disincentivize clinically appropriate use of novel, non-opioid pain treatments in favor of lower cost generic opioids;

[40] 86 Fed. Reg. at 44,965.

- Implement policies designed to support appropriate pain medication prescribing, including through beneficiary incentives, primary-care transition planning, and shared learning; and
- Assess the impact of these policies by evaluating rates of opioid prescribing and opioid use disorder as part of the model's evaluation.

Background on Pain Medication Prescribing

Treating and managing pain places an extreme burden on the U.S. healthcare system ($180 billion annually); meanwhile, individuals suffering from pain face disability, increased use of medical services, and reduced quality of life and work productivity.[48] Further, patients emerging from surgery—such as the surgical procedures that would trigger episodes under TEAM—are at risk for developing persistent opioid use after surgery.[49]

In an episode-based payment model, like TEAM, hospitals are incentivized to use lower-cost generic drugs (such as opioids) over novel non-opioid because they are evaluated on how effectively they are managing cost. While opioids may be a suitable option to providing effective pain relief, but they are also associated with significant risks including abuse liability, which risk opioid misuse and opioid use disorder, which contribute to the nationwide overdose epidemic, itself a challenge for the Medicare program. Nearly a quarter of Medicare beneficiaries—more than 12 million people—were prescribed opioids in 2021, with at least 50,000 Medicare beneficiaries experiencing an opioid-related overdose.[50] The opioid crisis also presents a health equity challenge, disproportionately affecting low-income and rural populations and certain racial and ethnic populations such as American Indians and Alaska Natives.[51]

Quality Measures to Incentivize Appropriate Pain Medication Prescribing

Vertex supports CMS' efforts to test new incentives for hospitals to coordinate patient care, avoid duplicative or unnecessary services, and improve the beneficiary care experience during care transitions. However, as CMS has recognized, reimbursement models that hold hospitals accountable for the total cost of care can result in inadvertently incentivizing the use of lower-cost opioid medications that may be inappropriate for some or present a risk of opioid misuse or opioid use disorder.[52]

In general, we agree with CMS that payment and service delivery models should include pay-for-performance methodologies that track quality measures and incentivize improvements in patient outcomes. For this reason, we support CMS's proposal that TEAM would incorporate quality measures that focus on care coordination, patient safety, and patient-reported outcomes (PROs), which we agree represent areas of quality that are particularly important to patients undergoing acute procedures. We also specifically support the proposed inclusion of a readmission measure, and we agree with CMS that such measure will incentivize improved transitions in care among TEAM participants.

However, we further agree with CMS that there are still gaps in the proposed measure set, and we believe CMS should develop additional measures.[53] Specifically, we recommend that CMS consider including additional quality measures as part of core measures set for TEAM to address potential unintended consequences of the model incentivizing inappropriate prescribing of opioids and limiting access to non-opioid alternatives. For instance, CMS should consider adding two measures: the" Multi-Modal Pain Management" and the "Use of High-Risk Medications in Older Adults" measure. These measures are currently used in Medicare Incentive Payment System (MIPS) and meets two criteria for measure selection: alignment with the goals of TEAM and alignment to CMS priorities, including the CMS National Quality Strategy which has goals that support safety, outcomes, and engagement. If the agency is unable to operationalize the implementation of this metric, we would propose a fallback option of "Safe Use of Opioids-Concurrent Prescribing." This measure is already

used in hospital inpatient quality reporting, so TEAM participants are already familiar with it, and its use can help incentivize appropriate pain medication prescribing by holding hospitals accountable for their concurrent prescribing practices. We also believe CMS's efforts to promote appropriate prescribing of pain medications would benefit from the development of a new measure that addresses the prescription of opioid and non-opioid pain medications, for inclusion in TEAM and beyond.

Separate Payment to Support Appropriate Pain Medication Prescribing Related to Inpatient Procedures

Vertex recommends that CMS also include a separate payment for FDA-approved non-opioid pain medications in the model's design, including oral non-opioid pain management drugs furnished in either inpatient or outpatient settings. This would further mitigate the unintended incentive TEAM may create for prescribing low-priced opioid medications, in lieu of safer treatment options, as it would ensure that there is not an undue financial incentive for TEAM providers to shift to opioids in light of the episode-based payment model.

There is also precedent for the policy effectiveness of separate payment to encourage access to non-opioid pain management alternatives. Since CY 2019, CMS has paid separately for qualifying FDA-approved non-opioid pain management medications in the ambulatory surgical center setting and, beginning in 2025, the agency will also pay separately for such medications in the hospital outpatient setting.[54] Given the success of this policy in promoting access to non-opioid pain medications in outpatient settings, CMS should use the Center for Medicare and Medicaid Innovation's (CMMI's) authority to extend this policy to the inpatient setting as part of the TEAM model test, as well as oral non-opioid pain management drugs furnished in outpatient settings. Doing so would recognize the value of access to innovative treatment options and implement a consistent policy across settings and treatment options.

