Advances in Bleeding Disorders 2024 ASH Classical Hematology Highlights

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Disclosures

AA-MDSIF - Speaker
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Objectives

1. Review recent outcomes of bleeding disorder treatments
2. Discuss HHT and symptomatic carrier status in women with bleeding disorders
3. Grow our list of new therapies for sickle cell disease

Bleeding Outcomes in Participants with Factor VIII Activity <5 IU/DL Post–Gene Transfer in GENEr8-1 - Mahlangu J.

ORIGINAL ARTICLE

Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A

Margareth C. Ozelo, M.D., Ph.D., Johnny Mahlangu, M.B., B.Ch., M.Med., K. John Pasi, M.D., Ph.D., Adam Giermasz, M.D., Ph.D., Andrew D. Leavitt, M.D., Michael Laffan, M.D., Ph.D., Emily Symington, M.D., Doris V. Quon, M.D., Ph.D., Jiaan-Der Wang, M.D., Ph.D., Kathelijne Peerlinck, M.D., Ph.D., Steven W. Pipe, M.D., Bella Madan, M.D., et al., for the GENEr8-1 Trial Group*

March 17, 2022
N Engl J Med 2022; 386:1013-1025

"Few adverse events related to treatment occurred after year 1; no participants chose to resume prophylaxis. In this phase 3 study of the dose of 6×1013 vg per kilogram, the median factor VIII activity level was 23.9 IU per deciliter at weeks 49 through 52; among the participants who received the infusion 2 years before, the median factor VIII activity level was 14.7 IU per deciliter at week 104."

Table 1. Extrapolated Factor VIII Activity.*

Time after Infusion	Factor VIII Level	
	Mean	Median (Range)
	IU per deciliter	
Wk 104	22.3±29.7	11.1 (BLQ–171)
Wk 156	16.9±25.0	8.9 (BLQ–156)
Wk 208	13.6±22.4	7.2 (BLQ–143)
Wk 260	11.8±21.0	5.7 (BLQ–131)

Mahlangu J. Bleeding Outcomes in Participants with Factor VIII Activity <5 IU/DL Post–Gene Transfer in GENEr8-1. In: ASH; 2023.

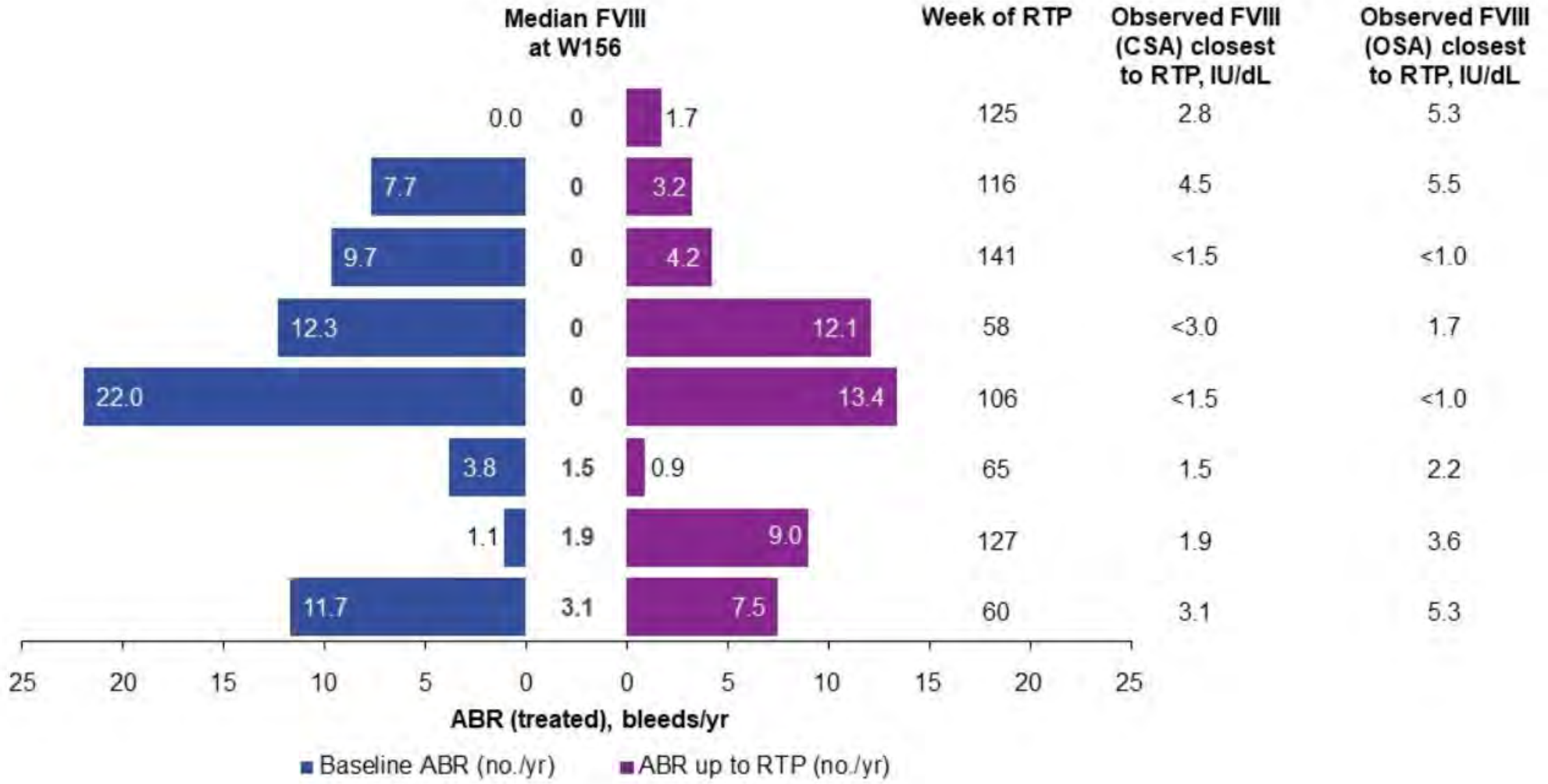
134 adult males (intention-to-treat [ITT] population) with severe HA (FVIII activity <1 IU/dL) previously receiving regular FVIII prophylaxis and with no history of FVIII inhibitors received a single dose of $6x10^{13}$ vg/kg valoctocogene roxaparvovec.

