Supplementary Information

PharmacoEconomics

Cost-Effectiveness of Lovotibeglogene Autotemcel (Lovo-Cel) Gene Therapy for Patients with Sickle Cell Disease and Recurrent Vaso-Occlusive Events in the United States

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1 Supplemental Methods

1.1 Details of the Modeling Approach

1.1.1 Patient-level Simulation Rationale

Our patient-level simulation modeling approach was developed to predict the lifetime health and economic outcomes of patients with sickle cell disease (SCD) treated with lovotibeglogene autotemcel (lovo-cel) gene therapy in comparison with common care (see Figure 1 in the main text). This approach was selected for the analysis in alignment with good modeling practice guidelines[1-3] and with recommended criteria for cost-effectiveness (CE) modeling for one-time gene therapies with curative intent for SCD.[4] Specifically, this approach meets the following criteria for decision-analytic modeling of gene therapies for SCD[4]:

- Capture the heterogeneity of the SCD population leading to differences in disease progression
- Include a comprehensive set of future SCD-related events and complications that a gene therapy may avoid or reduce the risk of
- Model the occurrence of time-dependent events and their influence on future outcomes and mortality

A review of economic analyses in SCD conducted prior to 2020 found that most models relied on Markov-based frameworks and failed to meet these criteria.[4] The shortcomings of published CE analyses for SCD were similarly highlighted in a systematic literature review which found that most studies were limited to only a narrow subset of SCD complications, despite the implications of these complications for survival, costs, and quality of life.[5] Our use of a patient-level simulation modeling approach allows a comprehensive consideration of the heterogeneity of the SCD population and of the interconnected and time-dependent relationships among SCD events and complications. This rationale is similarly reflected in other recent CE modeling efforts for gene therapies in SCD.[6-8]

1.1.2 Target Population Considerations

The target population for the CE analysis includes patients in the United States (US) aged 12 years or older with SCD with the hemoglobin SS (HbSS) genotype and at least 4 vaso-occlusive events (VOEs) in the prior 24 months, reflecting the primary efficacy population (transplant population for VOE [TPVOE] from the Group C treatment cohort) in the HGB-206 clinical trial (NCT02140554).[9,10] A summary of the subject dispositions in the HGB-206 trial is presented in Table S1.

The trial exclusion criterion for patients over age 50 years was not enforced in the model. Patients with a history of stroke were not excluded from the trial according to the initial protocol, although they were excluded in later protocol revisions.[11] In the model, we did not exclude patients with prior stroke from the analysis, reflecting the characteristics observed in the TPVOE population. Although patients with genotypes HbSS, HbSβ^0, or HbSβ^+ were permitted per the trial protocol, the TPVOE population only included patients with genotype HbSS. As a result, our base-case analysis was limited to patients with genotype HbSS. We did not restrict the population by payer type (e.g., Medicaid vs. commercial); however, most patients with SCD in the US are covered by Medicaid, making Medicaid an important stakeholder in funding care for patients with SCD in the US.[12]

1.1.3 Events and Complications Included in the Model

The selection of the acute events (vaso-occlusive crisis [VOC], acute chest syndrome [ACS], priapism, splenic sequestration, venous thromboembolism [VTE], stroke, and sepsis/bacteremia) and chronic complications (pulmonary hypertension [PH], chronic kidney disease [CKD], retinopathy, avascular necrosis [AVN], gallstones, heart failure [HF], chronic lung disease, leg ulcers, and neurocognitive impairment [excluding due to overt stroke]) included in the model (Figure S1 and Table 1 in the main text) was informed by the HGB-206 VOE primary efficacy endpoint definition, a targeted review of the SCD clinical literature (see Section 1.3 for more details), recent comprehensive CE analysis approaches for SCD,[6,8,13] and recommendations from clinical and patient advisors. The availability of supporting data from the SCD clinical literature (in terms of quantity, quality, and suitability for use in the model) was a primary factor.

In select instances, events or complications with limited data from the literature but established modeling precedent or identified as relevant from a patient perspective were included. In particular, although the HGB-206 VOE endpoint included hepatic sequestration, this event was not included in the model due to a lack of supporting evidence in the literature. Additionally, although there is extensive literature on pain in SCD, the literature on other patient-relevant outcomes such as fatigue, depression, anxiety, and sleep disturbances was found to be more limited. These relevant patient-reported outcomes were assumed to be reflected in the health-related quality-of-life utility values used in the model.

1.2 HGB-206 Data Used in the Model

Data from the pivotal HGB-206 clinical trial were used in the model to inform baseline patient characteristics (demographics and SCD status [Table S2]), lovo-cel efficacy (resolution or reduction of VOEs [Table S3], change from baseline in total hemoglobin [Hb] [Table S4]), lovo-cel quality-of-life impacts (change from baseline in EQ-5D-3L utility values [Table S5]), and lovo-cel administration (e.g., mobilization, apheresis [Table S6]). Details

on the specific HGB-206 analysis populations and treatment groups used for each of these parameters are presented in Table S1.

For continuous variables, the number of patients, mean, and standard deviation (SD) are presented. For categorical variables, summary tabulations of the number and percentage of patients are presented. Where applicable, 95% confidence intervals (CIs) were calculated using the Clopper-Pearson exact method.

1.3 Targeted Review of Clinical Literature

1.3.1 Research Questions and Search Strategy

To inform the development of the CE model, we conducted a targeted review of the clinical literature on SCD-related events and complications and associated risk factors. The review focused on the following research questions:

- What is the timing of the development and the progression of chronic complications?
- What are the risk factors and other predictive factors (if any) for the development and the progression of chronic complications?
- What is the timing of the development and the progression of acute events?
- What are the predictive factors (if any) for acute events?
- What are the associations (if any) among the occurrence of acute events and chronic complications?

We conducted a structured review of the literature published since 2000 by searching MEDLINE, conference abstracts, and Google Scholar for original, review, and health technology assessment (HTA) publications addressing these research questions. Landmark studies published before 2000 also were considered. Additional studies reporting on SCD events and complications and relationships among SCD events and complications were identified from recommendations from clinical advisors and studies cited in recent comprehensive SCD models.[6,7,13,14]

Titles and abstracts were screened against prespecified criteria, and full texts of eligible studies were assessed further for inclusion. Studies were selected for inclusion according to the following priorities:

- Studies reflecting contemporary use of hydroxyurea (HU) and its impact on SCD outcomes
- Studies reporting data for genotypes HbSS, HbSβ^0, and HbSβ^+ to align with the HGB-206 trial population

- Studies reporting longitudinal data, such as data from the Cooperative Sickle Cell Disease Study, with the objective of understanding the natural history of SCD and factors affecting patient morbidity
- Observational studies, registry studies, and clinical trials deemed by the model development team to be robust and reliable (e.g., large populations, reputable study groups, highly cited)
- Studies presenting outcomes in a format that could be used in the CE model (e.g., incidence, prevalence, risk ratios)
- Studies investigating acute events or chronic complications known to influence patient costs, quality of life, or mortality

Original research studies were then rated subjectively as high, moderate, or low-quality, and low-quality studies were excluded from further review. Reviews, HTAs, and other references not presenting original research were included but did not receive quality ratings.

1.3.2 Body of Literature Identified

Of 977 abstracts screened, 149 studies were included: 136 original research studies, 10 review articles, 2 HTAs, and 1 book chapter. Overall, our review identified 90 unique studies presenting data related to acute events (including potential relationships among events and complications) and 73 unique studies presenting data related to chronic complications. Of the 136 original research studies, 130 were subjectively rated as being of at least moderate quality.

Among the studies rated as being of at least moderate quality, the most frequently studied acute events were stroke (including silent cerebral infarcts), VOCs, and ACS and the most frequently studied chronic complications were CKD and PH. Other acute events and chronic complications studied less frequently but still appearing in multiple studies were priapism, VTE, retinopathy, AVN, gallstones, leg ulcers, neurocognitive impairment, and chronic pain. Other acute events and chronic complications with limited data among our identified studies included splenic sequestration, myocardial infarction, acute kidney injury, lung function, cardiac disease, asthma, depression, sleep apnea, and fertility.

Among the studies focused on the relationships among acute events and chronic complications,[15] VOCs and ACS had the greatest number of quantified associations with other events and complications included in this review. PH also was found to be associated with multiple other events and complications. Comparatively fewer associations were identified for other cardiovascular and neurological complications.

The suitability of individual studies from the SCD literature for use in our model was assessed in collaboration with patient and clinical advisors and in the context of the HGB-

206 study design and the economic literature in SCD. The specific studies and parameters selected for our model are discussed in the next section.

1.3.3 Data Selected for the Model

The clinical relationships and parameters used in the model are described in detail in Table S7 (summary of key risk factors and relationships), Table S8 (acute events), and Table S9 (chronic complications).

Data were first required for the model to inform patients' baseline acute event history (i.e., the proportions of patients with prior events) and chronic complication status (i.e., the prevalence of complications) at the time of treatment with lovo-cel (Table S8 and Table S9). For acute events contributing to the HGB-206 VOE criteria (VOC, ACS, priapism, splenic sequestration, and stroke) (Figure S1), the proportions of patients with prior histories were taken from the trial data (Table S2). All other baseline event and complication data were obtained from the literature.

Of the 3 identified studies with chronic complication prevalence by age,[16-18] we considered the McClish et al.[16] observational study to be most representative of the target population, with the Paramore et al.[17] claims analysis subsequently preferred to the Medicare-only Wilson-Frederick et al.[18] study. Data for VTE and neurocognitive impairment were not available in the HGB-206 data or any of these 3 studies and thus were identified from other clinical literature.[19,20] While new silent cerebral infarcts were not explicitly modeled, a history of these events at baseline[21] was included owing to their impact on future stroke events.[22]

Data also were required for the model to inform acute event incidence rates (Table S8) and chronic complication incidence probabilities (Table S9). We sought to identify differences by age range (12-17 years, 18-30 years, 31-45 years, > 45 years) where available to reflect changes across the transition period as patients with SCD move from childhood to adulthood.[16,23,24] We also prioritized contemporary studies where available to reflect advances in SCD treatment and management in recent years, including use of HU and chronic transfusions as part of common care.[24,25] Finally, we sought differences by genotype (HbSS/Sβ^0 vs. HbSβ^+/SC/other) to adjust for the HbSS-only HGB-206 trial population and for use in scenario analyses including other genotypes.

Incidence data for VOCs were aligned with the baseline frequency of prior events in the HGB-206 trial (Table S2). Incidence data for ACS, splenic sequestration, stroke, PH, and gallstones in pediatric and adult patients were drawn from a recent Medicaid claims analysis.[26] Other studies contributing incidence data for multiple complications included a landmark longitudinal study from the University of Southern California (retinopathy, AVN, chronic lung disease, leg ulcers)[27] and a claims analysis conducted alongside a recent SCD

economic evaluation (CKD, HF).[13] Data from the landmark Cooperative Study of Sickle Cell Disease (CSSCD) also were leveraged to inform age- and genotype-specific differences for VOCs, ACS, and AVN.[28-30] In select instances, we relied on incidence data from studies focused on individual events or complications (priapism,[31] VTE,[32] and neurocognitive impairment[20]). For select events and complications, data on severity and progression (VOC [Table S2], VTE,[32] CKD,[33-35] and gallstones[36]) or on resolution (PH[37]) also were used.

Our review also identified studies presenting evidence on risk factors for and relationships among SCD events and complications.[15] Of particular relevance for the model, given the complete resolution of VOE endpoint for lovo-cel, were the quantified relationships between the frequency and severity of VOCs and the risk of multiple other events and complications.[26,32,35,38,39] A recent meta-analysis also estimated the relationship between differences in total Hb and risk of stroke, PH, and CKD.[40] For patients in the common care arm treated with HU or with chronic red blood cell transfusions, the model also includes the effect of these treatments on VOC and stroke risk, respectively.[41,42] An overview of the relationships included in the model is presented in Table S7; specific parameter values are presented in Table S8 and Table S9.

1.4 Mortality

Although advances in management and treatment have helped SCD to evolve from a life-threatening disease of children to a chronic disease of adults,[43] the median life expectancy of patients with SCD treated with common care remains far below that of the general population.[44,45] In addition to the general mortality risk associated with SCD observed in landmark studies[46] and persisting in more contemporary analyses,[44,45,47,48] specific acute events and chronic complications have been found to increase mortality risk.[19,27,32,49-53]

In our model, underlying mortality for patients with SCD treated with common care (i.e., in the absence of events or complications) was estimated by applying sex-specific SCD standardized mortality ratios (SMR) for genotypes HbSS/Sβ^0 to age-, sex-, and race-specific general population mortality risks in the US.[54] The SCD SMRs were derived from an analysis of landmark CSSCD data[46] performed for a United Kingdom (UK) economic evaluation.[55] To accurately predict underlying SCD mortality in the absence of VOCs, we adjusted the identified SMRs down based on the VOC rate in the CSSCD study[28] and the impact of VOCs on mortality.[49] The specific parameters used for underlying SCD mortality are presented in Table S10. This approach was preferred to using more contemporary data due to the limitations of cause-of-death data in SCD.[47,56] Also, use of US general population mortality risks provides an appropriate reference point when considering the potential impact of lovo-cel on mortality.

