Abstract: S303

Title: A PHASE 3 STUDY (ATLAS-PPX) TO EVALUATE EFFICACY AND SAFETY OF FITUSIRAN IN PEOPLE WITH HAEMOPHILIA A OR B WHO HAVE SWITCHED FROM PRIOR CLOTTING FACTOR CONCENTRATE OR BYPASSING AGENT PROPHYLAXIS

Abstract Type: Oral Presentation

Session Title: Advances in the science and care of persons with bleeding disorders

Background:

Fitusiran, a subcutaneous (SC) investigational siRNA therapeutic, targets antithrombin to rebalance haemostasis in people with haemophilia A or B (PwHA/B), irrespective of inhibitor status. In previous Phase 3 trials, once-monthly fitusiran prophylaxis significantly reduced annualised bleeding rate (ABR) in PwHA/B, with or without inhibitors versus episodic/on-demand treatment.

Aims:

To evaluate the efficacy and safety of fitusiran versus prior clotting factor concentrate (CFC)/bypassing agent (BPA) prophylaxis in PwHA/B, with or without inhibitors.

Methods:

This Phase 3, multinational, open-label study (NCT03549871) included males aged ≥12 years with hemophilia A or B, with or without inhibitors, who had prior CFC/BPA prophylaxis. Participants continued CFC/BPA prophylaxis (6 months) before switching to once-monthly 80 mg SC fitusiran prophylaxis (7 months). Primary endpoint was ABR in the CFC/BPA prophylaxis period (Day 168 to Day 1) and fitusiran efficacy period (Day 29 to Day 190). Secondary endpoints included spontaneous ABR (AsBR), joint ABR (AjBR), and health-related quality of life (HRQoL). Safety and tolerability were assessed.

Results:

Of 80 enrolled participants, 65 (inhibitor/non-inhibitor, n=19/46; haemophilia A/haemophilia B, n=50/15) were eligible for ABR analyses. Median observed (IQR) ABRs were 4.4 (2.2; 10.9) with CFC/BPA and 0.0 (0.0; 2.3) with fitusiran prophylaxis; 41 participants (63.1%) experienced zero treated bleeds with fitusiran. Fitusiran achieved statistically significant reductions in estimated ABR, AsBR and AjBR versus CFC/BPA prophylaxis (**Table 1**). Fitusiran significantly improved HRQoL versus CFC/BPA as measured by Haem-A-QOL total score (LS mean difference -4.6 [95% CI: -7.6; -1.5; p<0.01]). Serious adverse events (SAEs) occurred in 5/65 participants (7.7%) with CFC/BPA and 9/67 (13.4%) with fitusiran prophylaxis. A total of 17 (25.4%) participants experienced alanine aminotransferase or aspartate transaminase elevations >3x the upper limit of normal in the fitusiran prophylaxis period. Two participants (3.0%) experienced suspected or confirmed thromboembolic events with fitusiran.

Summary/Conclusion: Once-monthly fitusiran prophylaxis significantly reduced bleeding versus CFC/BPA prophylaxis with a median ABR of zero in PwHA/B with and without inhibitors, resulting in a meaningful improvement in HRQoL. Reported AEs were generally consistent with previously identified risks of fitusiran.

Table 1: Bleeding events in the ATLAS-PPX study (fitusiran efficacy and CFC/BPA prophylaxis period*)

	CFC/BPA Prophylaxis (N=65†)	Fitusiran 80mg Prophylaxis (N=65†)	P-value‡
Any treated bleeding event			
Estimated ABR (95% CI)	7.5 (5.5, 10.1)	2.9 (1.7, 4.9)	
% ABR reduction (95% CI)		61.1 (32.5, 77.6)	0.0008
Observed ABR Median (IQR)	4.4 (2.2; 10.9)	0.0 (0.0; 2.3)	
Observed ABR Mean (SD)	7.6 (9.5)	3.2 (7.8)	
Participants with zero treated bleeds, n (%)	11 (16.9)	41 (63.1)	
Treated spontaneous bleeds			
Estimated AsBR (95% CI)	5.0 (3.4, 7.3)	2.2 (1.2, 4.2)	
% AsBR reduction (95% CI)		55.6 (15.8, 76.6)	0.0129
Observed AsBR Median (IQR)	2.2 (0.0; 6.5)	0.0 (0.0; 2.3)	
Observed AsBR Mean (SD)	5.1 (7.9)	2.5 (7.3)	
Participants with zero spontaneous treated bleeds, n (%)	23 (35.4)	46 (70.8)	
Treated joint bleeds			
Estimated AjBR (95% CI)	5.3 (3.6, 7.7)	2.6 (1.4, 4.6)	
% AjBR reduction (95% CI)		51.5 (9.0, 74.1)	0.0242
Observed AjBR Median (IQR)	2.2 (0.0; 6.5)	0.0 (0.0; 2.3)	
Observed AjBR Mean (SD)	5.4 (8.2)	2.8 (7.5)	
Participants with zero joint treated bleeds, n (%)	22 (33.8)	44 (67.7)	

*Fitusiran efficacy period (fitusiran prophylaxis) was defined as starting on Day 29 after the first dose of fitusiran up to Day 190, or the last day of bleeding follow up, whichever is the earliest. The CFC/BPA prophylaxis period was defined as starting on Day -168 to Day -1, or the last day of bleeding follow up, whichever is the earliest; †Includes all participants who received CFC/BPA prophylaxis and at least one dose of fitusiran before dose resumption (after the Sponsor initiated pause in dosing); ‡P-value | from a negative binomial regression model with study period (fitusiran efficacy period or CFC/BPA prophylaxis period) as a fixed effect and a robust sandwich covariance matrix constructed to account for the within subject dependence, the logarithm of the duration (in years) that each participant spends in each study period matching the bleeding episode data being analysed as an offset variable (p-value versus null hypothesis of ratio = 1).

Keywords: Hemophilia