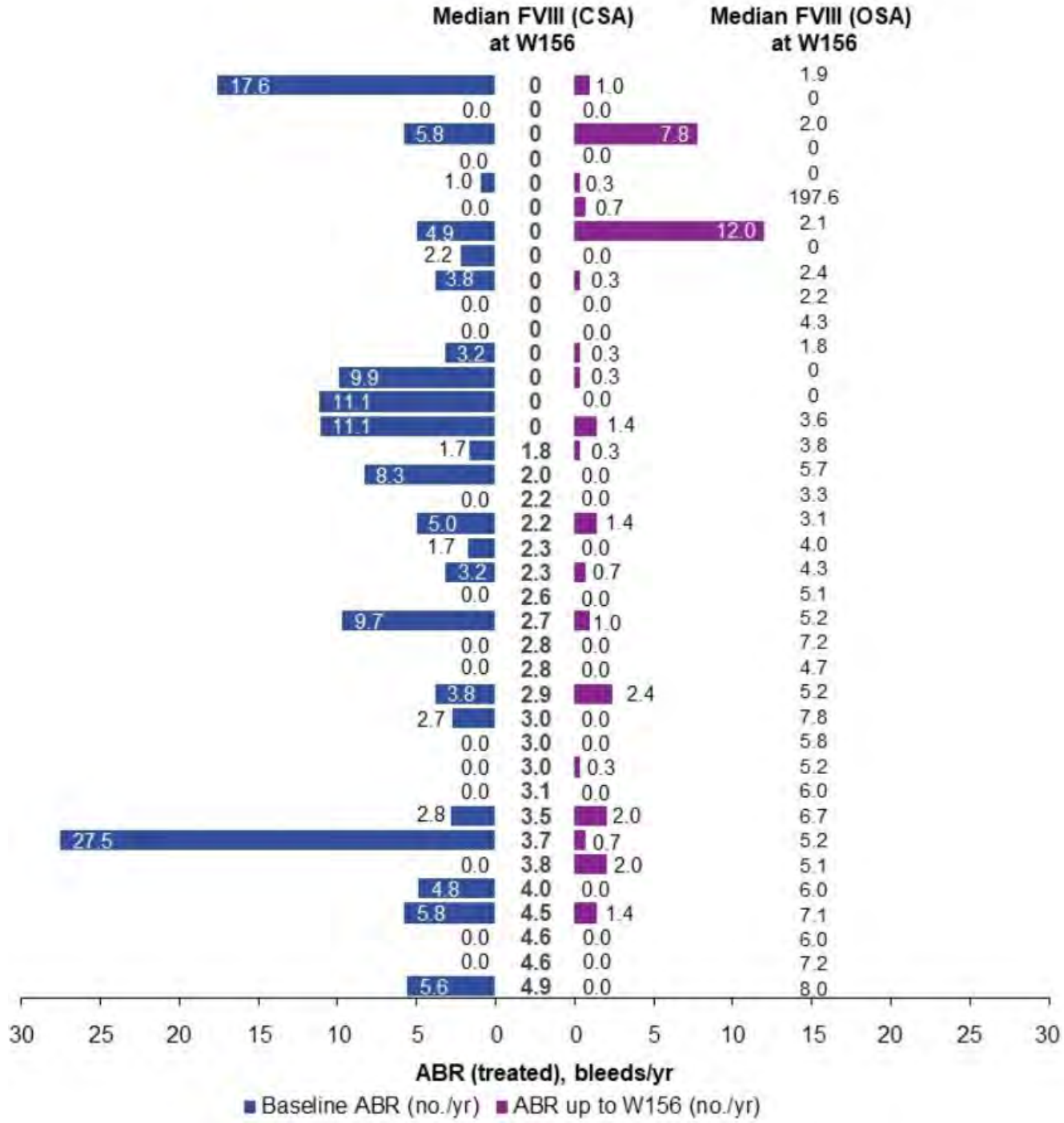
For participants who resumed prophylaxis, the valid FVIII measurement closest to, but not after, return to prophylaxis (RTP) is reported. Presented FVIII activity at a visit week is the median value in the 4- or 6-week window around the target date.

RTP was defined per-protocol as usual FVIII prophylaxis administered ≥1 time/week for ≥4 consecutive weeks or ≥2 emicizumab injections/month. Outcomes are reported for up to 156 weeks.

Of 134 ITT participants, 131 completed the week 156 visit.
Mean FVIII activity at week 156 was 18.2 (30.6) IU/dL in the ITT population.
At week 156, 46 of 134 (34.3%) ITT participants had median FVIII activity <5 IU/dL.

Of these 46 participants, 8 resumed prophylaxis before week 156 (range, 58–141 weeks) and 38 did not RTP before week 156.


Median FVIII at W156
Week of RTP
Observed FVIII (CSA) closest to RTP, IU/dL
Observed FVIII (OSA) closest to RTP, IU/dL
0.0
0
1.7
125
2.8
5.3
7.7
0
3.2
116
4.5
5.5
9.7
0
4.2
141
<1.5
<1.0
12.3
0
12.1
58
<3.0
1.7
22.0
0
13.4
106
<1.5
<1.0
3.8
1.5
0.9
65
1.5
2.2
1.1
1.9
9.0
127
1.9
3.6
11.7
3.1
7.5
60
3.1
5.3
25 20 15 10 5 0 0 5 10 15 20 25
ABR (treated), bleeds/yr
Baseline ABR (no./yr)
ABR up to RTP (no./yr)


Median FVIII (CSA) at W156
Median FVIII (OSA) at W156
17.6 0 1.0 1.9
0.0 0 0.0 0
5.8 0 7.8 2.0
0.0 0 0.0 0
1.0 0 0.3 0
0.0 0 0.7 197.6
4.9 0 12.0 2.1
2.2 0 0.0 0
3.8 0 0.3 2.4
0.0 0 0.0 2.2
0.0 0 0.0 4.3
3.2 0 0.3 1.8
9.9 0 0.3 0
11.1 0 0.0 0
11.1 0 1.4 3.6
1.7 1.8 0.3 3.8
8.3 2.0 0.0 5.7
0.0 2.2 0.0 3.3
5.0 2.2 1.4 3.1
1.7 2.3 0.0 4.0
3.2 2.3 0.7 4.3
0.0 2.6 0.0 5.1
9.7 2.7 1.0 5.2
0.0 2.8 0.0 7.2
0.0 2.8 0.0 4.7
3.8 2.9 2.4 5.2
2.7 3.0 0.0 7.8
0.0 3.0 0.0 5.8
0.0 3.0 0.3 5.2
0.0 3.1 0.0 6.0
2.8 3.5 2.0 6.7
27.5 3.7 0.7 5.2
0.0 3.8 2.0 5.1
4.8 4.0 0.0 6.0
5.8 4.5 1.4 7.1
0.0 4.6 0.0 6.0
0.0 4.6 0.0 7.2
5.6 4.9 0.0 8.0
30 25 20 15 10 5 0 0 5 10 15 20 25 30
ABR (treated), bleeds/yr
Baseline ABR (no./yr)
ABR up to W156 (no./yr)

Most participants with low FVIII activity had low bleeding rates, suggesting that low endogenous FVIII expression may provide protective hemostatic benefits.

Many participants who resumed prophylaxis had clinical presentation consistent with moderate hemophilia; the individual decision to RTP was multifactorial and influenced by FVIII activity, bleeding rates, desired physical activity levels, and personal preferences.

Long-Term Bleeding Protection, Sustained FIX Activity, Reduction of FIX Consumption and Safety of Hemophilia B Gene Therapy: Results from the HOPE-B Trial 3 Years after Administration of a Single Dose of Etranacogene Dezaparvovec in Adult Patients with Severe or Moderately Severe Hemophilia B - Pipe, S

Severe or moderately severe hemophilia B (FIX ≤2%), with or without preexisting AAV5 neutralizing antibodies were infused with a single dose (2×10^{13} gc/kg) of etranacogene dezaparvovec

Mean annualized bleeding rate (ABR) for all bleeds during Months 7-36 post-treatment was significantly reduced by 64% (mean ABR 1.52) compared with the ≥6-month lead-in period (mean ABR 4.17; *P*=0.0004).

Median [range] bleeds per participant decreased from 2.0 [0-10] during the lead-in period and remained stable to 0.0 [0-4] during Year 1, 0.0 [0-10] during Year 2, and 0.0 [0-8] during Year 3.

The mean±SD (median; range) endogenous FIX activity level of participants was 41.5 IU/dL ±21.7 (39.9; 5.9-113, n=50) at Year 1, 36.7 IU/dL ±19.0 (33.9; 4.7-99.2, n=50) at Year 2, and sustained at 38.6 IU/dL ±17.8 (36.0; 4.8-80.3, n=48) at Year 3 post-treatment.

Pharmacodynamic profile was not significantly different in participants with AA5 NAb undetected or titer ≤1:678.

At 3 years post-treatment, 51 (94%) remained free of continuous FIX prophylaxis.

