Indirect treatment comparison of marstacimab versus fitusiran antithrombin-based dose regimen among individuals with hemophilia A/B, without inhibitors, who previously received on-demand therapy

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INTRODUCTION

- Hemophilia A and B are rare inherited bleeding disorders caused by deficiencies or dysfunction of FVIII and FIX, respectively, and are characterized by spontaneous bleeding and prolonged bleeding after trauma or surgery.
- Individuals with severe hemophilia may experience recurrent joint and muscle bleeds, which can contribute to chronic arthropathy, functional impairment, and reduced health-related quality of life if inadequately controlled.
- Although prophylaxis with factor replacement therapy is recommended as the standard of care for severe hemophilia to prevent bleeding episodes and preserve joint health, a subset of patients continue to receive on-demand treatment.
- Marstacimab is a subcutaneously administered, fully human monoclonal antibody targeting tissue factor pathway inhibitor. It was evaluated as prophylaxis therapy among adolescents and adults with severe hemophilia A or moderately severe to severe hemophilia B in the Phase 3 BASIS trial.[1]
- Fitusiran is a subcutaneously administered prophylactic therapy evaluated using an antithrombin-based dose regimen (AT-DR) in the ATLAS-OLE trial.[2]
- In the absence of direct comparative evidence, population-adjusted indirect treatment comparison methods can estimate relative efficacy while accounting for cross-trial heterogeneity.

OBJECTIVE

- To estimate the comparative efficacy of marstacimab versus fitusiran among adolescents and adults with inherited severe hemophilia A or moderately severe to severe hemophilia B, without inhibitors, who had received prior on-demand therapy, as assessed by the primary outcome of treated bleeds and other secondary bleeding outcomes.

METHODS

Evidence base

- A systematic literature review identified clinical trial evidence for treatments in adolescents and adults with severe hemophilia A or moderately severe to severe hemophilia B without inhibitors.
- The feasibility assessment included the Phase 3 BASIS trial for marstacimab and ATLAS-OLE trial for fitusiran.

Study populations

- Individual patient-level data (IPD) for marstacimab were obtained from the BASIS non-inhibitor modified intent-to-treat population, including patients who transitioned from prior on-demand factor replacement therapy to marstacimab 150 mg once weekly.[1]
- Published aggregate-level data for fitusiran were obtained from ATLAS-OLE Pool B, which included patients without inhibitors who had received prior on-demand therapy in the ATLAS-A/B parent study and were subsequently treated with fitusiran AT-DR in ATLAS-OLE.[2] ATLAS-OLE included two additional subgroups (Pool A and C); however, these subgroups were excluded from the analyses because Pool A was exclusively comprised of patients with inhibitors and Pool C was comprised of patients with and without inhibitors. Data from the ATLAS-A/B parent study was not included because fitusiran was administered according to a nonapproved dosing schedule; therefore, aggregate data from ATLAS-OLE Pool B were used to reflect the approved fitusiran regimen and non-inhibitor population.

Outcomes

- Outcomes included annualized bleeding rates (ABR) and the percentage of patients with 0 to 1 bleeding events for treated, treated spontaneous, and treated joint bleeds. To align with the reporting period used in ATLAS-OLE, ABRs for marstacimab were re-derived using BASIS IPD limited to the first 196 days (approximately 28 weeks) of follow-up. Total bleeding events were not reported for ATLAS-OLE Pool B.
- Rate ratios were estimated for annualized bleeding rate outcomes and odds ratios were estimated for binary zero-bleed outcomes, with rate ratios below 1.00 and odds ratios above 1.00 favoring marstacimab.

Statistical analysis

- Unanchored indirect treatment comparison was used as both BASIS and ATLAS-OLE did not include a common comparator arm. Simulated treatment comparison (STC) methods were used instead of a matching-adjusted indirect comparison (MAIC) approach due to large baseline covariate imbalances between trials and small sample size.[3-5]
- STC is an outcome regression-based approach. Analyses were implemented following the approach outlined in Ren et al. (2024)[6] in which an outcome regression model was fit on the IPD from the BASIS trial, baseline covariate data were simulated for the ALTAS-OLE trial population, and the STC-adjusted marginal outcome was estimated by using the outcome regression model fit on the IPD to predict outcomes in the simulated comparator trial dataset. The standard error of the STC-adjusted outcomes was estimated using bootstrapping.
- Covariate profiles were jointly simulated using the marginal covariate summaries reported for ATLAS-OLE and the correlation structure observed in BASIS. Prior bleeding events were simulated using a negative binomial distribution, other continuous covariates using normal distributions.
- All analyses were conducted using R version 4.4.2.