Studies of SCD mortality have identified a range of SCD events and complications as risk factors (VOC[49,51,53]; ACS[27]; VTE[32]; stroke history[50]; sepsis/bacteremia[27]; PH[49,52]; CKD[19,50,52];

retinopathy[27]; chronic lung disease[27,52]; and leg ulcers[50]). Out of concern for potential double counting, we only modeled the increased mortality risks associated with a hospitalized VOC[51] and with multiple end-organ involvement (at least 2 of the following complications: PH, CKD, and chronic lung disease).[52] Specific SMRs for underlying SCD mortality risks and for events and complications are presented in Table S10.

1.5 Costs and Health-Related Quality of Life

1.5.1 Direct and Indirect Costs

The model captured direct SCD-related associated with common care use (HU and chronic red blood cell transfusions), the costs per event for all acute events, and the annual costs for all chronic complications (Table S11). We prioritized the identification of Medicaid- and SCD-specific sources[57-60] given that Medicaid is the primary funder of care for patients with SCD in the US. We relied on non-Medicaid SCD-specific sources,[13,61-64] non–SCD-specific sources,[65,66] and standard US-specific costing sources[67-69] when required. Costs identified in the literature were inflated to 2022 US $ using the US Consumer Price Index for medical care.[70] Multiplicative age-adjustment factors from an SCD-specific claims analysis[59] were applied to per-event costs for acute events and to annual costs for complications. Costs for multiple events and complications present within the same annual model cycle were applied additively. In a scenario analysis, we considered non–SCD-related direct medical costs[71] during years of extended survival associated with lovo-cel.

Our co-base-case societal perspective also included indirect costs in the form the value of unpaid caregiving and patient productivity impacts (Table S11). The annual value of unpaid caregiving was estimated from an SCD-specific study on hours of unpaid caregiving per year[72] and US average hourly wage data.[73] A recent modeling study on economic disparities in SCD estimated that patients with SCD had average annual earnings that were 56% of the general population.[74] This same study estimated that annual earnings would increase for cured individuals based on the age at which treatment was received (to 92% of general population earnings if treated prior to age 15 years and to 78% of general population earnings if treated at age 15 years or older).[74] We used these findings combined with race-specific average annual earnings for the US[75] to estimate the potential productivity gains for patients achieving complete resolution of VOEs after lovo-cel treatment. In a scenario analysis, we considered consumption costs associated with consumer expenditures[76] during years of extended survival associated with lovo-cel.

1.5.2 Lovo-cel Administration and Monitoring Costs

In addition to the direct acquisition cost of the lovo-cel drug product, the model included the direct costs associated with the administration of lovo-cel (preparatory transfusions, stem cell mobilization and apheresis, myeloablative conditioning, and autologous hematopoietic

stem cell transplantation) and with ongoing monitoring required after lovo-cel treatment (physician visits, laboratory tests, imaging tests).[10] The details of the micro-costing approaches used to estimate these lovo-cel–specific direct costs are presented in Table S12 and Table S13.

1.5.3 Health-Related Quality of Life Utility Values

The model captured the quality-of-life impacts of SCD on both patients and their caregivers (Table S14). The underlying utility value of 0.75 for patients with SCD was obtained from an SCD-specific study in the UK[77]; this value was similar to the baseline EQ-5D utility value for patients in the HGB-206 trial (mean [SD] = 0.716 [0.2245]) (Table S5). The health-related quality-of-life impact of common care was assumed to be reflected in the underlying SCD utility. With the exception of VOCs, which also were studied in the same UK analysis,[77] SCD-specific disutilities for other events and complications were not identified in the SCD literature. As such, we relied on condition-specific estimates from US population-level survey data.[78,79] Disutilities for acute events were applied for the duration of the event only using durations of impact aligned with prior SCD economic evaluations[13,80] and survey recall periods.[78,79] Because the underlying SCD utility from the literature would reflect existing complications in the studied population,[77] we applied chronic complication disutilities only for complications developed after model entry for as long as the complications were prevalent. Health-related quality-of-life impacts for multiple events and complications present within the same annual model cycle were applied additively.

The caregiver quality-of-life impact for patients with SCD was modeled using a disutility from a recent UK study.[81] We conservatively assumed 1 caregiver would be impacted per patient in our base-case analysis and considered impacts on multiple caregivers per patient in scenario analysis.

2 Supplemental Tables

Table S1. HGB-206 subject disposition and populations used in the model

HGB-206 populations	Number of subjects by treatment group*			
	Overall	**Group A**	**Group B**	**Group C**
Subject disposition				
Screened	61	NA	NA	NA
Meeting inclusion criteria	55	NA	NA	NA
Initiating stem cell collection (ITT population)	54	9	2	43
Infused with lovo-cel drug product (TP population)	45	7	2	36
Infused with lovo-cel drug product with ≥ 4 protocol VOEs in the 24 months prior to informed consent (TPVOE population)	40	6	2	32
Populations used in the model				
ITT Group C	▪ Number of preparatory transfusions per patient (n = 43) (Table S6)			
ITT Groups B and C	▪ Number of mobilization cycles and apheresis procedures per patient (n = 44, patients receiving mobilization) (Table S6)			
TP Group C	▪ Total Hb efficacy (n = 23, patients with total Hb change from baseline available at 12 months after transplantation) (Table S4 and Table 1) ▪ Utility gain due to PRO improvement (n = 21, patients ages ≥ 18 years at the time of EQ-5D-3L utility index assessment with change from baseline available at 12 months after transplantation) (Table S5 and Table 1)			
TPVOE (all treatment groups)	▪ Baseline patient characteristics (n = 40) (Table S2 and Table 1)			
TPVOE Group C	▪ VOE-CR and sVOE-CR efficacy endpoints (n = 32, evaluable patients with at least 18 months of follow-up) based on adjudicated VOEs (Table S3 and Table 1) ▪ Reduction in VOEs and sVOEs for patients without VOE-CR or sVOE-CR, respectively (n = 32, evaluable patients with at least 18 months of follow-up), derived using adjudicated VOE data (Table S3 and Table 1)			

ITT = intention-to-treat; NA = not applicable; PRO = patient-reported outcome; sVOE = severe vaso-occlusive event; sVOE-CR = complete resolution of severe vaso-occlusive events; TP = transplant population; TPVOE = transplant population for VOE; VOE = vaso-occlusive event; VOE-CR = complete resolution of vaso-occlusive events.

* Treatment groups refer to the process of optimizing the lovo-cel treatment process; Group C represents the most current treatment process. The HGB-206 criteria and treatment groups are described in Kanter et al.[11]

Table S2. Baseline patient characteristics for the HGB-206 TPVOE population

Patient characteristics	HGB-206, TPVOE (N = 40)
Demographics	
Age, years	
Mean (SD)	24.2 (7.10)
Ages 12-17 (n, %)	8 (20.0%)
Ages 18-50 (n, %)	32 (80.0%)
Sex (n, %)	
Male	27 (67.5%)
Female	13 (32.5%)
Race (n, %)	
American Indian or Alaska Native	0 (0.0%)
Asian	1 (2.5%)
Black or African American	38 (95.0%)
Native Hawaiian or Other Pacific Islander	0 (0.0%)
White	0 (0.0%)
Other	0 (0.0%)
Not reported	1 (2.5%)
SCD status	
Hb genotype (n, %)	
HbSS	40 (100.0%)
HbSβ^0	0 (0.0%)
HbSβ^+	0 (0.0%)
Annualized VOEs* (mean, SD) (from adjudicated episodes in prior 2 years)	
All VOEs (mean, SD)	5.70 (4.146)
Severe VOEs (mean, SD)	4.20 (3.107)
VOE-related hospitalization (mean, SD)	4.33 (3.565)
Total Hb level, g/dL† (n = 28)	
Mean (SD)	8.38 (1.326)
Prior treatment (n, %)	
Hydroxyurea, ever received	36 (90.0%)
Regular RBC transfusions, ever received	24 (60.0%)

Patient characteristics	HGB-206, TPVOE (N = 40)
History of SCD events (n, %)	
VOC	40 (100.0%)
ACS	21 (52.5%)
Priapism (of males only)	6 (22.2%)
Splenic sequestration (based on prior splenectomy)	2 (5.0%)
Stroke	2 (5.0%)

ACS = acute chest syndrome; Hb = hemoglobin; HbSS = hemoglobin SS; HbSβ = hemoglobin Sβ-thalassemia; RBC = red blood cell; SCD = sickle cell disease; SD = standard deviation; TPVOE = transplant population for vaso-occlusive event; VOC = vaso-occlusive crisis; VOE = vaso-occlusive event.

* VOEs were defined in the HGB-206 protocol as any of the following (with or without hospitalization): VOC lasting ≥ 2 hours and requiring care at a medical facility, ACS, acute hepatic sequestration, acute splenic sequestration, or acute priapism lasting ≥ 2 hours and requiring care at a medical facility. Protocol sVOEs were defined as any protocol VOE requiring ≥ 24-hour hospital or emergency department visit or ≥ 2 visits to a day unit or emergency department over 72 hours, each requiring intravenous treatment. Baseline VOEs were defined as the annualized number in the 24 months prior to informed consent. All reported VOEs were adjudicated by an independent event adjudication committee, and only adjudicated VOEs were considered for the VOE endpoint analysis.

† Baseline total Hb was defined as the average of the 2 most recent qualifying Hb assessments made prior to or during screening that met the following criteria: assessments were separated by at least 1 month; assessments were drawn no earlier than 24 months prior to informed consent and could include the Hb results from screening; and the subject did not receive a packed RBC transfusion within 3 months prior to each Hb assessment. Note that not all infused patients had a qualifying total Hb at baseline.

Table S3. Reduction in vaso-occlusive events

Parameter	HGB-206, TPVOE + Group C (N = 32)
All VOEs*	
VOE-CR	
Subjects achieving (n, %)	28 (87.5%)
95% CI (%)	71.0%-96.5%
Annualized VOEs	
Baseline (mean, SD)	5.53 (3.920)
6 to 18 months post–lovo-cel infusion (mean, SD)	0.22 (0.603)
Change from baseline (%) (mean, SD)	-96.9% (9.94%)
VOEs in those without VOE-CR (derived†)	
Annualized VOEs, 6-18 months post–lovo-cel infusion	1.76
Reduction in VOEs (relative to baseline) (%)	68.2%
Severe VOEs*	
sVOE-CR	
Subjects achieving (n, %)	30 (93.8%)
95% CI (%)	79.2%-99.2%
Annualized sVOEs	
Baseline (mean, SD)	4.06 (3.050)
6 to 18 months post–lovo-cel infusion (mean, SD)	0.09 (0.383)
Change from baseline (%) (mean, SD)	-97.3% (12.20%)
sVOEs in those without sVOE-CR (derived†)	
Annualized sVOEs, 6-18 months post–lovo-cel infusion	1.44
Reduction in sVOEs (relative to baseline) (%)	64.5%

CI = confidence interval; SD = standard deviation; sVOE = severe vaso-occlusive event; sVOE-CR = complete resolution of severe vaso-occlusive events; TPVOE = transplant population for vaso-occlusive event; VOE = vaso-occlusive event; VOE-CR = complete resolution of vaso-occlusive events.

* VOEs were defined in the HGB-206 protocol as any of the following (with or without hospitalization): VOC lasting ≥ 2 hours and requiring care at a medical facility, ACS, acute hepatic sequestration, acute splenic sequestration, or acute priapism lasting ≥ 2 hours and requiring care at a medical facility. Protocol sVOEs were defined as any protocol VOE requiring ≥ 24-hour hospital or emergency department visit or ≥ 2 visits to a day unit or emergency department over 72 hours, each requiring intravenous treatment. All reported VOEs were adjudicated by an independent event adjudication committee, and only adjudicated VOEs were considered for the VOE endpoint analysis.