Overall mean annualized FIX consumption decreased by 96% over 3 years post-treatment compared to the ≥6-month lead-in period

Emicizumab Versus Immunosuppression for Acquired Hemophilia A - Hart C.

Prospective exploratory analysis of the GTH-AHA-EMI trial vs GTH-AH-01/2010

Open-label, single-arm, phase 2 clinical trial

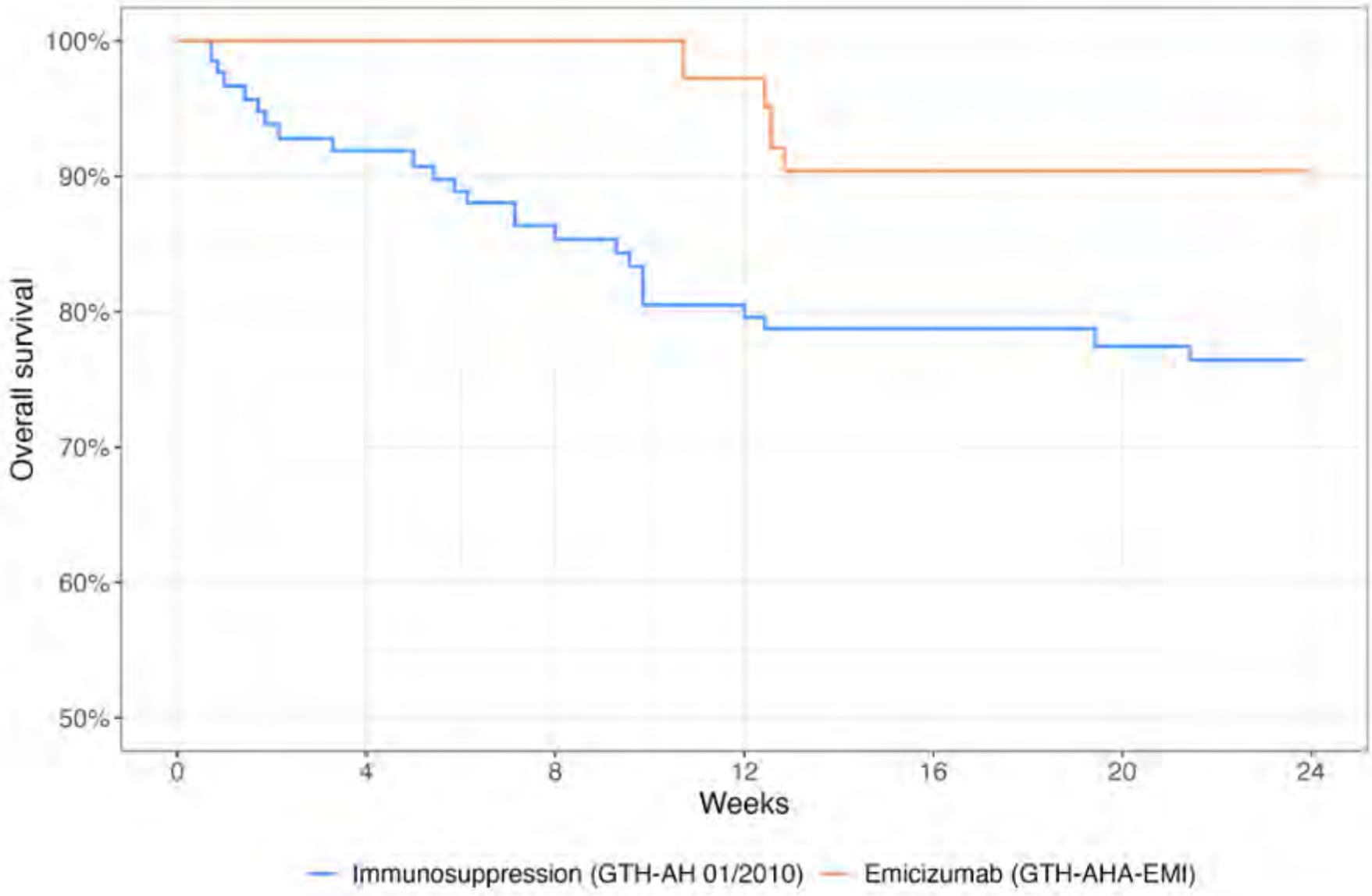
Adult Acquired hemophilia A not previously received immunosuppression (n=47)

Patients received emicizumab subcutaneously (6 and 3 mg/kg on days 1 and 2, 1·5 mg/kg weekly until week 12), but no immunosuppression.

Follow-up was until week 24.

The primary endpoint was the number of clinically relevant bleeds per patient-week until week 12.

Emicizumab was considered effective if the mean bleeding rate was significantly below 0.15 bleeds per week, the rate observed in study of and immunosuppression with propensity score matching (n=101).


100%
90%
80%
70%
60%
50%
Overall survival
0
4
8
12
16
20
24
Weeks
Immunosuppression (GTH-AH 01/2010)
Emicizumab (GTH-AHA-EMI)

Characterization of Joint Disease in Women with Hemophilia: The Carriers Ultrasound Project (CUP) Study – Kronenfeld, R

Between 2017-2023, women aged 18 to 40 yearsdivided in 2 cohorts.

The “carrier cohort” included women with a confirmed hemophilia A or B diagnosis, regardless of factor activity level.

Collected clinical information included presence of bleeding symptoms, joint-related symptoms, and historical use of hemostatic medications.

The “control cohort” included women without personal or family history of a bleeding disorder.

Participants underwent clinical and radiological assessment of bilateral elbows, knees, and ankles using the Hemophilia Joint Health Score (HJHS) and HEAD-US protocol. Factor activity levels were measured in the carrier cohort.

Carriers reported significantly higher prevalence of bleeding symptoms when compared to controls

heavy menstrual bleeding - epistaxis - gingival bleeding - easy bruising.

The majority (53.5%, n=15) of carriers joint-related symptoms when compared to controls, joint pain and joint swelling.

Three (10.7%) carriers reported history of overt joint bleeds.

Baseline factor activity level (>40% versus <40%), the prevalence of bleeding manifestations and joint-related symptoms were similar Carriers with factor levels <40% were more likely to require factor replacement on-demand (60% vs. 17.4%, p=0.046) and anti-fibrinolytics (60% vs. 17.4%, p=0.046) than carriers with factor levels >40%.

Table 1: Clinical Characteristics (N=58)			
Clinical Characteristic	Carriers (n=28)	Controls (n=30)	P Value
Age (years)			
Mean (SD)	31.4 (6.1)	30.2 (4.1)	P=0.39
Median (95% CI)	33.5 (29-35)	29.0 (28-33)	P=0.12
BMI			
Mean (SD)	25.9	24.5	P=0.24
Median (95% CI)	24.7	23.7	P=0.43
Factor Activity (%)			
Range	20-110	N/A	N/A
Mean (SD)	56 (21)	N/A	N/A
Median (95% CI)	54 (44-61)	N/A	N/A
Bleeding Tendency (N,%)			
Any Bleeding Tendency	23 (82.1%)	4 (13.3%)	**P<0.001**
Heavy Menstrual Bleeding	18 (64.3%)	3 (10.0%)	**P<0.001**
Epistaxis	7 (25%)	1 (3.3%)	**P=0.017**
Gingival Bleeding	7 (25%)	1 (3.3%)	**P=0.017**
Easy bruising	14 (50%)	1 (3.3%)	**P<0.001**
Joint Symptoms (N, %)			
Joint Pain	14 (50%)	1 (3.3%)	**P<0.001**
Joint Swelling	8 (28.6%)	0 (0%)	**P=0.02**
Joint Bleeding	3 (10.7%)	0 (0%)	P=0.07
Medications Prescribed (N, %)			
Factor Replacement	7 (25%)	0 (0%)	**P=0.003**
On-Demand	7 (25%)		
Prophylaxis	0 (0%)		
DDAVP	5 (17.9%)	0 (0%)	**P=0.015**
Anti-Fibrinolytic	7 (25%)	0 (0%)	**P=0.003**
HJHS Score			
Mean HJHS (SD)	4.7 (3.3)	1.5 (2.6)	**P<0.001**
Median HJHS (95% CI)	5.0 (4-6)	0	**P<0.001**
Abnormal HJHS (N, %)	24 (85.7%)	13 (43.3%)	**P=0.001**
HEAD-US Score			
Mean HEAD-US (SD)	0.04 (0)	0.17 (0.1)	P=0.24
Median HEAD-US (95% CI)	0	0	N/A
Abnormal HEAD-US (N, %)	1 (4%)	3 (10%)	P=0.41