RESULTS

Baseline comparability

- The analysis included 33 individuals from BASIS and 80 individuals from ATLAS-OLE Pool B. Baseline characteristics are presented in Table 1.
- STC analyses adjusted for baseline imbalances in age (continuous), number of bleeding events in the prior six months (continuous), and weight (continuous). Because all patients in the BASIS prior on-demand subgroup had at least 1 target joint, this variable could not be adjusted for in the analysis.

Table 1: Baseline characteristics for individuals with hemophilia A/B without inhibitors who had prior on-demand therapy for marstacimab (BASIS) versus fitusiran (ATLAS-OLE, Pool B)

Baseline covariate	BASIS (Hem A/B and prior OD) N = 33	ATLAS-OLE (Pool B) N = 80	ASD
Patient characteristics			
*Age (years), mean (SD)	31.9 (11.0)	33.9 (14.6)	0.155
Adolescent (12 to <18 years), n (%)	2 (6.1%)	NR	-
Male, n (%)	33 (100.0%)	80 (100.0%)	0.000
White, n (%)	11 (33.3%)	33 (41.3%)	0.164
Hispanic/Latino, n (%)	3 (9.1%)	3 (3.9%)	0.209
Body mass index (kg/m2), mean (SD)	23.2 (5.6)	NR	-
*Weight (kg), mean (SD)	68.2 (19.1)	73.0 (19.1)	0.251
Disease characteristics			
Hemophilia A, n (%)	26 (78.8%)	62 (77.5%)	0.031
Without inhibitors, n (%)	33 (100.0%)	80 (100.0%)	0.000
Severe disease, n (%)	33 (100.0%)	80 (100.0%)	0.000
*Bleeding events in prior 6 months, mean (SD)	23.9 (13.1)	11.5 (6.4)[a]	1.202
≥1 target joints, n (%)	33 (100.0%)	53 (66.3%)	1.009
Prior treatment characteristics			
Prior on-demand, n (%)	33 (100.0%)	80 (100.0%)	0.000
Prior extended half-life, n (%)	6 (18.2%)	NR	-

Covariates adjusted for in the analysis; ASD ≥ 0.10 may indicate meaningful imbalance in baseline characteristics between trials
[a]*Mean (SD) of bleeding events in prior 6 months was derived from median with interquartile range (10 [8.0,16.5]) using approach described by Wan et al. (2014)[7]*
Abbreviations: ABR, annualized bleeding rate; ASD, absolute standardized difference; NR, not reported; SD, standard deviation

Comparative efficacy

- After a median follow-up of approximately 28 weeks and after adjusting for baseline imbalances, marstacimab was associated with statistically significantly lower ABRs relative to fitusiran with respect to all available ABR outcomes and percentage of 0 to 1 bleeding events (primary and secondary), including treated bleeds, treated spontaneous bleeds, and treated joint bleeds (Table 2, Table 3).
- After adjustment, the primary outcome treated ABR for marstacimab was 77% lower than that of fitusiran (rate ratio [95% CI]: 0.23 [0.08, 0.70]; p = 0.009).
- These findings were consistent when assessing outcomes as the percent of patients with 0-1 bleeding events (Table 3).

Table 2: Results from the simulated treatment comparisons of marstacimab (BASIS) versus fitusiran (ATLAS-OLE, Pool B): Annualized bleeding rate

Outcome	Trial	Number of patients	ABR (95% CI)	Rate ratio (95% CI)	P-value
Treated bleeds	A) BASIS: Unadjusted	33	3.85 (2.31, 6.43)	0.43 (0.21, 0.86)	0.017
	B) BASIS: STC (marginal)	33	2.10 (0.78, 5.63)	0.23 (0.08, 0.70)	0.009
	C) ATLAS-OLE, Pool B	80	9.01 (5.59, 14.53)	Reference	-
Treated spontaneous bleeds	A) BASIS: Unadjusted	33	2.72 (1.74, 4.26)	0.50 (0.28, 0.91)	0.024
	B) BASIS: STC (marginal)	33	1.76 (0.79, 3.91)	0.33 (0.13, 0.79)	0.013
	C) ATLAS-OLE, Pool B	80	5.40 (3.65, 7.98)	Reference	-
Treated joint bleeds	A) BASIS: Unadjusted	33	3.34 (2.00, 5.58)	0.54 (0.28, 1.03)	0.062
	B) BASIS: STC (marginal)	33	1.50 (0.65, 3.45)	0.24 (0.10, 0.61)	0.003
	C) ATLAS-OLE, Pool B	80	6.18 (4.18, 9.14)	Reference	-