† The annualized rate of VOEs in those not achieving complete resolution was derived by dividing the annualized rate among all patients (0.22) by the proportion of patients not achieving complete resolution (12.5%). A similar derivation was used for the annualized rate of sVOEs in those not achieving complete resolution. Reductions in the annualized rates of VOEs and sVOEs among those not achieving complete resolution were estimated relative to the baseline rates across all TPVOE + Group C patients.

Table S4. Change from baseline in total hemoglobin

HGB-206, TP + Group C (N = 36), Timepoint	Total Hb		Total Hb, change from baseline	
	n	Mean (SD)	n	Mean (SD)
Baseline*	23	8.52 (1.508)		
3 months	36	11.06 (1.632)	23	2.86 (1.696)
6 months	33	11.38 (1.695)	21	3.51 (1.645)
9 months	33	11.66 (1.542)	21	3.70 (1.531)
12 months	36	11.78 (1.642)	23	3.50 (1.514)
15 months	31	11.85 (1.535)	18	3.84 (1.340)
18 months	32	12.04 (1.562)	20	4.10 (1.280)
21 months	29	11.84 (1.502)	18	4.03 (1.307)
24 months	34	11.90 (1.751)	22	3.68 (1.794)

Hb = hemoglobin; SD = standard deviation; TP = transplant population.

* Baseline total Hb was defined as the average of the 2 most recent qualifying Hb assessments made prior to or during screening that met the following criteria: assessments were separated by at least 1 month; assessments were drawn no earlier than 24 months prior to informed consent and could include the Hb results from screening; and the subject did not receive a packed RBC transfusion within 3 months prior to each Hb assessment. Note that not all infused patients had a qualifying total Hb at baseline. Change from baseline estimates were only available for those patients with a qualifying total Hb at baseline.

Table S5. Change from baseline in EQ-5D-3L utility values

HGB-206, TP + Group C (N = 36), Timepoint	EQ-5D-3L utility index values*		EQ-5D-3L utility index values, change from baseline	
	n	Mean (SD)	n	Mean (SD)
Baseline†	22	0.716 (0.2245)	-	-
3 months	17	0.743 (0.2208)	14	0.056 (0.2120)
6 months	29	0.859 (0.1366)	19	0.146 (0.1790)
12 months	30	0.816 (0.1691)	21	0.088 (0.2095)
18 months	28	0.866 (0.1352)	18	0.123 (0.1584)
24 months	25	0.884 (0.0994)	18	0.107 (0.1518)

SD = standard deviation; TP = transplant population.

* EQ-5D-3L utility index values estimated for patients aged ≥ 18 years at the time of assessment. EQ-5D-3L responses were mapped to utility index values using norm-based scale scores estimated from the 2009 general US population.

† Change from baseline estimates were only available for those patients with a qualifying EQ-5D-3L assessment at baseline.

Table S6. Resource utilization associated with lovo-cel administration

Resource	Utilization	HGB-206 Population (n)
Preparatory RBC transfusions per patient (mean, SD)	7.63 (6.32)	ITT + Group C (n = 43)
Mobilization cycles per patient (mean, SD)	1.8 (0.80)	ITT + Groups B and C (n = 44)
Plerixafor dose (mg/kg) per mobilization cycle (mean, SD)	0.448 (0.1530)	ITT + Groups B and C (n = 44)
Apheresis procedures per mobilization cycle (mean, SD)	1.9 (0.64)	ITT + Groups B and C (n = 44)

ITT = intention-to-treat; RBC = red blood cells; SD = standard deviation.

Table S7. Key risk factors and relationships for SCD events and complications included in the model

Outcomes	SCD or treatment characteristics	Other events or complications
VOC	Genotype*[28] HU use[41]	-
ACS	Genotype*[29]	Recent† VOC(s)[38] Prior ACS[82] PH[83]
Priapism	Genotype*[31]	Recent† VOC(s)[38] Prior priapism[31]
Splenic sequestration	-	-
VTE	Genotype*[19]	Recent† hospitalized VOC(s)[32] Prior VTE[32] PH[19]
Stroke	Chronic transfusions[42] Total Hb[40]	Recent† VOC(s)[26] Prior SCI[22] PH[83]
Sepsis/bacteremia	-	Recent† VOC(s)[38]
PH	Total Hb[40]	Recent† VOC(s)[26]
CKD	Genotype*[84] Total Hb[40]	Recent† hospitalized VOC(s)[35]
Retinopathy	Genotype*[85]	-
AVN	Genotype*[30]	Recent† VOC(s)[86] Prior ACS[86]
Gallstones	-	Recent† hospitalized VOC(s)[38]
HF	-	None
Chronic lung disease	-	Prior ACS[27] Prior priapism[27]
Leg ulcers	-	Recent† hospitalized VOC(s)[38]
Neurocognitive impairment	-	Prior stroke or SCI[87]

ACS = acute chest syndrome; AVN = avascular necrosis; CKD = chronic kidney disease; HF = heart failure; HU = hydroxyurea; PH = pulmonary hypertension; SCI = silent cerebral infarct; VOC = vaso-occlusive crisis; VTE = venous thromboembolism.

* Differences in risk between genotypes were used for scenario analysis only (see Table S16 for scenario settings).

† For the purposes of the model, recent VOCs were considered to be those occurring in the prior year only (e.g., VOCs occurring in year 1 were considered recent in year 2).

Table S8. Clinical input parameters for acute events

Parameter	Base-case value	Notes
VOC		
Prior history at baseline		
All ages and genotypes	100%	HGB-206 TPVOE (Table S2)
Annual incidence, by age, HbSS/Sβ^0 (events per person-year)		
12-17 years	4.32	Estimate for ages 18-30 years aligned with baseline annualized VOE rate from HGB-206 TPVOE (Table S2); other ages derived using ratios derived from landmark CSSCD data[28]
18-30 years	5.70	
31-45 years	5.26	
> 45 years	3.67	
Rate ratios for incidence		
Genotype,* HbSβ$^+$/SC/other vs. HbSS/Sβ^0	0.492	Derived from landmark CSSCD data[28]
Common care, on HU vs. not on HU	0.556	Derived from clinical trial data[41]
Severity		
Hospitalized	76%	Set to equal the proportion of prior VOEs that were hospitalized in the HGB-206 TPVOE population (Table S2)
ACS		
Prior history at baseline		
All ages and genotypes	52.5%	HGB-206 TPVOE (Table S2)
Annual incidence, by age, HbSS/Sβ^0 (events per person-year)		
12-17 years	0.082	Estimate for ages 12-17 years derived from Medicaid data for all genotypes[26] and between genotype ratios from landmark CSSCD data[29]; other ages derived using ratios from landmark CSSCD data[29] and MarketScan data[57]
18-30 years	0.076	
> 30 years	0.027	
Rate ratios for incidence		
Genotype,* HbSβ$^+$/SC/other vs. HbSS/Sβ^0	0.376	Derived from landmark CSSCD data[29]
VOC, > 2 recent† vs. ≤ 2	5.330	Obtained from a UK HES database study[38]
ACS, prior vs. no prior	3.906	Derived from PUSH data[82]
PH, present vs. not present	1.672	Derived from HCUP data[83]
Priapism (males only)		
Prior history at baseline		
All ages and genotypes	22.2%	HGB-206 TPVOE (Table S2)

Parameter	Base-case value	Notes
Annual incidence, by age, HbSS/Sβ^0 (events per person-year)		
12-17 years	0.016	Estimates by age derived from digitized priapism-free Kaplan-Meier curves for all genotypes and between genotype ratios from the REDS-III study in Brazil[31]; incidence in ages > 45 years assumed to be 0
18-30 years	0.022	
31-45 years	0.014	
> 45 years	0.000	
Rate ratios for incidence		
Genotype,* HbSβ$^+$/SC/other vs. HbSS/Sβ^0	0.230	Derived from REDS-III study in Brazil[31]
VOC, > 2 recent† vs. ≤ 2	7.580	Obtained from a UK HES database study[38]
Priapism, prior vs. no prior	11.047	Derived from REDS-III study in Brazil[31]
Splenic sequestration		
Prior history at baseline		
All ages and genotypes	5.0%	HGB-206 TPVOE (Table S2)
Annual incidence, by age, all genotypes (events per person-year)		
12-17 years	0.011	Estimates for ages 12-17 years and ≥ 18 years taken from Medicaid data[26]; incidence assumed to be constant for all ages ≥ 18 years
≥ 18 years	0.002	
VTE		
Prior history at baseline, all ages		
HbSS/Sβ^0	22.6%	Obtained from a study of Johns Hopkins University data in the US (n = 279)[19]
HbSβ$^+$/SC/other	30.4%	
Annual incidence, by age, HbSS/Sβ^0 (events per person-year)		
12-17 years	0.0004	Estimate for ages 18-30 years obtained from a California hospital database study[32]; estimate for ages 12-17 years derived using a ratio between age ranges from Medicaid data[26]; estimate for all ages > 30 years derived by applying a ratio between age ranges from Johns Hopkins University data[19]
18-30 years	0.0046	
> 30 years	0.0058	
Rate ratios for incidence		
Genotype,* HbSβ$^+$/SC/other vs. HbSS/Sβ^0	1.770	Derived from Johns Hopkins University data[19]
VOC, > 2 recent† hospitalizations vs. ≤ 2	2.860	Obtained from a California database study[32]
VTE, prior (within last 5 years) vs. not	8.611	Obtained from a California database study[32]
PH, present vs. not present	1.650	Derived from Johns Hopkins University data[19]

Parameter	Base-case value	Notes
Type (% distribution)		
Pulmonary embolism	51.6%	Distribution derived from a California database study[32]
Deep vein thrombosis only	48.4%	
Stroke (including SCI)		
Prior history at baseline, all ages and genotypes		
SCI	42.6%	Obtained from a Vanderbilt University study (n = 54)[21]
Overt stroke	5.0%	HGB-206 TPVOE (Table S2)
Annual incidence, by age, all genotypes (events per person-year)		
12-17 years	0.011	Estimates for ages 12-17 years and ≥ 18 years taken from MarketScan claims data[13]; incidence assumed to be constant for all ages ≥ 18 years
≥ 18 years	0.021	
Rate ratios for incidence		
VOC, ≥ 1 recent† vs. 0	2.260	Obtained from Medicaid data[26]
Total Hb, per 1 g/dL increase	0.590	Obtained from a meta-analysis of published total Hb relationships[40]
SCI, prior vs. no prior	1.907	Obtained from landmark CSSCD data[22]
PH, present vs. not present	2.516	Derived from HCUP data[83]
Common care, on chronic transfusions vs. not	0.220	Obtained from a Cochrane Review[42]
Sepsis and/or bacteremia		
Prior history at baseline		
All ages and genotypes	1.8%	Obtained from the transition cohort (age 16-25 years) in the PiSCeS study (n = 71)[16]
Annual incidence, by age, all genotypes (events per person-year)		
12-17 years	0.0009	Estimates derived from cumulative incidence estimates reported for the PiSCeS study[16] with assumptions required to align the reported age ranges with the age ranges in the model
18-30 years	0.0010	
31-45 years	0.0018	
> 45 years	0.0026	
Rate ratios for incidence		
VOC, > 2 recent† vs. ≤ 2	2.760	Obtained from a UK HES database study[38]

ACS = acute chest syndrome; CSSCD = Cooperative Study of Sickle Cell Disease; Hb = hemoglobin; HbSC = hemoglobin SC; HbSS = hemoglobin SS; HbSβ = hemoglobin Sβ-thalassemia; HCUP = Healthcare Cost and Utilization Project; HES = hospital episode statistics; HU = hydroxyurea; PH = pulmonary hypertension; PiSCeS = Pain in Sickle Cell Epidemiology Study; PUSH = Pulmonary Hypertension and the Hypoxic Response in SCD; REDS-III = Recipient Epidemiology and Donor Evaluation Study III; SCI = silent cerebral infarct; TPVOE = transplant population for vaso-occlusive event; UK = United Kingdom; US = United States; VOC = vaso-occlusive crisis; VOE = vaso-occlusive event; VTE = venous thromboembolism.

* Differences in risk between genotypes were used for scenario analysis only (see Table S16 for scenario settings).

† For the purposes of the model, recent VOCs were considered to be those occurring in the prior year only (e.g., VOCs occurring in year 1 were considered recent in year 2).