Table 2: Comparison of Carriers by Factor Activity			
Characteristic	Factor Activity >40% (n=23)	Factor Activity <40% (n=5)	P Value
Age (years)			
Mean Age (SD)	31.1 (5.9)	32.6 (7.8)	P=0.63
Median Age (95% CI)	33.0 (29-36)	35 (34-39)	P=0.33
BMI			
Mean BMI (SD)	26.9 (5.3)	21.4 (2.7)	**P=0.03**
Median BMI (95% CI)	24.8 (23.4-30.1)	20.8 (20.3-26.1)	P=0.33
Factor Activity (%)			
Mean (SD)	61 (18)	30 (8)	P=0.001
Median (95% CI)	58 (53-71)	29 (27-39)	P=0.001
Bleeding Tendency (N, %)			
Any Bleeding Tendency	19 (82.6%)	4 (80%)	P=0.89
Heavy Menses	16 (69.6%)	2 (40%)	P=0.21
Epistaxis	6 (26.1%)	1 (20%)	P=0.78
Gingival Bleeding	6 (26.1%)	1 (20%)	P=0.78
Easy bruising	11 (47.8%)	3 (60%)	P=0.62
Joint Symptoms (N, %)			
Joint Pain	10 (43.5%)	3 (60%)	P=0.14
Joint Swelling	5 (21.7%)	4 (80%)	P=0.09
Joint Bleeding	3 (13%)	0 (0%)	P=0.39
Medications Prescribed (N, %)			
Factor Replacement	4 (17.4%)	3 (60%)	**P=0.046**
On-Demand	4 (17.4%)	3 (60%)	
Prophylaxis	0 (0%)	0 (0%)	
DDAVP	3 (13%)	2 (40%)	P=0.15
Anti-Fibrinolytic	4 (17.4%)	3 (60%)	**P=0.046**
HJHS Score			
Mean HJHS (SD)	4.3 (3.4)	6.6 (2.6)	P=0.16
Median HJHS (95% CI)	4.0 (3-6)	6 (6-10)	P=0.06
Abnormal HJHS (N, %)	19 (82.6%)	5 (100%)	P=0.31
HEAD-US Score			
Mean HEAD-US (SD)	0	0.2 (0.5)	P= 0.31
Median HEAD-US (95% CI)	0	0	N/A
Abnormal HEAD-US (N, %)	0	1 (20%)	P=0.06

Hereditary Hemorrhagic Telangiectasia May be the Most Clinically Significant and Morbid Inherited Bleeding Disorder of Women – Zhang, E

Observational cohort study of women with HHT or VWD

Using an electronic patient data registry, a representative sample of 100 randomly selected women with HHT were age-matched to 100 randomly selected women with VWD for analysis.

In women with HHT compared with VWD, recurrent epistaxis and GI bleeding were more likely and heavy menstrual bleeding was less likely.

Iron deficiency anemia was significantly more likely, and lowest hemoglobin significantly lower, in HHT versus VWD. Requirements for IV iron and RBC transfusion were significantly more likely in HHT versus VWD. Women with HHT had 17-fold higher odds of iron infusion dependence and 8-fold higher odds of requiring hemostatic surgical procedures than women with VWD.

	Hereditary hemorrhagic telangiectasia N = 100	Von Willebrand disease N = 100	Odds ratio (95% CI) for incidence in HHT group relative to VWD group	*P* value
Incidence of Bleeding by Site				
Recurrent epistaxis, n (%)	92 (92)	26 (26)	32.73 (13.81-71.80)	<0.0001†
Gastrointestinal bleeding, n (%)	36 (36)	9 (9)	5.69 (2.59-12.89)	<0.0001†
Heavy menstrual bleeding, n (%)	35 (35)	63 (63)	0.32 (0.18-0.57)	<0.0001†
Other bleeding, n (%)	12 (12)	16 (16)	0.72 (0.31-1.57)	0.42†
Hemoglobin, Hematologic Support Requirements, and Interventions				
Lowest measured hemoglobin, median (IQR)	10.7 (7.9-12.6)	11.4 (9.9-12.5)	n/a	0.02^
Iron deficiency anemia, n (%)	66 (66)	50 (50)	1.94 (1.09-3.41)	0.02†
Requirement for intravenous iron, n (%)	41 (41)	10 (10)	6.25 (2.99-12.78)	<0.0001†
Intravenous iron dependence*, n (%)	26 (26)	2 (2)	17.22 (4.49-74.77)	<0.0001‡
Requirement for red cell transfusion, n (%)	42 (42)	21 (21)	2.72 (1.45-4.99)	0.001†
Requirement for hemostatic procedure**, n (%)	78 (78)	31 (31)	7.89 (4.16-14.60)	<0.0001†
Hemostatic procedures, per 100 patient-years	27.2	3.0	n/a	<0.0001ᵛ
Death due to bleeding complications, n (%)	3 (3)	0 (0)	n/a	0.25‡

*Defined as a requirement for ≥2000 mg elemental iron infused over any contiguous 12-month period.
**Included surgical or other interventional procedures in the uterus to manage heavy menstrual bleeding (e.g., hysterectomy), nasal cavity to manage epistaxis (e.g., nasal cautery), GI tract to manage GI bleeding (e.g., endoscopy), or other interventional procedures done to manage bleeding at any site.