Consistent with CMS's proposal to exclude items covered by the NTAP program from performance year expenditures,[55] CMS should exclude any separate payment for non-opioid pain management from the model's episode expenditures to avoid inadvertently discouraging use of these products.

b. Other Strategies to Promote Appropriate Prescribing of Pain Management Options

Beneficiary Incentives - We agree with CMS that the beneficiary incentives included in the model should be designed to achieve the clinical aims of the model.[56] In addition to the in-kind beneficiary incentives outlined in the Proposed Rule, Vertex recommends adding additional flexibilities for TEAM participants to provide limited financial assistance to beneficiaries aligned with the model's four clinical aims. Specifically, CMS should consider allowing the TEAM hospital participants to provide cost-sharing assistance to beneficiaries for non-opioid prescriptions provided at discharge to equalize the cost of those drugs relative to opioids. Allowing TEAM participants to lower the cost to patients of taking non-opioid alternatives would achieve the aim of promoting beneficiary adherence to drug regimens and to the care plan, while also potentially reducing readmissions and complications by reducing the risk of opioid misuse.[57] We note that CMS proposed a similar beneficiary incentive in the new Increasing Organ Transplant Access (IOTA) model.[58]

Primary care transitions - As CMS notes in the Proposed Rule,"[t]ransitional care includes effective discharge planning, transfer of information at the time of discharge, patient assessment and education, and coordination of care and monitoring in the post-discharge period."[59] Vertex supports CMS's proposal to require TEAM participants to include in hospital discharge planning a referral to a supplier of primary care services for a TEAM beneficiary, on or prior to discharge from an anchor hospitalization or anchor procedure. In response to CMS's solicitation for comment regarding whether there are other mechanisms or ways to connect the TEAM beneficiary back to a supplier of primary care services that would support a patient's continuum of care, Vertex recommends that

CMS consider ways to ensure that primary care suppliers involved in care transitions take steps to prevent opioid misuse. This could include requiring TEAM participants to:

- Counsel patients prior to discharge about their pain management options to ensure they are adequately informed about the benefits and risks of each potential treatment plan.
- Document in the medical record a rationale for prescribing opioids, if applicable, together with a plan for (to the extent clinically appropriate) transitioning the beneficiary to a non-opioid alternative over the course of the patient's treatment journey.
- For beneficiaries prescribed opioids at discharge, establishing a care plan that involves joint monitoring by the TEAM participant and primary care supplier to monitor for any signs of opioid misuse or opioid use disorder.

Learning system -A number of CMMI models involve a learning system or other mechanism for CMS to provide technical assistance to model participants and to facilitate peer-to-peer sharing of best practices. Along these lines, given the likely significant need for pain management among patients receiving care within the TEAM model, we recommend that CMS offer TEAM participants training regarding risk mitigation on opioid prescriptions, as well as options for non-opioid prescriptions.

Assessing the Impact of Pain Management Policies on the Development of Opioid Use Disorder

Vertex notes that the development of opioid use disorder resulting from a discharge prescription would likely occur well beyond the 30-day episode duration outlined in the Proposed Rule, and therefore may not be accurately captured within the model's evaluation efforts. Therefore, we urge CMS to include, as part of the evaluation of outcomes/quality, an assessment of the rates of opioid use disorder among the patients included in TEAM episodes relative to Medicare beneficiaries generally. To help inform this evaluation, CMS could revise its proposed regulation at 42 C.F.R § 512.584 to require TEAM participants to report information, including protected health information (PHI), regarding the prescription of opioids vs. non-opioid pain management drugs pursuant to Social Security Act § 1115A(b)(4) and CMMI's existing regulation at 42 C.F.R. § 403.1110(b).

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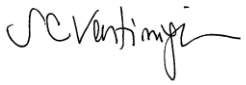
Vertex thanks CMS for this opportunity to comment on the FY 2025 IPPS Proposed Rule. Vertex is committed to enabling access to innovative gene and cell therapies that have the potential to alleviate chronic and debilitating conditions for patients. To this end, Vertex will continue to provide flexible and creative access solutions and is eager to work with CMS to deliver tailored policy approaches that are as innovative as the medicines we develop. We believe in the long-term value of our therapies and are committed to ongoing real-world demonstration of the holistic benefits of our treatments to patients and the health care system.

If you have any questions about Vertex's comment letter or if it would be helpful to discuss any of our comments in more detail, please do not hesitate to contact me at samantha_ventimiglia@vrtx.com.



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