Table S9. Clinical input parameters for chronic complications

Parameter	Base-case value	Notes
PH		
Prevalence at baseline, by age, all genotypes		
Ages 12-17 years	1.6%	Obtained from a combined Medicaid and Commercial/Medicare MarketScan analysis[17]
Ages 18-30 years	8.4%	
Ages 31-45 years	9.4%	
Ages > 45 years	10.2%	
Development and resolution, all genotypes (%)		
Annual probability of development, by age		
Ages 12-17 years	0.3%	Estimates for ages 12-17 years and ≥ 18 years taken from Medicaid data[26]; probability of development assumed to be constant for all ages ≥ 18 years
Ages ≥ 18 years	1.6%	
Annual probability of resolution, all ages	7.9%	Derived from a University of North Carolina cohort study[88]
Risk ratios for development		
VOC, ≥ 1 recent* vs. 0	4.120	Obtained from Medicaid data[26]
Total Hb, per 1 g/dL increase	0.430	Obtained from a meta-analysis of published total Hb relationships[40]
CKD		
Prevalence at baseline, by age, all genotypes		
12-17 years	0.9%	Derived from age-specific estimates in the PiSCeS study[16]; prevalence in ages 12-17 years assumed to be half the prevalence in ages 18-30 years (transition cohort sample size of n = 71 used in PSA for all ages)
18-30 years	1.8%	
31-45 years	4.2%	
> 45 years	5.8%	
Annual probability of development, by age, HbSS/Sβ^0		
12-30 years	1.4%	Estimates for ages 12-30 years and ≥ 30 years taken from MarketScan claims data[13]; probability of development assumed to be constant for all ages > 30 years
> 30 years	3.8%	
Severity and progression, all ages		
Baseline severity among prevalent, all genotypes		
eGFR, mean (SD) (mL/min per 1.73 m^2)	56.5 (15.0)	Taken from a cohort study in Nigeria[33]
Severity at incidence, all genotypes		
eGFR, mean (SD) (mL/min per 1.73 m^2)	91.8 (15.0)	Derived from a cohort study in Georgia[34]

Parameter	Base-case value	Notes
Progression, HbSS/Sβ^0		
eGFR decline per year, mean (SD) (mL/min per 1.73 m^2)	2.777 (0.693)	Derived from a Massachusetts cohort study for all genotypes[35] and between genotype differences from a Duke University study[84]
Risk ratios for development and progression		
Genotype,† HbSβ$^+$/SC/other vs. HbSS/Sβ^0	0.721	Derived from a Duke University cohort study[84]
VOC, > 2 recent* hospitalizations vs. ≤ 2	1.417	Derived from a Massachusetts cohort study[35]
Total Hb, per 1 g/dL increase	0.470	Obtained from a meta-analysis of published total Hb relationships[40]
Retinopathy		
Prevalence at baseline, by age, all genotypes		
12-17 years	0.9%	Obtained from a combined Medicaid and Commercial/Medicare MarketScan analysis[17]
18-30 years	1.9%	
31-45 years	2.9%	
> 45 years	4.1%	
Annual probability of development, by age, HbSS/Sβ^0		
12-17 years	0.1%	Estimate for ages 18-30 years derived from cumulative estimates in a longitudinal University of Southern California study[27]; probabilities for other ages estimated using age ratios derived from digitized Kaplan-Meier curves from the Creteil, France cohort[85]
18-30 years	0.8%	
31-45 years	1.7%	
> 45 years	3.4%	
Risk ratios for development		
Genotype,† HbSβ$^+$/SC/other vs. HbSS/Sβ^0	0.706	Derived from digitized cumulative incidence curves in the Creteil, France cohort[85]
AVN		
Prevalence at baseline, by age, all genotypes		
12-17 years	3.5%	Derived from age-specific estimates in the PiSCeS study[16]; prevalence in ages 12-17 years assumed to be half the prevalence in ages 18-30 years (transition cohort sample size of n = 71 used in PSA for all ages)
18-30 years	7.0%	
31-45 years	21.1%	
> 45 years	27.9%	
Annual probability of development, by age, HbSS/Sβ^0		
12-17 years	1.8%	Estimate for ages 18-30 years derived from cumulative estimates in a longitudinal University of Southern California study[27]; probabilities for other ages derived using ratios from age- and genotype-specific incidence in landmark CSSCD data[30]
18-30 years	2.2%	
31-45 years	2.5%	
> 45 years	2.8%	

Parameter	Base-case value	Notes
Risk ratios for development		
Genotype,† HbSβ$^+$/SC/other vs. HbSS/Sβ^0	0.902	Derived from genotype-specific incidence in the landmark CSSCD study[30]
VOC, ≥ 1 recent* vs. 0	2.770	Obtained from a retrospective California database study[86]
ACS, prior vs. no prior	1.610	Obtained from a retrospective California database study[86]
Gallstones		
Prevalence at baseline, by age, all genotypes		
12-17 years	23.7%	Derived from age-specific estimates in the PiSCeS study[16]; prevalence in ages 12-17 years assumed to be half the prevalence in ages 18-30 years (transition cohort sample size of n = 71 used in PSA for all ages)
18-30 years	47.4%	
31-45 years	46.5%	
> 45 years	58.7%	
Annual probability of development, by age, all genotypes		
Ages 12-17 years	2.9%	Estimates for ages 12-17 years and 18-30 years taken from Medicaid claims data[26]; probability of development assumed to be 0 for ages > 30 years
Ages 18-30 years	4.5%	
Ages > 30 years	0.0%	
Risk ratios for development		
VOC, > 2 recent* hospitalizations vs. ≤ 2	2.700	Obtained from a UK HES database study[38]
Management approach		
Treated with surgery	59.3%	Derived from a Brazil cohort study[89]
HF		
Prevalence at baseline, by age, all genotypes (%)		
Ages 12-17 years	1.8%	Derived from age-specific estimates in the PiSCeS study[16]; prevalence in ages 12-17 years assumed to be half the prevalence in ages 18-30 years (transition cohort sample size of n = 71 used in PSA for all ages)
Ages 18-30 years	3.5%	
Ages 31-45 years	4.2%	
Ages > 45 years	12.5%	
Annual probability of development, by age, all genotypes		
Ages 12-30 years	0.8%	Estimates for ages 12-30 years and ≥ 30 years taken from MarketScan claims data[13]; probability of development assumed to be constant for all ages > 30 years
Ages > 30 years	3.2%	

Parameter	Base-case value	Notes
Chronic lung disease		
Prevalence at baseline, by age, all genotypes (%)		
12-17 years	10.3%	Estimates by age obtained from Medicare Chronic Conditions Warehouse data[18]; prevalence in ages 12-17 years assumed to be half the prevalence in ages 18-30 years
18-30 years	20.6%	
31-45 years	37.9%	
> 45 years	43.0%	
Annual probability of development		
All ages and genotypes	3.4%	Estimate obtained from incidence data in a MarketScan Medicaid and Medicare claims study[7]; evidence for difference in incidence by age not identified
Risk ratios for development		
ACS, prior vs. no prior	1.460	Obtained from a longitudinal University of Southern California study[27]
Priapism, prior vs. no prior	1.700	Obtained from a longitudinal University of Southern California study[27]
Leg ulcers		
Prevalence at baseline, by age, all genotypes (%)		
12-17 years	0.9%	Derived from age-specific estimates in the PiSCeS study[16]; prevalence in ages 12-17 years assumed to be half the prevalence in ages 18-30 years (transition cohort sample size of n = 71 used in PSA for all ages)
18-30 years	1.8%	
31-45 years	5.6%	
> 45 years	20.2%	
Annual probability of development		
All ages and genotypes	1.4%	Estimate derived from cumulative incidence estimates in a longitudinal University of Southern California study[27]; evidence for difference in incidence by age not identified
Risk ratios for development		
VOC, > 2 recent* hospitalizations vs. ≤ 2	2.100	Obtained from a UK HES database study[38]
Neurocognitive impairment		
Prevalence at baseline, by age, all genotypes (%)		
12-17 years	1.2%	Estimates derived from age-specific incidence data from an Optum claims analysis[20]
18-30 years	2.4%	
31-45 years	4.9%	
> 45 years	11.0%	

Parameter	Base-case value	Notes
Annual probability of development, by age, all genotypes		
12-17 years	0.1%	Estimates obtained from age-specific incidence data in an Optum claims analysis[20]
18-45 years	0.2%	
> 45 years	0.6%	
Risk ratios for development		
Stroke or SCI, any prior history vs. no prior	2.760	Obtained from a multicenter cohort study in France[87]

ACS = acute chest syndrome; AVN = avascular necrosis; CKD = chronic kidney disease; CSSCD = Cooperative Study of Sickle Cell Disease; eGFR = estimated glomerular filtration rate; Hb = hemoglobin; HbSC = hemoglobin SC; HbSS = hemoglobin SS; HbSβ = hemoglobin Sβ-thalassemia; HES = hospital episode statistics; HF = heart failure; PH = pulmonary hypertension; PiSCeS = Pain in Sickle Cell Epidemiology Study; PSA = probabilistic sensitivity analysis; SCI = silent cerebral infarct; SD = standard deviation; UK = United Kingdom; VOC = vaso-occlusive crisis.

* For the purposes of the model, recent VOCs were considered to be those occurring in the prior year only (e.g., VOCs occurring in year 1 were considered recent in year 2).

† Differences in risk between genotypes were used for scenario analysis only (see Table S16 for scenario settings).

Table S10. Clinical input parameters for mortality

Parameter	Base-case value	Notes
General SCD mortality		
General population mortality	Age-, sex-, and race-dependent	Annual probabilities by age, sex, and race (Black or other) obtained from US life tables[54]
SCD mortality ratios, by sex, HbSS/Sβ^0 (vs. general population)		
Males	7.095	SCD-specific mortality ratios for HbSS/Sβ^0 derived from values estimated from landmark CSSCD data[46] for a prior economic evaluation[55] (males = 8.23; females = 7.56); ratios adjusted down to reflect risk without VOCs using CSSCD annual VOC rates[28] (mean = 0.814) and the effect of VOCs on mortality (HR = 1.20) based on a University of North Carolina cohort study[49]
Females	6.518	
SCD mortality ratios, by genotype*		
HbSβ$^+$/SC/other vs. HbSS/Sβ^0	0.590	Estimate for ratio between genotypes obtained from a Vanderbilt University cohort study[52]
Mortality due to SCD events and complications		
Mortality ratios, acute events		
Hospitalized VOC in current year (SE)	2.680 (1.38)	Mortality ratio for VOC hospitalization within the current year obtained from Bethesda Sickle Cell Cohort Study data[51]
Mortality ratios, organ impairment†		
≥ 2 organs impaired vs. < 2 organs impaired (SE)	4.200 (2.34)	Mortality ratio for multiple end-organ impairment obtained from a Vanderbilt University cohort study[52]

CKD = chronic kidney disease; CSSCD = Cooperative Study of Sickle Cell Disease; HbSC = hemoglobin SC; HbSS = hemoglobin SS; HbSβ = hemoglobin Sβ-thalassemia; PH = pulmonary hypertension; SCD = sickle cell disease; SE = standard error; US = United States; VOC = vaso-occlusive crisis.

* Differences in risk between genotypes were used for scenario analysis only (see Table S16 for scenario settings).

† Multiple organ impairment evaluated among PH, CKD, and chronic lung disease.[52]

Table S11. SCD-related costs

	Cost*	Notes
Direct costs, common care		
HU, per year	$1,605	Red Book Online[67]; Droxia PI[90]
HU, adherence†	71.2% (24.9%)	Shah et al.[57]
Chronic transfusion, per transfusion	$6,180	Kalpatthi et al.[60]
Chronic transfusion, no. per year†	10.8 (0.7)	
Direct costs, acute events	**(per event)**	
VOC, hospitalized	$14,653	Shah et al.[58]
VOC, not hospitalized	$1,152	Shah et al.[58]
ACS	$28,839	Bradt et al.[13]
Priapism	$2,342‡	Stein et al.[91]
Splenic sequestration	$9,796	Bou-Maroun et al.[61]
VTE, pulmonary embolism	$11,373‡	HCUPnet[68]
VTE, deep vein thrombosis	$1,293‡	CMS[69]; Shet and Wun[63]; Ziakas et al.[65]
Stroke, event	$62,372	Campbell et al.[59]
Stroke, history	$72,880 per year	Campbell et al.[59]
Sepsis or bacteremia	$19,851	HCUPnet[68]
Direct costs, chronic complications	**(per year)**	
PH	$89,075	Campbell et al.[59]
CKD, pre-ESRD	$80,302	Campbell et al.[59]
CKD, ESRD	$161,954	Campbell et al.[59]
Retinopathy	$1,885‡	CMS[69]; Menaa et al.[62]; Red Book Online[67]
AVN	$74,229	Campbell et al.[59]
Gallstones, chronic management	$1,366	Udeze et al.[64]
Gallstones, surgical management	$71,530	Campbell et al.[59]
HF	$35,645	Bradt et al.[13]
Chronic lung disease	$6,398‡	Chapel et al.[66]
Leg ulcers	$40,489	Campbell et al.[59]
Neurocognitive impairment	$12,816	Bradt et al.[13]
Direct costs, age-adjustment factors	**(multipliers)**	
Ages 12-17 years	0.55	Campbell et al.[59]; applied to acute event and chronic complication costs only; costs assumed to be constant for ages > 45 years
Ages 18-30 years (reference)	1.00	
Ages 31-45 years	0.87	
Ages > 45 years	0.60	

	Cost*	Notes
Indirect costs		
Value of unpaid caregiving per year	$16,404	Holdford et al.[72] (hours of unpaid caregiving); US BLS[73] (average hourly wage)
Average earnings per year, general population by race		Applied during ages 18-65 years only
Black	$48,297	US Census Bureau[75]
Other	$76,076	
Reduction in annual earnings for patients with SCD		
SCD overall (i.e., without VOE-CR)	56.0%	Graf et al.[74]
VOE-CR achieved at age < 15 years	92.0%	
VOE-CR achieved at age ≥ 15 years	78.0%	

ACS = acute chest syndrome; AVN = avascular necrosis; BLS = Bureau of Labor Statistics; CKD = chronic kidney disease; CMS = Centers for Medicare and Medicaid Services; ESRD = end-stage renal disease; HF = heart failure; HU = hydroxyurea; PH = pulmonary hypertension; PI = prescribing information; SCD = sickle cell disease; SD = standard deviation; US = United States; VOC = vaso-occlusive crisis; VOE-CR = complete resolution of vaso-occlusive events; VTE = venous thromboembolism.