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; STC, simulated treatment comparison
Note: RRs < 1.00 favor marstacimab and RRs > 1.00 favor the comparator treatment

Table 3: Results from the simulated treatment comparisons of marstacimab (BASIS) versus fitusiran (ATLAS-OLE, Pool B): Percent with 0-1 bleeds

Outcome	Trial	Number of patients	% with 0-1 bleeds (95% CI)	Odds ratio (95% CI)	P-value
Treated bleeds	A) BASIS: Unadjusted	33	66.7 (49.2, 80.5)	2.85 (1.18, 6.87)	0.020
	B) BASIS: STC (marginal)	33	87.2 (55.7, 97.4)	9.72 (1.67, 56.73)	0.011
	C) ATLAS-OLE, Pool B	63[a]	41.3 (29.9, 53.7)	Reference	-
Treated spontaneous bleeds	A) BASIS: Unadjusted	33	69.7 (52.3, 82.9)	2.09 (0.86, 5.10)	0.105
	B) BASIS: STC (marginal)	33	86.2 (57.0, 96.7)	5.68 (1.12, 28.92)	0.036
	C) ATLAS-OLE, Pool B	63[a]	52.4 (40.2, 64.3)	Reference	-
Treated joint bleeds	A) BASIS: Unadjusted	33	72.7 (55.3, 85.2)	2.93 (1.18, 7.30)	0.021
	B) BASIS: STC (marginal)	33	90.9 (54.4, 98.8)	11.02 (1.24, 98.01)	0.031
	C) ATLAS-OLE, Pool B	63[a]	47.6 (35.7, 59.8)	Reference	-

aOnly participants with at least 1 dose of treatment and an evaluable follow-up duration in the efficacy period were included
Abbreviations: CI, confidence interval; ESS, effective sample size, MAIC, matching-adjusted indirect comparison; STC, simulated treatment comparison
Note: ORs > 1.00 favor marstacimab and ORs < 1.00 favor the comparator treatment

DISCUSSION & LIMITATIONS

- This unanchored STC suggests that marstacimab may provide greater bleed protection than fitusiran among patients without inhibitors who had received prior on-demand therapy.
- Because the validity of unanchored STC results depends on the assumption that all relevant prognostic factors and effect modifiers have been adequately accounted for, residual confounding due to measured or unmeasured differences between studies cannot be fully excluded.
- Some potentially relevant covariates could not be evaluated or adjusted for. In particular, target joints could not be adjusted for because 100% of BASIS patients had at least one target joint (versus 66/3% in ATLAS-OLE Pool B), and prior factor class was not reported for ATLAS-OLE Pool B. However, these limitations would be expected to favor fitusiran, as the BASIS population appeared to have greater baseline disease burden.
- The relatively small sample sizes available for comparison may also limit the precision of the estimated treatment effects and increase uncertainty around the results. Nevertheless, the consistency of findings across multiple bleeding outcomes supports the overall robustness of the observed treatment effect.
- Differences in study design and outcome assessment should also be considered, including the shorter follow-up period in ATLAS-OLE Pool B (for which BASIS ABRs were recalculated over a comparable duration) and the fitusiran treatment pause and restart at a revised dose schedule. The analysis was based on 28 weeks of follow-up, so findings may not be generalizable to longer follow-up durations.

CONCLUSIONS

- Among adolescents and adults with severe hemophilia A or moderately severe to severe hemophilia B without inhibitors who had received prior on-demand therapy, marstacimab may provide superior bleed protection relative to fitusiran based on an unanchored population-adjusted indirect comparison.
- Results were consistent across multiple bleeding related outcomes, although interpretation should account for residual confounding, limited covariate reporting, and dosing context.
- Further evidence would be valuable to evaluate comparative efficacy among patients who previously received prophylaxis and to assess longer-term outcomes.

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