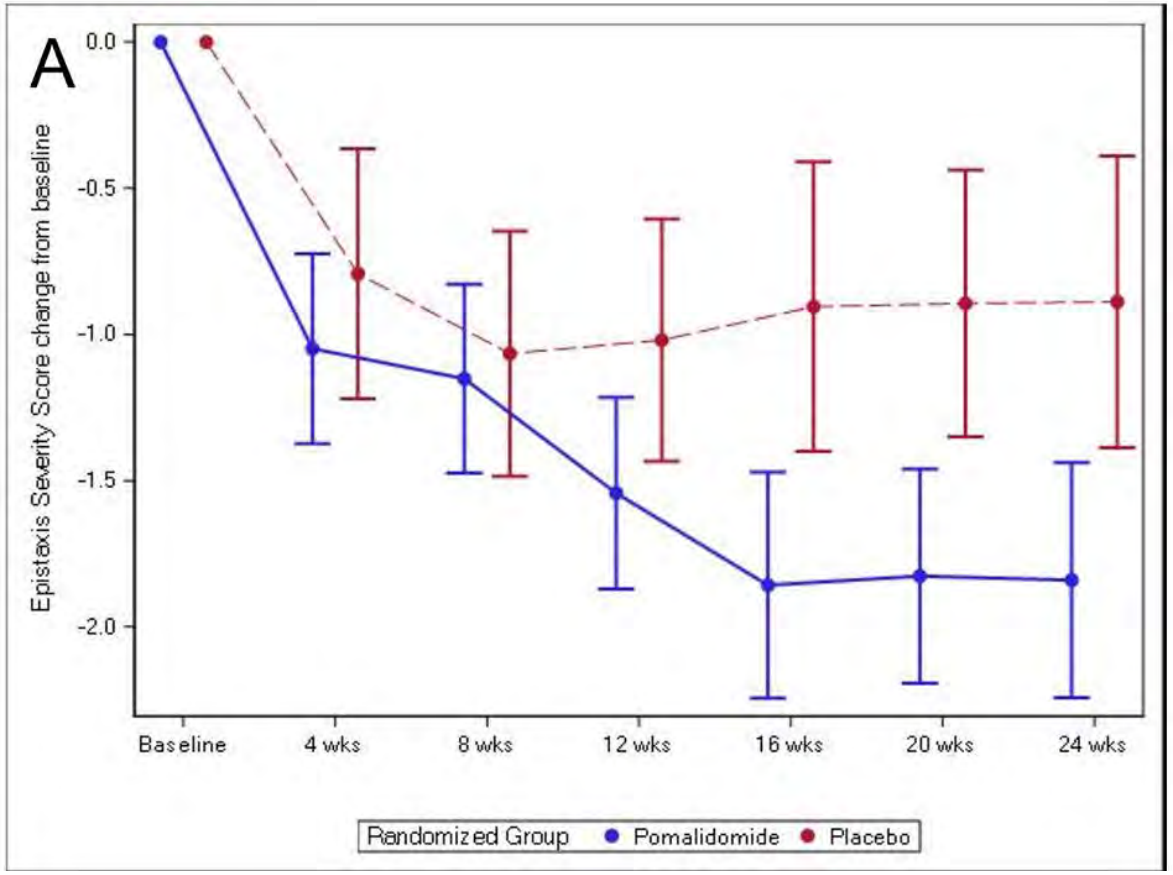
	Hereditary hemorrhagic telangiectasia N = 100	Von Willebrand disease N = 100	*P* value‡
Emergency Department (ED) Visits and Hospital Admissions Specifically for HHT or VWD Management			
Requirement for ED visit*, n (%)	25 (25)	8 (8)	0.001†
ED visits, per 100 patient-years	10.3	0.74	0.001
Requirement for hospital admission, n (%)	50 (50)	12 (12)	<0.0001†
Hospital admissions, per 100 patient-years	14.4	1.0	<0.0001
Length of hospital stay, mean (range)	5.5	4.3	0.47
*Outpatient Encounters** Specifically for HHT or VWD Management*			
Any outpatient encounter, per 100 patient-years	386.5	43.7	<0.0001
Primary care provider, per 100 patient-years	37.9	19.1	0.28
Hematology, per 100 patient-years	62.3	11.3	0.005
Pulmonology, per 100 patient-years	36.5	0.1	<0.0001
Cardiology, per 100 patient-years	4.3	0.9	0.005
Gastroenterology, per 100 patient-years	14.7	0.9	<0.0001
Otolaryngology, per 100 patient-years	18.3	0.7	<0.0001
Obstetrics & Gynecology, per 100 patient-years	4.4	5.9	0.003
Medical Genetics, per 100 patient-years	7.7	0.0	<0.0001
Dermatology, per 100 patient-years	5.1	0.0	0.003
Outpatient infusion, per 100 patient-years	97.6	5.3	<0.0001
Radiology/imaging, per 100 patient-years	74.0	0.3	<0.0001
Other, per 100 patient-years	23.3	1.3	<0.0001

LBA-3 PATH-HHT, a Double-Blind, Randomized, Placebo-Controlled Trial in Hereditary Hemorrhagic Telangiectasia Demonstrates That Pomalidomide Reduces Epistaxis and Improves Quality of Life -

Patients were randomized in a 2:1 ratio to receive pomalidomide 4 mg daily or matching placebo for 6 months. Dose reductions were allowed for toxicity.

The primary endpoint was the change in the Epistaxis Severity Score (ESS) from baseline (randomization) to the end of the six-month treatment period

1) change in the average daily self-reported epistaxis duration from the four weeks preceding the baseline visit to weeks 20-24 of treatment, 2) amount of parenteral iron infused or blood transfused, and 3) change in QOL measurements, including an HHT-specific QOL score.



Early study discontinuation was 25% in pomalidomide: 14% AE, 11% withdrawn, 1 unrelated death, compared with placebo (4% withdrawn). Across groups, 8% were terminated after 12 weeks for early study closure.

At 24 weeks, the ESS in patients treated with pomalidomide decreased by a mean [95% CI] of -1.84 [-2.24, -1.44] and in the placebo group decreased by -0.89 [-1.39, -0.39] (mean difference -0.95 [-1.58, -0.32], p = 0.003)

Adverse events that occurred more in the pomalidomide group included mild to moderate neutropenia (45% vs. 10%), constipation/diarrhea (60% vs. 37%), and rash (36% vs. 10%). Venous thrombosis occurred in 2% of patients in each group.

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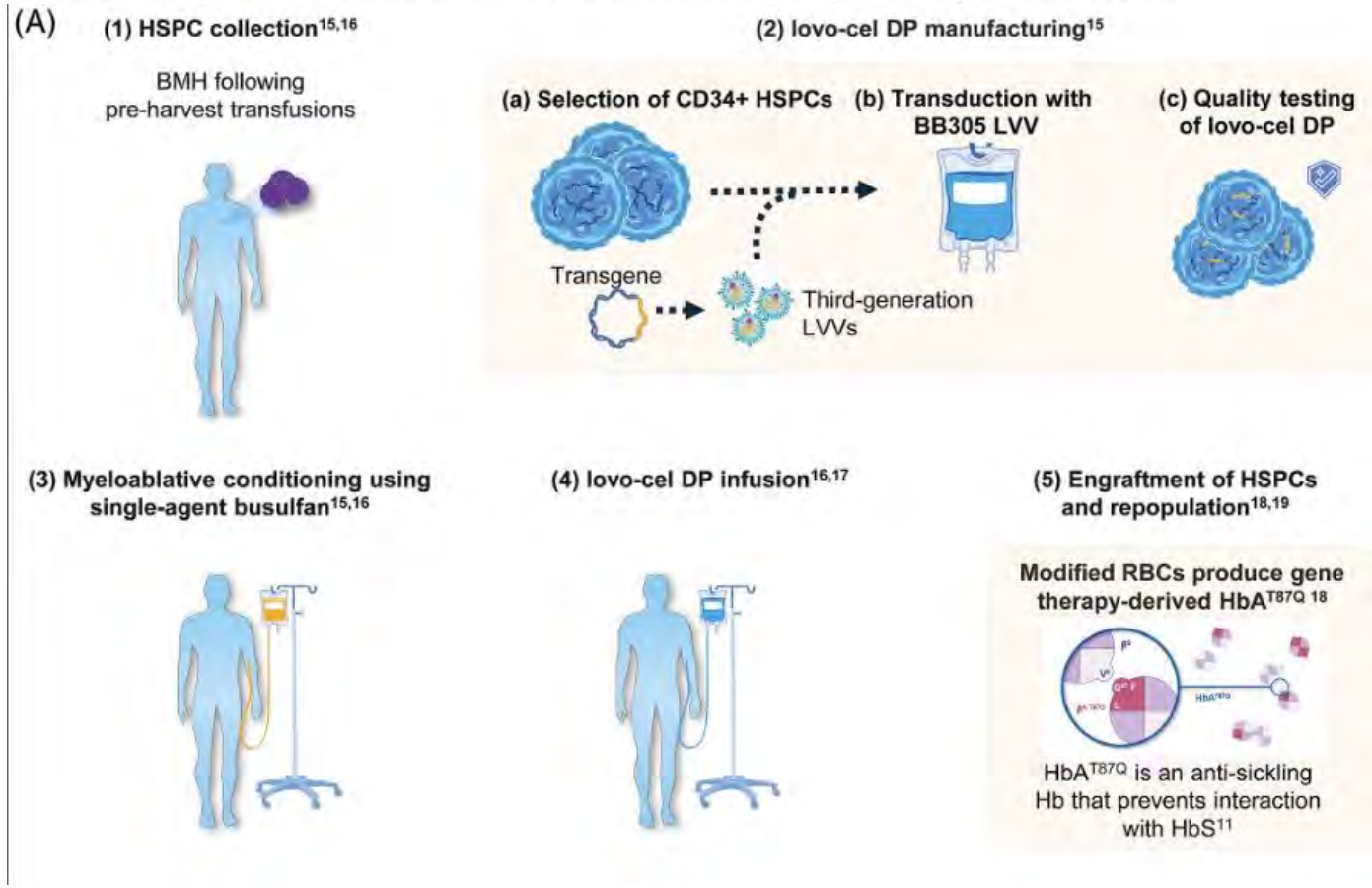
RESEARCH ARTICLE | Open Access