* Costs inflated when required to 2022 US dollars using the US Consumer Price Index for medical care.[70]

† Values presented as mean (SD).

‡ Presented values are not SCD specific.

Table S12. Micro-costing details for lovo-cel one-time administration costs

Activities	Units	Unit cost	Total cost*	Notes
Pre-transplant				
Preparatory transfusions	7.63			▪ HGB-206, ITT Group C (Table S6)
Simple transfusion procedures	7.63	$324.29	$2,474	▪ CPT 36430 in hospital outpatient setting[92]
Red blood cell units	7.63	$200.00	$1,526	▪ Unit cost from Jacobs et al.[93]
Mobilization and apheresis				
Number of mobilization cycles	1.8			▪ HGB-206, ITT Groups B and C (Table S6)
Treatment per mobilization cycle				
Administration	1	$63.69	$114.63	▪ CPT 96372 (inflated) in hospital outpatient setting[94]
Plerixafor, ages < 18 years	22.83 mg	$415.34	$17,064.54	▪ HGB-206 dosing (0.448 mg/kg for ITT Groups B and C) (Table S6) and average US weight by age[95] ▪ Unit cost from Red Book Online[67]
Plerixafor, ages ≥ 18 years	37.65 mg	$415.34	$28,150.63	
Apheresis/harvest procedures per mobilization cycle	1.9	$1,114.41	$3,811.28	▪ HGB-206, ITT Groups B and C (Table S6) ▪ CPT 38206 in hospital outpatient setting[92]
Veno-occlusive disease prophylaxis				
Ursodeoxycholic acid	180 doses	$0.79	$142.20	▪ Dosing based on 300 mg twice per day for 90 days[96] ▪ Unit cost from Red Book Online[67]
Total pre-transplant costs, ages < 18 years			**$25,017.25**	▪ Costs of conditioning assumed to be captured in transplant hospitalization costs
Total pre-transplant costs, ages ≥ 18 years			**$36,103.34**	

Activities	Units	Unit cost	Total cost*	Notes
Transplant				
Total transplant hospitalization costs, ages < 18 years			**$187,595.85**	▪ HCUP KID 2019 costs (inflated) for MS-DRGs 016 and 017[97]
Total transplant hospitalization costs, ages ≥ 18 years			**$100,525.33**	▪ HCUP NIS 2020 costs (inflated) for MS-DRGs 016 and 017[68]

CPT = Current Procedural Terminology; HCUP KID = Healthcare Cost and Utilization Project Kids' Inpatient Database; HCUP NIS = Healthcare Cost and Utilization Project National Inpatient Sample; ITT = intention-to-treat; MS-DRG = Medicare-Severity Diagnosis-Related Group; US = United States.

* Costs inflated where noted to 2022 US dollars using the US Consumer Price Index for medical care.[70]

Table S13. Micro-costing details for lovo-cel annual monitoring costs

	Number of units			Total cost (2022 US $)		
Parameter	**Years 1-2**	**Years 3-15**	**Unit cost**	**Years 1-2**	**Years 3-15**	**Notes**
Examination						HCRU from Kansal et al.[96]
Physical examination	2	1	$129.77	$259.54	$129.77	CPT 99214[69]
Laboratory tests						
Complete blood count	2	1	$6.47	$12.94	$6.47	CPT 85027[98]
Iron testing	2	1	$6.47	$12.94	$6.47	CPT 83540[98]
Fasting glucose	1	1	$3.93	$3.93	$3.93	CPT 82947[98]
Adrenocorticotropic hormone	1	1	$38.62	$38.62	$38.62	CPT 82024[98]
Thyroid stimulating hormone	1	1	$16.80	$16.80	$16.80	CPT 84443[98]
Liver function test	1	1	$8.17	$8.17	$8.17	CPT 80076[98]
Hematologic malignancy testing	2	2	$0.00	$0.00	$0.00	Paid by manufacturer
ß-globin gene analysis						
Duplication/deletion variants	2	1	$324.58	$649.16	$324.58	CPT 81364[98]
Full gene sequence	2	1	$202.40	$404.80	$202.40	CPT 81364[98]
Imaging						
Cardiac MRI	1	1	$401.09	$401.09	$401.09	CPT 75561[69]
Liver MRI	1	1	$370.29	$370.29	$370.29	CPT 74183[69]
12-lead ECG	1	1	$14.54	$14.54	$14.54	CPT 93000[69]
X-ray	1	1	$103.13	$103.13	$103.13	CPT 77075[69]
DEXA scan: axial skeleton	1	1	$38.07	$38.07	$38.07	CPT 77080[69]
DEXA scan: appendicular skeleton	1	1	$31.84	$31.84	$31.84	CPT 77081[69]
DEXA scan: axial skeleton + vertebral fracture	1	1	$52.26	$52.26	$52.26	CPT 77085[69]
Total monitoring costs per year				**$2,418.12**	**$1,748.43**	

CPT = Current Procedural Terminology; DEXA = dual-energy X-ray absorptiometry; ECG = electrocardiogram; HCRU = healthcare resource utilization; MRI = magnetic resonance imaging; US = United States.

Table S14. SCD-related utility values

	Utility		Notes
General SCD	0.750		Anie et al.[77]
Common care			
HU use, per year	-		Assumed to be reflected in general SCD utility value
Chronic transfusion use	-		
Acute events	**(disutility)**	**(duration)**	
VOC (all severities)	0.230	14 days	Anie et al.[77]; Bradt et al.[13]
ACS	0.560*	14 days	NICE[80]; Bradt et al.[13]
Priapism	0.000	0 days	Assumption
Splenic sequestration	0.230	14 days	Assumed equal to VOC
VTE (all types)	0.038*	91 days	Sullivan et al.[78]
Stroke, event	0.304*	14 days	Bradt et al.[13]
Stroke, history	0.055*	indefinite	Song et al.[79]
Sepsis or bacteremia	0.160*	30 days	NICE[80]
Chronic complications	**(disutility)**		
PH	0.060*		Keogh et al.[99]
CKD, pre-ESRD	0.031*		Song et al.[79]
CKD, ESRD	0.060*		Sullivan et al.[78]
Retinopathy	0.016*		Sullivan et al[78]
AVN	0.018*		Sullivan et al[78]
Gallstones (all severities)	0.029*		Sullivan et al.[78]
HF	0.045*		Song et al.[79]
Chronic lung disease	0.033*		Song et al.[79]
Leg ulcers	0.110*		NICE[80]
Neurocognitive impairment	0.049*		Sullivan et al.[78]
Other impacts			
Caregiver disutility†	0.227		Barcelos et al.[81]

ACS = acute chest syndrome; AVN = avascular necrosis; CKD = chronic kidney disease; ESRD = end-stage renal disease; HF = heart failure; HU = hydroxyurea; NICE = National Institute for Health and Care Excellence; PH = pulmonary hypertension; SCD = sickle cell disease; VOC = vaso-occlusive crisis; VTE = venous thromboembolism.

* Presented values are not SCD specific.

† Applied to one caregiver per patient in the base-case analysis.

Table S15. Probabilistic sensitivity analysis uncertainty parameter settings and probability distributions

Parameter category	Uncertainty parameter (source)	Probability distribution
Baseline characteristics		
Prior VOE history and total Hb levels	SEs (estimated from SDs and sample sizes [Table S2])	Normal (mean, SE)
Common care treatment status	N (sample size in Medicaid claims analysis in original source [Table 1 in main text])	Dirichlet (derived from percentage distribution and sample size)
Acute events		
Prior history, by age	N (sample size in HGB-206 trial [Table S2] or from individual sources [Table S8])	Beta (parameters derived from proportions and sample sizes)
Annual incidence, by age	SE (assumed to be 20% of means [Table S8] due to lack of consistent evidence across individual studies)	Normal (mean, SE)
Chronic complications		
Baseline prevalence, by age	N (transition cohort sample size used for estimates from the PiSCeS study [Table S9]; sample size assumed to be 100 for other complications)	Beta (parameters derived from proportions and sample sizes)
Annual probability of development, by age	SE (assumed to be 20% of means [Table S9] due to lack of consistent evidence across individual studies)	Beta (parameters derived from means and SEs)
Mortality		
SMRs for SCD vs. general population	SE (assumed to be 20% of means due to lack of evidence)	Log-normal (parameters derived from means and SEs)
SMRs for hospitalized VOCs and multiple end-organ damage	SE (derived from 95% CIs in individual sources [Table S10])	Log-normal (parameters derived from means and SEs)
Lovo-cel attributes		
Proportions with complete resolution	SE (derived from 95% CIs in HGB-206 trial data [Table S3])	Beta (parameters derived from means and SEs)
Reductions in VOE rates without complete resolution	SE (assumed to be 20% of means [Table S3] due to lack of direct evidence)	Beta (parameters derived from means and SEs)
Change from baseline in total Hb	SE (estimated from SD and sample size in HGB-206 trial data [Table S4])	Normal (mean, SE)

Parameter category	Uncertainty parameter (source)	Probability distribution
Change from baseline in EQ-5D-3L utility value	SE (estimated from SD and sample size in HGB-206 trial data [Table S5])	Beta (parameters derived from means and SEs)
SMR due to myeloablative conditioning	SE (assumed to be 0.100)	Normal (mean, SE)
Costs for preparation, administration, and monitoring	SE (assumed to 20% of estimated one-time costs [Table S12] or annual recurring costs [Table S13])	Gamma (parameters derived from means and SEs)
QALY losses for transplantation and conditioning	SE (assumed to be 10% of means [Table 1 in main text] due to lack of direct evidence from individual sources)	Beta (parameters derived from means and SEs)
Costs		
Common care	SE (assumed to be 20% of means for unit costs [Table S11])	Gamma (parameters derived from means and SEs)
Age-specific event and complication cost multipliers	SE (derived from 95% CIs in original source [Table S11])	Gamma (parameters derived from means and SEs)
Acute event and chronic complication costs	SE (assumed to 20% of means [Table S11]) due to lack of consistent evidence across individual studies)	Gamma (parameters derived from means and SEs)
Value of unpaid caregiving and average annual earnings	SE (assumed to 20% of means [Table S11]) due to lack of consistent evidence across individual studies)	Gamma (parameters derived from means and SEs)
Utilities		
General SCD	SE (assumed to be 5% of mean [Table S14] due to lack of evidence in the original source)	Beta (parameters derived from means and SEs)
Disutilities for acute events and chronic complications	SE (assumed to be 10% of means [Table S14]) due to lack of consistent evidence across individual sources)	Beta (parameters derived from means and SEs)
Caregiver utility decrement	SE (derived from SD and sample size in original source [Table S14])	Beta (parameters derived from means and SEs)

CI = confidence interval; Hb = hemoglobin; PiSCeS = Pain in Sickle Cell Epidemiology Study; QALY = quality-adjusted life-year; SCD = sickle cell disease; SD = standard deviation; SE = standard error; SMR = standardized mortality ratio; VOC = vaso-occlusive crisis; VOE = vaso-occlusive event.

Table S16. Scenario analysis settings

Scenario category	Rationale	Model parameter(s)	Parameter values, details, and sources
Lovo-cel target population	Understand the impact of heterogeneity in baseline age and alternative prior VOE criteria at the time of treatment with lovo-cel	Age at treatment	▪ 12-17 years; evaluated as a subgroup (n = 395; 15.8%) of the base-case population
			▪ 18-30 years; evaluated as a subgroup (n = 1,555; 62.2%) of the base-case population
			▪ > 30 years; evaluated as a subgroup (n = 550; 22.0%) of the base-case population
		Prior VOE criteria	▪ Any history of VOE; all patients assumed to have 1 sVOE in the prior year ▪ Genotype distribution from ages 16-25 cohort in the PiSCeS study[16] ▪ Annual incidence of VOCs for genotypes HbSS/Sβ^0 ages 18-30 years = 1.00; other ages adjusted proportionally
Lovo-cel VOE and total Hb efficacy	Understand the impact of uncertainty in the magnitude of lovo-cel's primary and secondary efficacy endpoints	VOE-CR achievement	▪ 96.5% of patients achieve VOE-CR (upper 95% CI [Table S3]) ▪ 99.2% of patients achieve sVOE-CR (upper 95% CI [Table S3])
			▪ 71.0% of patients achieve VOE-CR (lower 95% CI [Table S3]) ▪ 79.2% of patients achieve sVOE-CR (lower 95% CI [Table S3])
		Partial VOE reduction in those not achieving VOE-CR	▪ Excluded (i.e., no reduction in VOEs or sVOEs for those not achieving complete resolution)
		Total Hb change from baseline	▪ Mean (SD) = 4.10 (1.28) (maximum of values in Table S4)
			▪ Mean (SD) = 2.86 (1.70) (minimum of values in Table S4)

Scenario category	Rationale	Model parameter(s)	Parameter values, details, and sources
Lovo-cel HRQOL impacts	Understand the impact of uncertainty in lovo-cel's impact on patients' HRQOL	Utility gain associated with PRO improvement	▪ Lovo-cel utility gain = 0.146 (maximum of values in Table S5) ▪ Lovo-cel utility gain = 0.056 (minimum of values in Table S5)
Partial loss of lovo-cel effect	Evaluate the impact of alternative assumptions about the long-term maintenance of lovo-cel's VOE and total Hb efficacy	Proportion of patients with partial loss of VOE and Hb effect and timing of the loss	▪ Proportion of patients with partial effect loss assumed to occur in 10% of patients based on the range of secondary graft failure rates observed in allogeneic HSCT literature[100,101] ▪ In those with partial effect loss, 50% of VOE and total Hb effects assumed to be lost ▪ Loss assumed to occur at 5 years based on duration of HGB-206 follow-up
VOE-CR impact assumptions for lovo-cel	Evaluate the impact of alternative assumptions about the long-term impact of VOE-CR on other SCD events, complications, and mortality	VOE-CR impact on events and complications with hemolytic and vascular components and on mortality (see Figure 2 in main text)	▪ 95%/90%/80% reduction in select events and complications for ages 12-17/18-30/> 30 years at treatment ▪ 100%/90%/80% reduction in mortality relative to general population for ages 12-17/18-30/> 30 years at treatment ▪ 95%/80%/60% reduction in select events and complications for ages 12-17/18-30/> 30 years at treatment ▪ 100%/80%/60% reduction in mortality relative to general population for ages 12-17/18-30/> 30 years at treatment
Lovo-cel drug product price	Understand the potential impact of population-level rebates or other performance-based arrangements	Drug product acquisition price for lovo-cel	▪ Drug project acquisition price reduced by 23.1% based on the minimum statutory rebate under the federal Medicaid Prescription Drug Rebate Program[102]

Scenario category	Rationale	Model parameter(s)	Parameter values, details, and sources
Event and complication costs and utilities	Evaluate the impact of parameter uncertainty in the costs and quality-of-life impacts of acute event and chronic complications	Direct costs, acute events and chronic complications	▪ 25% increase in the direct costs associated with all acute events and chronic complications
			▪ 25% decrease in the direct costs associated with all acute events and chronic complications
		Disutilities, acute events and chronic complications	▪ 25% increase in the disutilities for all acute events and chronic complications
			▪ 25% decrease in the disutilities for all acute events and chronic complications
Other scenarios of interest	Understand the impact of uncertainty due to data gaps or limitations in the available literature	VOC rate	▪ All base-case annual VOC incidence rates increased by 50% to reflect crises managed at home ▪ Proportion of all VOCs hospitalized reduced proportionally to 50.6% of VOCs (to keep overall rate of hospitalized VOCs constant) ▪ Costs of nonhospitalized VOCs reduced proportionally to $374 per event (assuming no cost for VOCs managed at home) ▪ VOCs managed at home assumed to have the same disutility as all other VOCs
		Unpaid caregiving	▪ Value of unpaid caregiving = $32,808 per year (100% higher than base-case analysis)
		Caregiver disutility	▪ Applied to 2 caregivers per patient (100% higher than base-case analysis)

Scenario category	Rationale	Model parameter(s)	Parameter values, details, and sources
Model settings	Demonstrate the impact of alternative discount rates and the inclusion of alternative cost categories	Discounting	▪ Undiscounted (i.e., discount rate = 0%) health and cost outcomes ▪ Discount rate = 1.5% for health and cost outcomes
		Unrelated direct medical costs	▪ Direct medical costs not related to SCD of $3,761 per year[71] (inflated to 2022 US dollars using the US Consumer Price Index for medical care[70])
		Consumption costs	▪ Annual nonhealthcare consumption set to 80.7% of annual earnings[76] (applied at all ages, including beyond age 65 years until death)

CI = confidence interval; HRQOL = health-related quality of life; PiSCeS = Pain in Sickle Cell Epidemiology Study; PRO = patient-reported outcome; SD = standard deviation; sVOE = severe vaso-occlusive event; sVOE-CR = complete resolution of severe vaso-occlusive events; US = United States; VOC = vaso-occlusive crisis; VOE = vaso-occlusive event; VOE-CR = complete resolution of vaso-occlusive events.

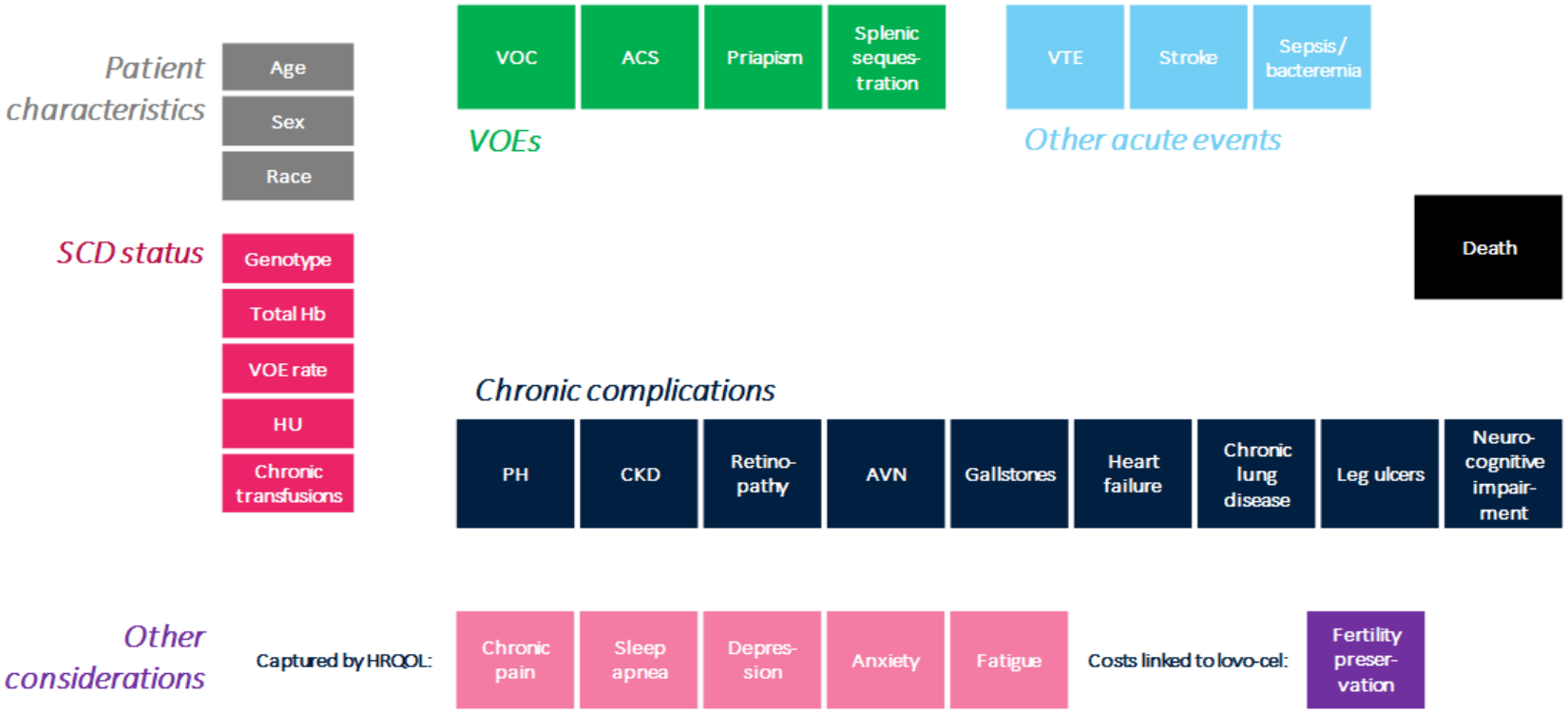
Table S17. Cross-validation of the current lovo-cel model versus published models for sickle cell disease gene therapy

	Current lovo-cel model			MEASURE[8]			ICER[14]		
Model outcome	**Lovo-cel**	**Common care**	**Incremental**	**Gene therapy**	**Common care**	**Incremental**	**Lovo-cel**	**Standard of care**	**Incremental**
Health outcomes									
Lifetime VOCs (acute pain crises)	7.74	91.29	−83.55	6.6	92.8	−86.2	4.18	119.26	−115.08
Undiscounted LYs	37.32	13.47	23.84	30.8	13.4	17.4	NR	NR	NR
Age at death (years)	62.24	38.40	23.84	54.8	37.4	17.4	NR	NR	NR
Discounted LYs	21.03	10.49	10.54	18.1	10.1	7.9	21.87	15.80	6.07
Discounted patient QALYs	16.44	6.25	10.20	12.4	2.6	9.8	16.38	9.44	6.94
Discounted caregiver QALYs	−1.19	−2.28	1.19	18.2	16.1	2.1	Not included	Not included	Not included
Discounted total QALYs	15.25	3.86	11.39	30.6	18.7	11.9	16.38	9.44	6.94
Cost outcomes									
Gene therapy acquisition costs	$3,100,000	-	$3,100,000	$2,000,000	-	$2,000,000	$2,000,000	-	$2,000,000
Other gene therapy costs	$182,009	-	$182,009	$470,796	-	$470,796	Not included	-	Not included
Other direct medical costs	$860,020	$2,189,221	−$1,329,201	$1,025,095	$1,197,111	−$172,065	$827,000	$1,490,000	−$663,000
Other societal costs	−$368,325	$172,090	−$540,416	−$1,457,164	−$657,672	−$799,492	$10,000	$224,000	−$214,000
Total costs, third-party payer	$4,142,030	$2,189,221	$1,952,808	$3,495,891	$1,197,111	$2,298,780	$2,827,000	$1,490,000	$1,337,000
Total costs, societal	$3,773,704	$2,361,311	$1,412,393	$2,038,410	$539,439	$1,498,971	$2,837,000	$1,714,000	$1,123,000
CE outcomes									
Incremental CE ratio, third-party payer	$191,519/ QALY gained			$193,000/ QALY gained			$193,000/ QALY gained		
VBP, third-party payer (WTP = $150,000 per QALY gained)	$2,676,653			$2,300,000			$1,700,000		
Incremental CE ratio, societal	$124,051/ QALY gained			$126,000/ QALY gained			$162,000/ QALY gained		
VBP, societal (WTP = $150,000 per QALY gained)	$3,395,445			$2,700,000			$1,910,000		

CE = cost-effectiveness; ICER = Institute for Clinical and Economic Review; LY = life-year; MEASURE = Model for Economic Analysis of Sickle Cell Cure; NR = not reported; QALY = quality-adjusted life-year; VBP = value-based price; VOC = vaso-occlusive crisis; WTP = willingness to pay.