Lovo-cel gene therapy for sickle cell disease: Treatment process evolution and outcomes in the initial groups of the HGB-206 study



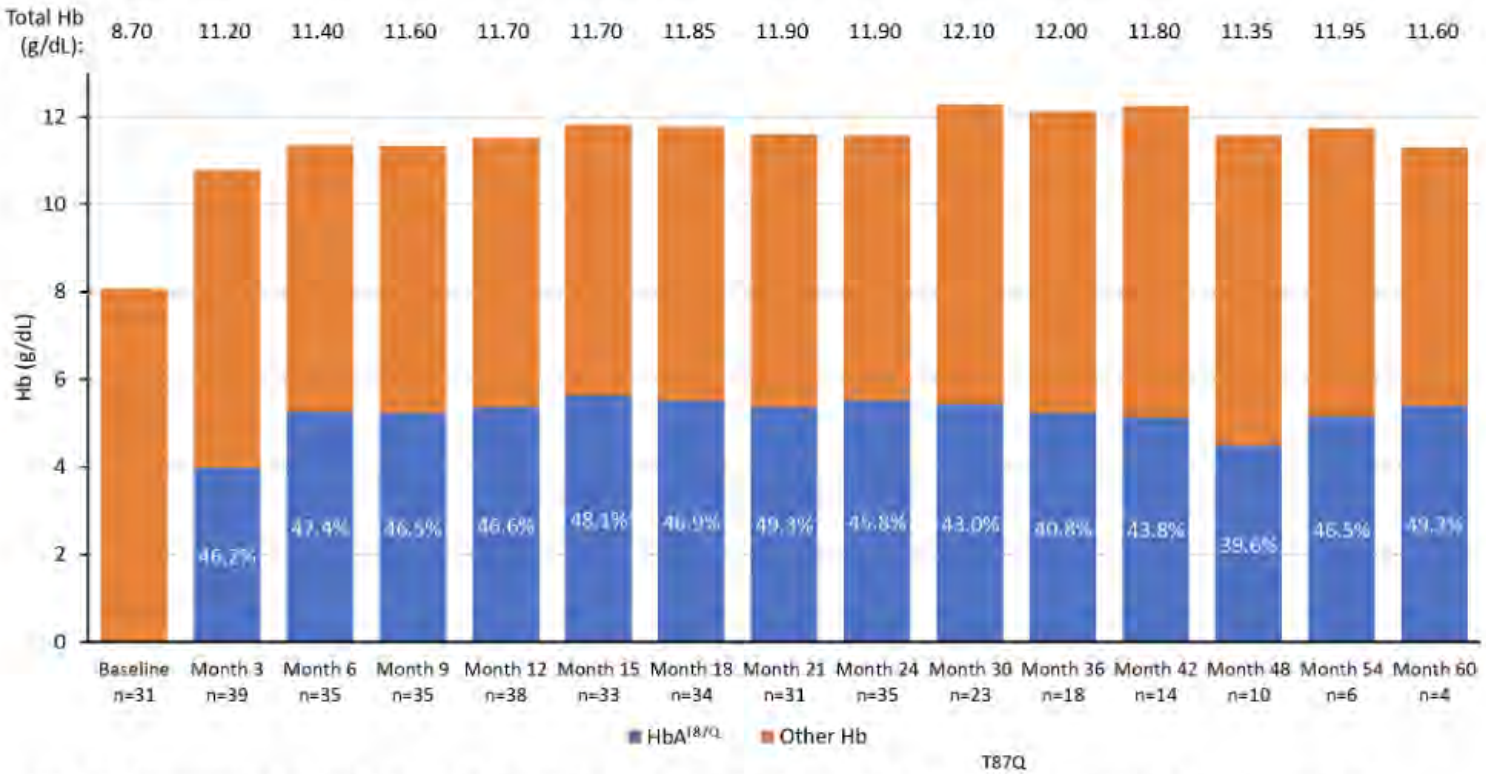
Efficacy, Safety, and Health-Related Qualiay of Life (HRQOL) in Patients with Sickle Cell Disease (SCD) Who Have Received Lovotibeglogene Autotemcel (Lovo-cel) Gene Therapy: Up to 60 Months of Follow-up - Kanter J.

Patients with SCD and recurrent severe vaso-occlusive events (VOEs) or history of overt stroke underwent plerixafor mobilization and apheresis followed by myeloablative busulfan conditioning and lovo-cel infusion. After 24 months of follow-up post lovo-cel infusion, patients enrolled in the long-term study LTF-307 Lab evaluations, SCD-related outcomes (eg, resolution of VOEs), globin response (a composite endpoint evaluating HbA^{T87Q} percentage and total Hb), and safety are reported up to 60 months.

47 patients (medianage, 23 y [12-38]) received a lovo-cel infusion. Median (range) time to neutrophil and platelet engraftment was 20 days (12-35) and 35 days (19-136). Peripheral blood vector copy number remained stable (median >1 c/dg through follow-up)

Median HbAT87Q levels were ≥4.5 g/dL from 6 months post infusion to last study visit. Median (range) total Hb level increased from 8.7 g/dL (6.1-12.5) at relative baseline to 11.8 g/dL (8.4-15.0) at last visit; median percent HbAT87Q of nontransfused total Hb was ≈40% or more

Figure. Total Hb and HbA^{T87Q} fraction for HGB-206 Group C and HGB-210 combined



Data are reported as of Feb 13, 2023. Percentages represent the median HbA fraction as a percentage of nontransfused total Hb. Values above each bar represent the median total Hb at each visit and are not equivalent to the sum of the individual Hb fraction medians. The baseline was an average of 2 qualified, total Hb values (measured in g/dL) during the 24 months before study enrollment.

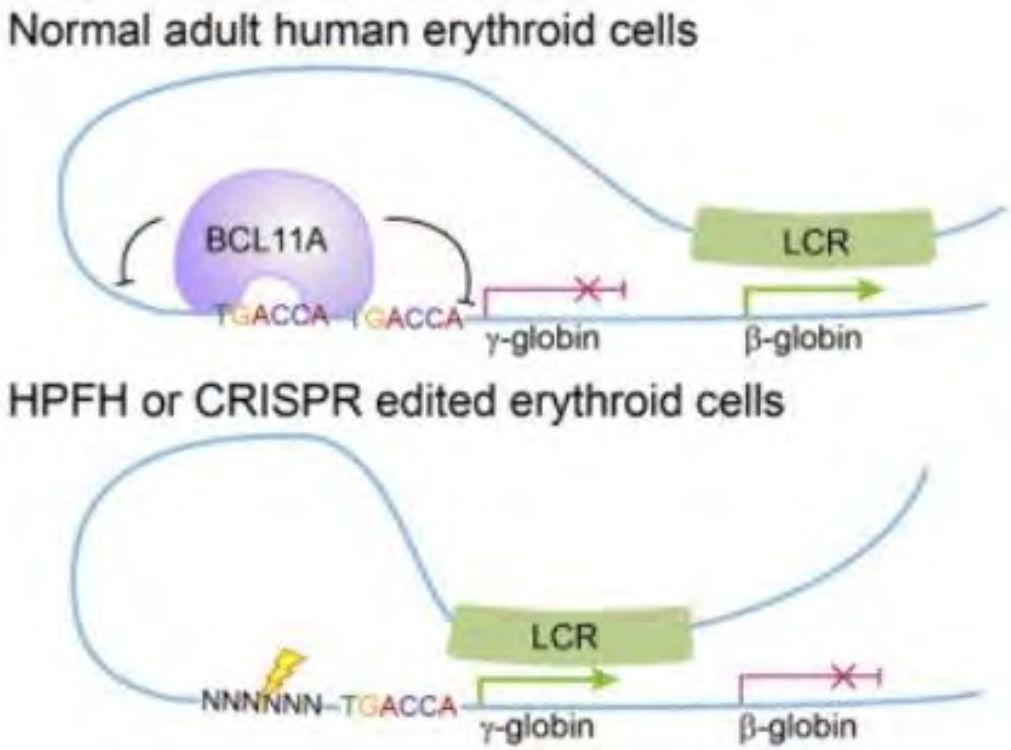
Hb, hemoglobin; HbA, adult Hb; HbA^{T87Q}, anti-sickling Hb.

Table. PROMIS-57 patient-reported HRQOL for HGB-206 Group C

	Pain intensity[a]	Pain interference[b]	Fatigue[b]
Baseline score, mean (SD) (n=25)	4.8 (2.49)	58.4 (10.24)	53.8 (10.57)
Change from baseline, mean (SD)			
Month 6 (n=20)	-3.0 (2.32)	-10.2 (8.80)	-6.2 (9.74)
Month 12 (n=22)	-2.4 (2.48)[c]	-9.3 (11.84)	-6.9 (11.78)
Month 24 (n=19)	-2.3 (2.70)[d]	-9.5 (9.41)	-8.7 (9.45)
Month 36 (n=14)	-2.2 (2.29)	-9.9 (11.86)	-7.7 (11.51)
Month 48 (n=9)	-1.9 (2.89)	-11.0 (8.13)	-1.4 (8.80)

Exagamglogene Autotemcel for Severe Sickle Cell Disease - Frangoul

Exagamglogene autotemcel (exa-cel) is a non-viral cell therapy designed to reactivate fetal hemoglobin via ex vivo CRISPR-Cas9 gene-editing of autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) at the erythroid-specific enhancer region of the BCL11A gene in patients (pts) with severe sickle cell disease (SCD).



CLIMB SCD-121 is an ongoing, 24-mo, phase 3 trial of exa-cel in pts age 12-35y with SCD and a history of ≥2 VOCs/y in 2y prior to screening.

Primary efficacy endpoint is proportion of pts free of severe VOCs for ≥12 consecutive months (mos) (VF12); key secondary efficacy endpoints are proportion of pts free from inpatient hospitalization for severe VOCs for ≥12 consecutive mos (HF12) and proportion of pts free from severe VOCs for ≥9 consecutive mos (VF9). Evaluable pts for VF12 and HF12 had ≥16 mos follow-up after exa-cel infusion; pts evaluable for VF9 had ≥12 mos follow-up after infusion.

42 pts with SCD (age 21.2 [range 12-34]y; 12[28.6%] age ≥12 to <18y; 4.2 VOCs/y at baseline) received exa-cel.

Following infusion, all pts engrafted neutrophils and platelets (median 27 and 34.5 days, respectively).

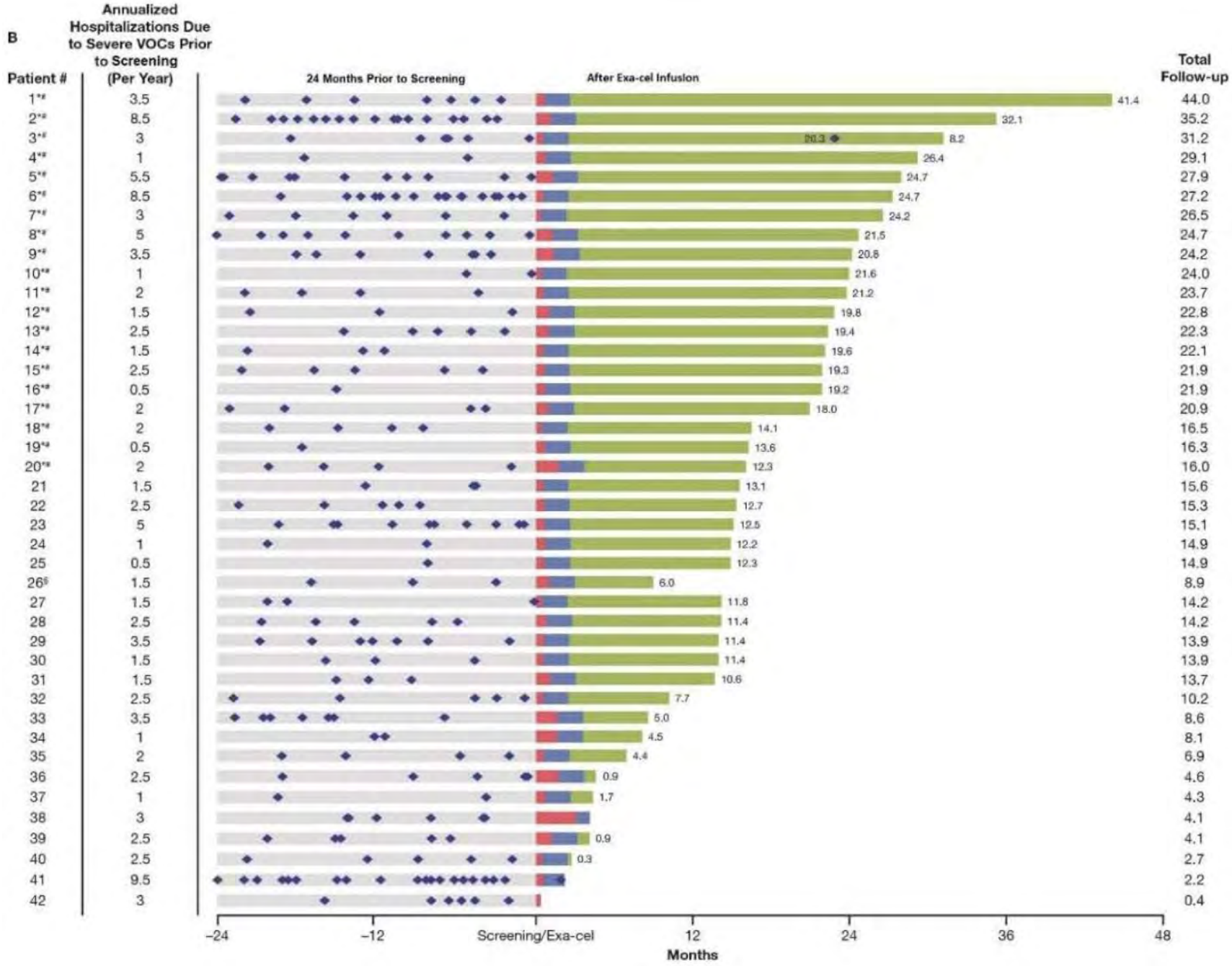
19/20 (95.0%) pts evaluable for primary endpoint were free of VOCs for ≥12 consecutive mos

20/20 (100%) were free from hospitalizations for VOCs for ≥12 consecutive mos (HF12; 95% CI, 83.2 to 100.0; P<0.0001)
29/30 (96.7%) were free of VOCs for ≥9 consecutive mos (VF9; 95% CI, 82.8 to 99.9; P<0.0001)

For all pts, total Hb was 12.1 g/dL at Month 3 and was maintained at ≥11.0 g/dL from Month 6 onward; HbF was 36.0% at Month 3 and was generally maintained at ≥ 40.0% from Month 6 onward with pancellular distribution (≥95% RBCs expressing HbF).