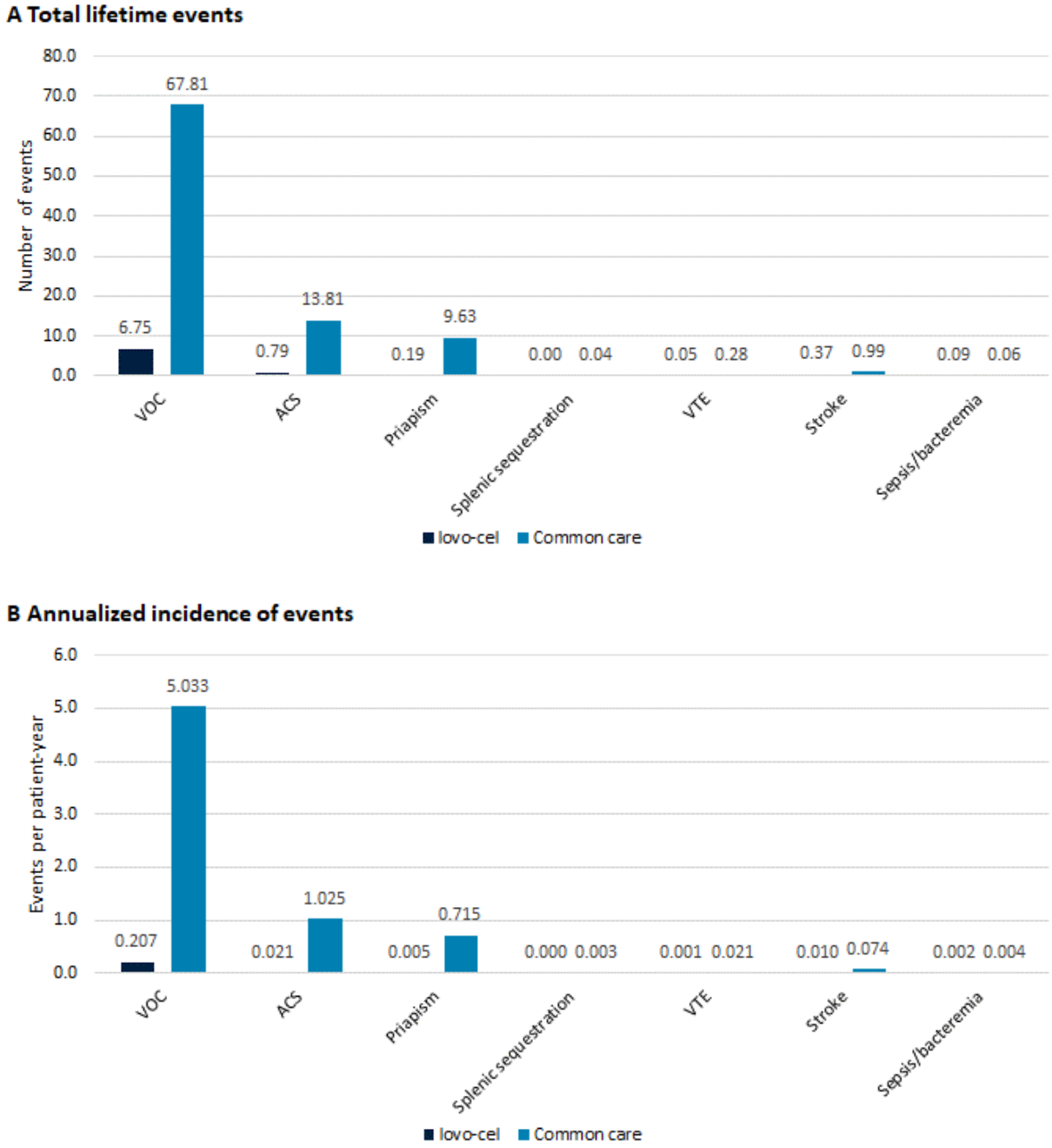
3 Supplemental Figures

Figure S1. Overview of the patient characteristics, events, and complications included in the model



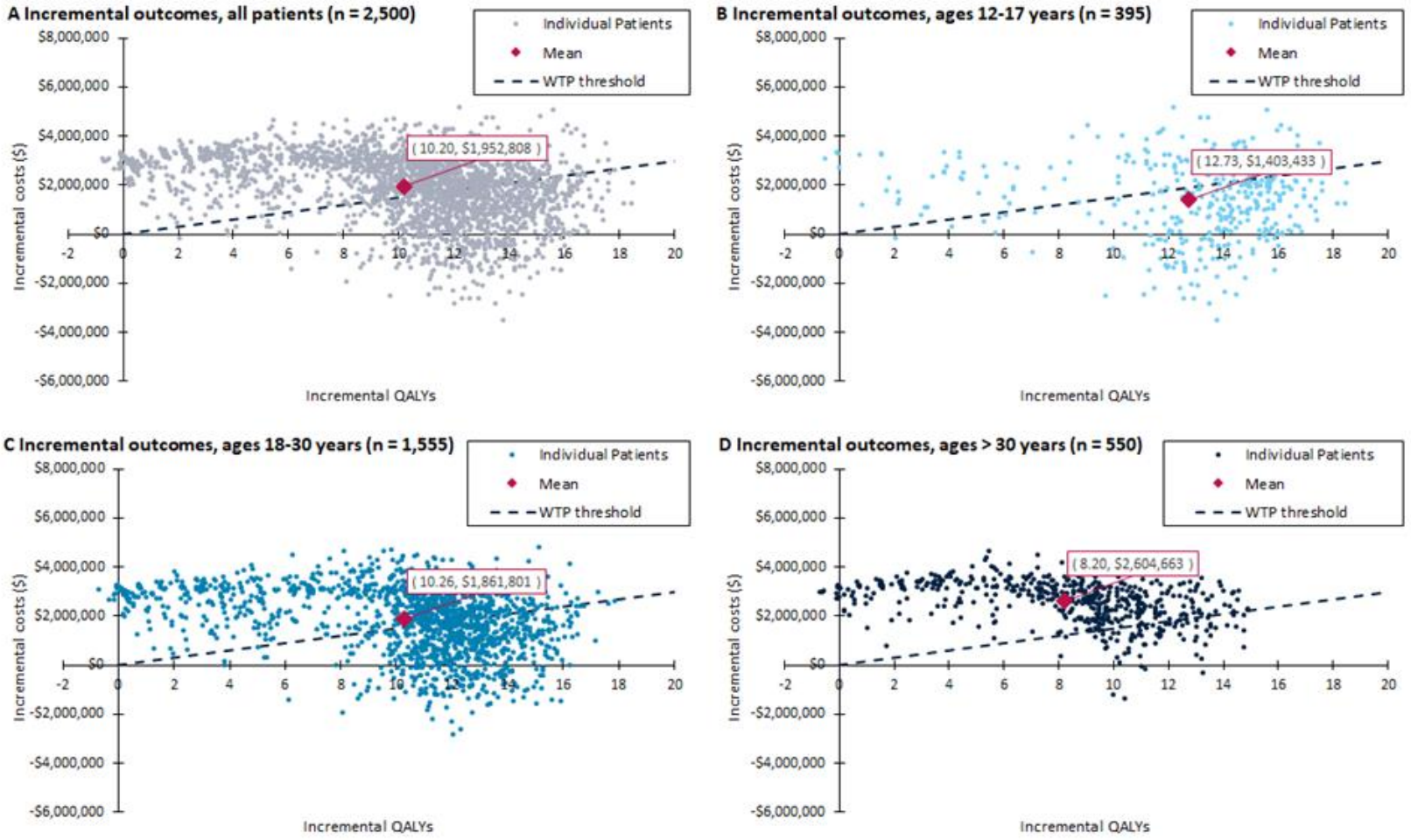
ACS = acute chest syndrome; AVN = avascular necrosis; CKD = chronic kidney disease; Hb = hemoglobin; HRQOL = health-related quality of life; HU = hydroxyurea; PH = pulmonary hypertension; SCD = sickle cell disease; VOC = vaso-occlusive crisis; VOE = vaso-occlusive event; VTE = venous thromboembolism.

Figure S2. Predicted lifetime and annualized incidence estimates for acute events



ACS = acute chest syndrome; VOC = vaso-occlusive crisis; VTE = venous thromboembolism.

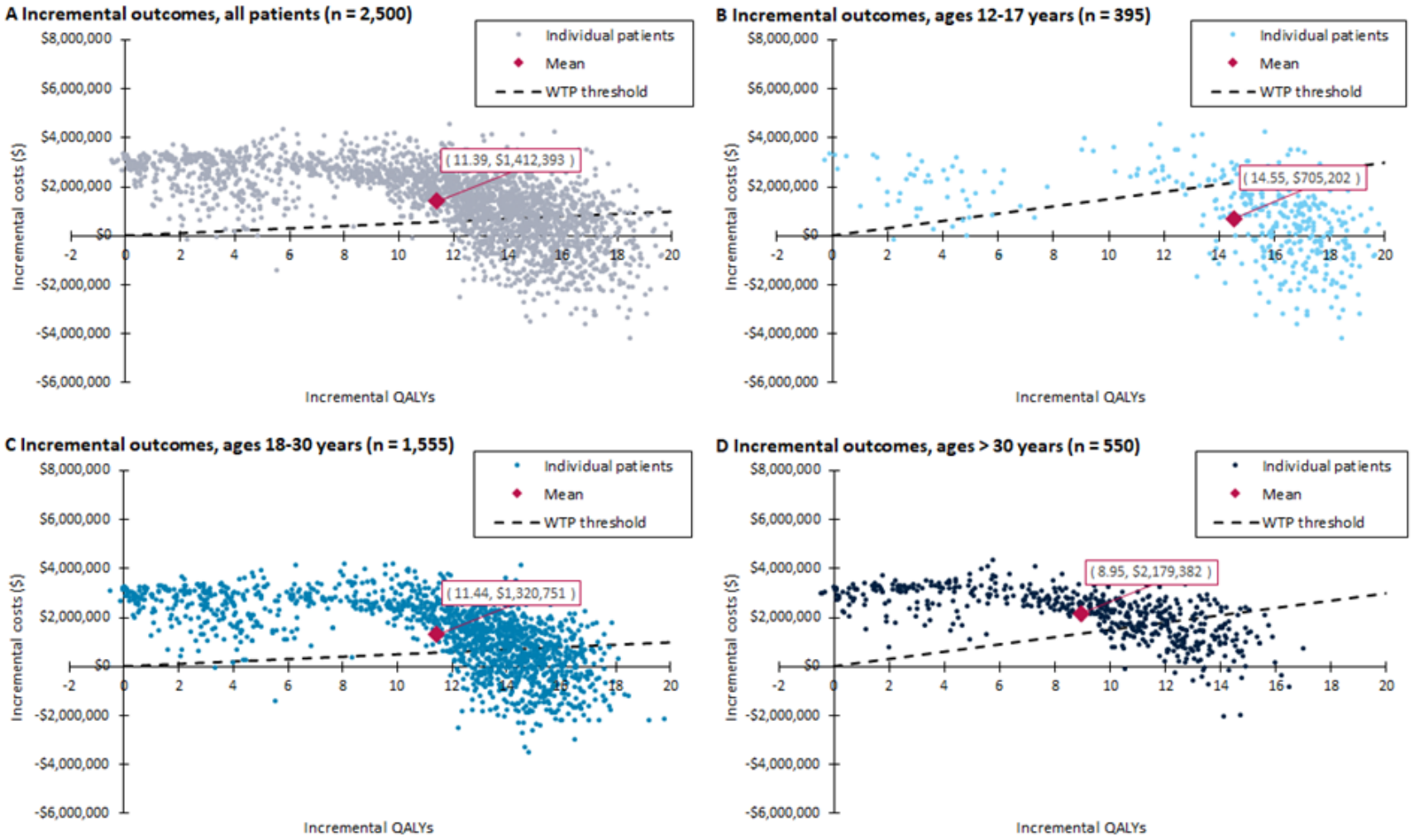
Figure S3. Scatterplot of patient-level incremental outcomes from a third-party payer perspective by age-specific subgroups



QALY = quality-adjusted life-year; WTP = willingness to pay.

Notes: The dashed lines reflect a WTP threshold of $150,000 per QALY gained. Baseline age scenarios were considered as post hoc subgroups (ages 12-17 years: n = 395 [15.8%]; ages 18-30 years: n = 1,555 [62.2%]; ages > 30 years: n = 550 [22.0%]).

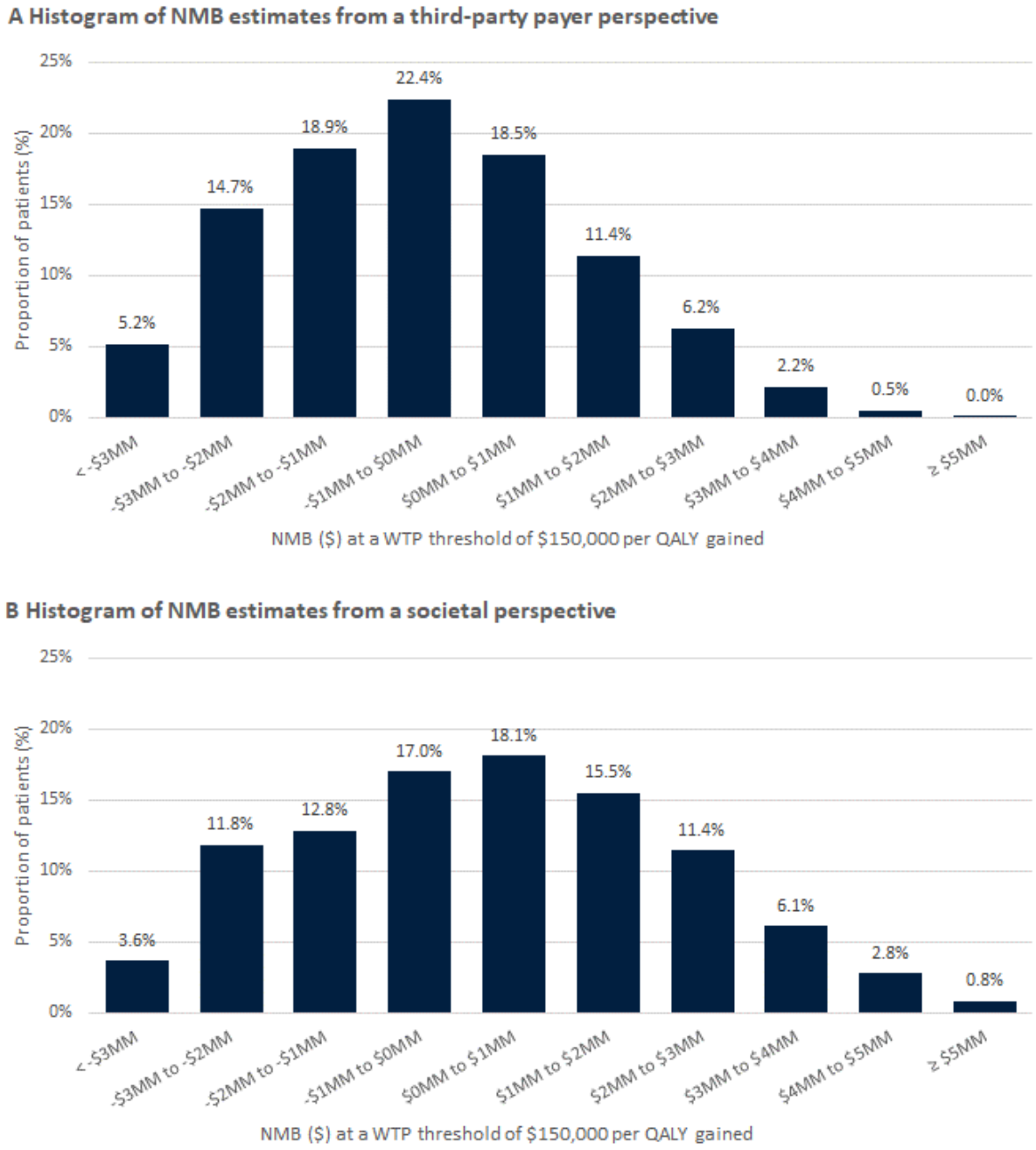
Figure S4. Scatterplot of patient-level incremental outcomes from a societal perspective by age-specific subgroups



QALY = quality-adjusted life-year; WTP = willingness to pay.

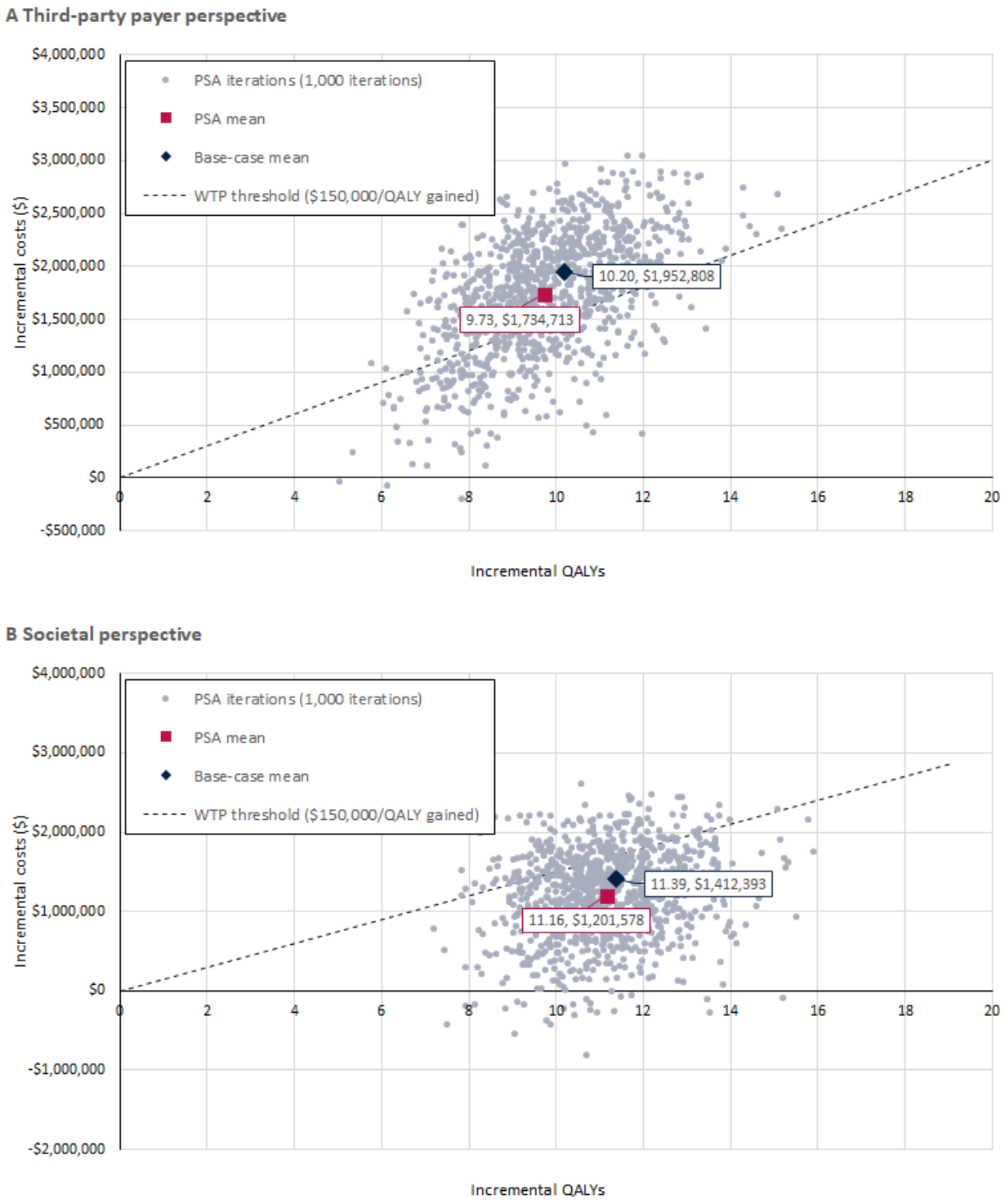
Notes: The dashed lines reflect a WTP threshold of $150,000 per QALY gained. Baseline age scenarios were considered as post hoc subgroups (ages 12-17 years: n = 395 [15.8%]; ages 18-30 years: n = 1,555 [62.2%]; ages > 30 years: n = 550 [22.0%]).

Figure S5. Heterogeneity of patient-level net monetary benefit estimates for lovo-cel vs. common care from third-party payer and societal perspectives



MM = million; NMB = net monetary benefit; QALY = quality-adjusted life-year; WTP = willingness to pay.

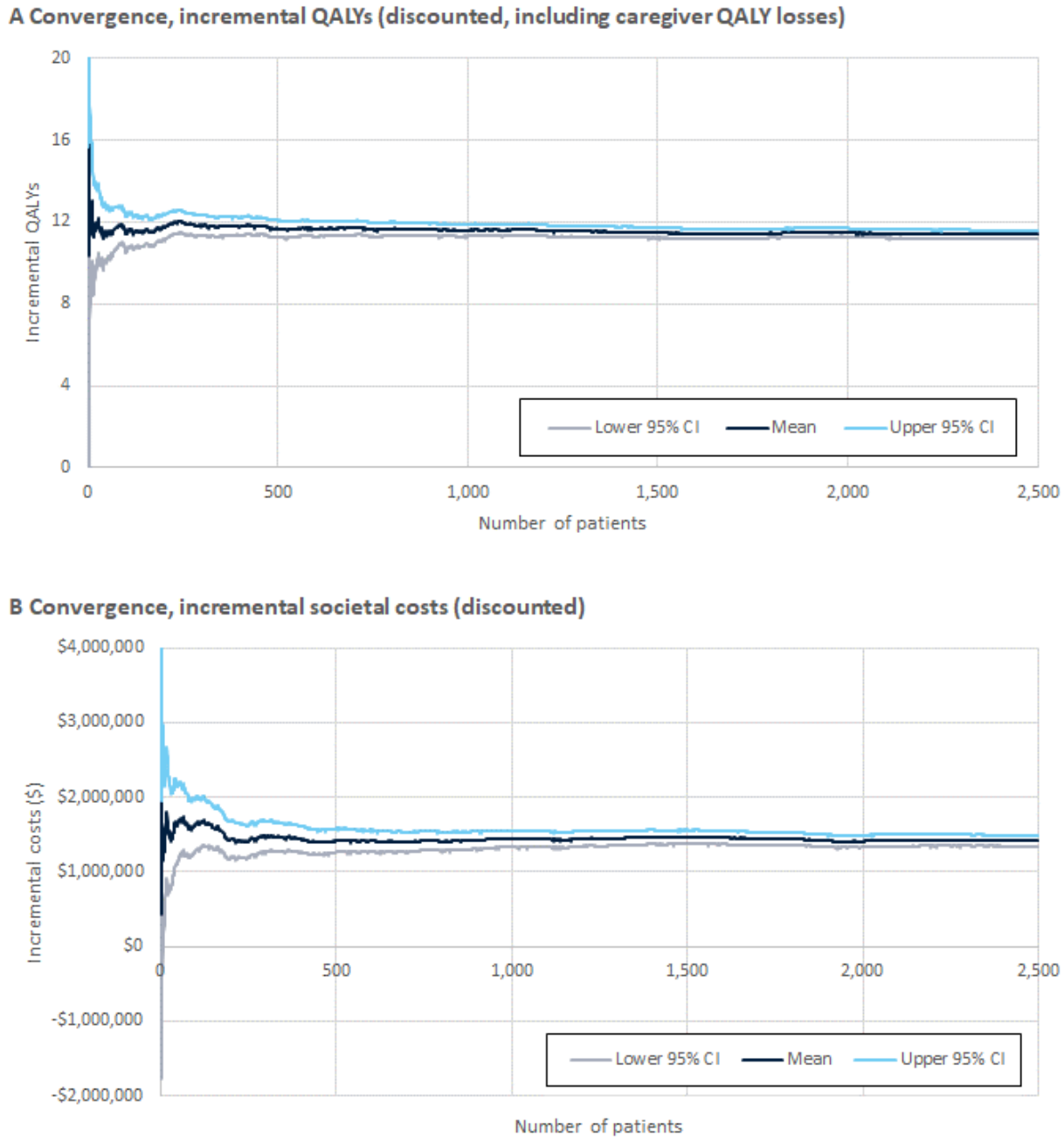
Figure S6. Cost-effectiveness scatterplots for the probabilistic sensitivity analysis from third-party payer and societal perspectives



PSA = probabilistic sensitivity analysis; QALY = quality-adjusted life-year; WTP = willingness to pay.

Note: The dashed lines reflect a WTP threshold of $150,000 per QALY gained.

Figure S7. Convergence plots for incremental QALYs and costs



CI = confidence interval; QALY = quality-adjusted life-year.

Note: Convergence plots provide insight into how large a cohort of patients (i.e., the sample size) is required to have confidence in the predicted mean outcomes per patient. These plots illustrate that a cohort of 2,500 patients is sufficient to generate stable estimates of the means and CIs for incremental QALYs and costs.

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