Proportion of edited *BCL11A* alleles was stable over time in bone marrow $CD34^+$ and peripheral blood nucleated cells. 36/39 pts with ≥60 days follow-up after last RBC transfusion (including those not yet evaluable) remained VOC free (up to 41.4 mos; Fig). Quality-of-life (QOL) measures showed clinically significant improvements from baseline.

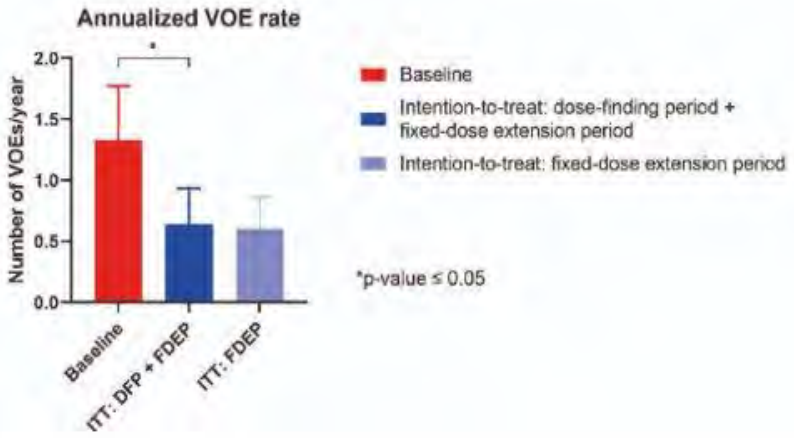
All pts had ≥1 adverse event (AE), most were Grade 1 or 2; 40 (95.2%) pts had AEs of Grade 3 or 4 severity. Most common AEs were nausea (66.7%), stomatitis (61.9%), febrile neutropenia (52.4%), headache (52.4%), and vomiting (52.4%). Most AEs and serious AEs (SAEs) occurred within first 6 mos after infusion. No pts had SAEs considered related to exa-cel. As previously reported, 1 pt died from respiratory failure due to COVID-19 unrelated to exa-cel. There were no study discontinuations or malignancies.


B
Annualized Hospitalizations Due to Severe VOCs Prior to Screening (Per Year)
Patient #
24 Months Prior to Screening
After Exa-cel Infusion
Total Follow-up
1*‡ 3.5 41.4 44.0
2*‡ 8.5 32.1 35.2
3*‡ 3 20.3 8.2 31.2
4*‡ 1 26.4 29.1
5*‡ 5.5 24.7 27.9
6*‡ 8.5 24.7 27.2
7*‡ 3 24.2 26.5
8*‡ 5 21.5 24.7
9*‡ 3.5 20.8 24.2
10** 1 21.6 24.0
11** 2 21.2 23.7
12** 1.5 19.8 22.8
13** 2.5 19.4 22.3
14** 1.5 19.6 22.1
15** 2.5 19.3 21.9
16** 0.5 19.2 21.9
17** 2 18.0 20.9
18** 2 14.1 16.5
19** 0.5 13.6 16.3
20** 2 12.3 16.0
21 1.5 13.1 15.6
22 2.5 12.7 15.3
23 5 12.5 15.1
24 1 12.2 14.9
25 0.5 12.3 14.9
26§ 1.5 6.0 8.9
27 1.5 11.8 14.2
28 2.5 11.4 14.2
29 3.5 11.4 13.9
30 1.5 11.4 13.9
31 1.5 10.6 13.7
32 2.5 7.7 10.2
33 3.5 5.0 8.6
34 1 4.5 8.1
35 2 4.4 6.9
36 2.5 0.9 4.6
37 1 1.7 4.3
38 3 4.1
39 2.5 0.9 4.1
40 2.5 0.3 2.7
41 9.5 2.2
42 3 0.4
−24
−12
Screening/Exa-cel
12
24
36
48
Months

A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study of Mitapivat in Patients with Sickle Cell Disease: RISE UP Phase 2 Results – va Dijk, M.

Mitapivat, an oral allosteric activator of pyruvate kinase (PK), has shown therapeutic potential by increasing adenosine triphosphate (ATP) and decreasing 2,3-diphosphoglycerate (2,3-DPG), a glycolytic red blood cell (RBC) intermediate. In addition to improving anemia and hemolysis, mitapivat may reduce HbS polymerization and inhibit sickling by decreasing 2,3-DPG levels in patients with SCD.

The ESTIMATE study is a phase 2, investigator initiated, open-label study in which subjects ≥16 years with SCD (HbSS, HbS/β0, HbS/β+) with a baseline hemoglobin (Hb) >4.0 g/dL and ≤11.1 g/dL, no chronic transfusion and adequate organ function were eligible. After the 8-week DFP in which patients were dosed mitapivat 20 mg, 50 mg or 100 mg twice daily depending on safety, patients could continue in the 1-year FDEP. The primary endpoints were safety, evaluated by frequency and severity of adverse events (AEs), and efficacy of mitapivat including the evaluation of a hematological response (improvement in mean Hb level of ≥1 g/dL compared to baseline during the FDEP).



	Baseline (n=9)	*End of DFP (n=9)*	Mean of FDEP (n=9)	p-value (baseline vs mean of FDEP)
Hb, g/dL	8.8 (1.8)	*10.3 (1.3)*	9.9 (1.8)	0.0014
Reticulocytes:				
ARC, 10^9/L	235 (88)	*141 (50)*	156 (50)	0.0038
% of RBCs	8.2 (2.3)	*4.2 (1.4)*	5.0 (1.4)	0.0003
Total bilirubin, mg/dL	2.6 (1.3)	*1.2 (0.5)*	1.4 (0.7)	0.0025
LDH, U/L	500 (307)	*328 (113)*	401 (224)	0.0217
ATP, mg/gHb	2.9 (0.7)	*3.6 (0.5)*	3.6 (0.5)	0.1386
2,3-DPG, mg/gHb	11.4 (1.0)	*7.9 (1.1)*	9.0 (1.1)	0.0004
ATP/2,3-DPG ratio	0.25 (0.05)	*0.46 (0.09)*	0.40 (0.06)	0.0009
p50, mmHg	24.0 (2.4)	*21.5 (1.4)*	22.5 (1.8)	0.0032
PoS, mmHg	40.2 (8.8)*	*33.1 (9.7)**	36.2 (6.3)*	0.0802
Annualized VOE rate:				
- DFP + FDEP	1.33 (1.32)	0.64 (0.87)		0.0489†
- FDEP	1.33 (1.32)	*0.72 (2.17)*	0.60 (0.78)	0.0625
Annualized SCD-related hospital admission days	5.3 (7.0)	*0.0 (0.0)*	4.1 (5.6)	0.4452

*Due to technical issues of the oxygen gradient ektacytometer, data is missing of n=1 patient, a week 52 visit (n=1 patient) and four visits from week 24 to week 52 in the FDEP (n=2 patients).

†ITT analysis of baseline versus the total period on study drug treatment (DFP and FDEP combined) instead of only the FDEP.

Many Thanks

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