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Abstract Title : Marstacimab prophylaxis in participants with Hemophilia A or B with inhibitors: Results from the Phase 3 BASIS trial

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Authors

Davide Matino[1], Suchitra Acharya[2, 3], Carrie Turich Taylor[4], Pengling Sun[5], Delphine Agathon[6], Travis Gould[7], Andrew Palladino[4], Johnny Mahlangu[8]

[1] Thrombosis and Atherosclerosis Research Institute and Department of Medicine, McMaster University, Hamilton, ON, Canada, [2] Northwell Health, New Hyde Park, NY, United States, [3] Cohen Children's Medical Center, Queens, NY, United States, [4] Pfizer Inc, Collegeville, PA, United States, [5] Pfizer Inc, Cambridge, MA, United States, [6] Pfizer Inc, Paris, France, [7] Pfizer Inc, New York, NY, United States, [8] Department of Molecular Medicine and Haematology, Faculty of Health Sciences, University of the Witwatersrand, National Health Laboratory Service, Johannesburg, South Africa

Abstract Body

Background Marstacimab is a monoclonal antibody that inhibits tissue factor pathway inhibitor to enhance thrombin generation and restore hemostasis in participants (pts) with hemophilia A (HA) or hemophilia B (HB). The phase 3 BASIS study (NCT03938792) evaluated the safety and efficacy of marstacimab in adults and adolescents with severe HA (factor VIII <1%) or moderately severe to severe HB (factor IX ≤2%), with or without inhibitors. Marstacimab was approved for prophylactic use in individuals with HA or HB without inhibitors. Here, we present results of the BASIS study in pts with inhibitors.

Methods This open-label, single-arm study enrolled males aged ≥12 to <75 years with current or historical high-titer inhibitors (≥5 BU/mL). After a 6-month observational phase (OP) on bypassing agents (on-demand [OD] or routine prophylaxis [RP]), pts received a subcutaneous loading dose of marstacimab 300 mg followed by 150 mg once weekly (QW) during the 12-month active treatment phase (ATP). The primary endpoint was annualized bleeding rate (ABR) for treated bleeds during marstacimab prophylaxis vs prior OD therapy with bypassing agents. Secondary endpoints included ABR for specific bleed types and patient-reported health-related quality of life (HRQoL). Safety, including the incidence and severity of adverse events (AEs) and immunogenicity, was evaluated in all dosed pts.

Results Sixty pts (44 adults, 16 adolescents) with HA (n=47) or HB (n=13) with inhibitors entered the OP (OD: n=57; RP: n=3), with 51 transitioning to the ATP (OD: n=48; RP: n=3). Median age was 23 (range 12–75) years. Most pts were Asian (53.3%) or White (31.7%). At baseline, 71.9% of OD pts and 66.7% of RP pts had ≥1 target joint. Median marstacimab treatment duration was 364 (range, 259–406) days. Marstacimab reduced the mean ABR for treated bleeds from 19.78 (95% CI: 16.12, 24.27) in the OP to 1.39 (95% CI: 0.85, 2.29) in the ATP, demonstrating superiority of marstacimab over OD therapy (estimated ABR ratio, 0.07 [95% CI: 0.042, 0.118]; 2-sided P<0.0001). Results were consistent by hemophilia type, age, and geographic subgroup. For all bleed types, mean ABR was consistently superior with marstacimab vs OD in the OP (joint: 1.10 vs 15.15; spontaneous: 0.87 vs 15.27; target joint: 0.79 vs 6.42; total [treated and untreated]: 4.36 vs 27.29; estimated ABR ratio, ≤0.16; 2-sided P≤0.0001 for all bleed types). Marstacimab also demonstrated superiority vs OD therapy in all patient-reported HRQoL endpoints, except EQ-visual analog scale (VAS). After 6 months in the ATP, pts reported significantly greater improvements in Haem-A-QoL Physical Health domain (estimated median difference vs OP, −25.9 [95% CI: −37.5, −14.2]; 2-sided P<0.0001), Haem-A-QoL total score (estimated median difference, −13.5 [95% CI: −19.8, −7.2]; 2-sided P<0.0001), and EQ-5D-5L index score (estimated median difference, 0.1043 [95% CI: 0.0060, 0.2027]; 2-sided P=0.0377). During the ATP, 38 (74.5%) pts reported AEs, mostly mild or moderate; the most frequent were COVID-19 (21.6%), upper respiratory tract infection (15.7%), fibrin D-dimer increased (9.8%), and headache (9.8%). A total of 5 pts reported serious AEs (SAEs) during the OP. One pt reported an SAE (treatment-related skin rash [grade 3], resolved at follow-up) during the ATP,

which led to study discontinuation. Ten pts had their marstacimab dose temporarily discontinued or reduced due to an AE, most commonly COVID-19 (7 pts). Antidrug antibodies (ADAs) were detected in 10/51 (19.6%) pts; titers were low and 9/10 cases resolved by end of study. ADA status had no impact on efficacy or safety endpoints. Neutralizing antibodies were detected in 2 pts; titers were low and antibodies were transient and resolved by end of study. No deaths or thrombotic events were reported.

Conclusion In pts with HA or HB and inhibitors, subcutaneous marstacimab QW significantly reduced ABR for all bleeding related endpoints vs prior OD therapy and improved HRQoL. Marstacimab demonstrated a favorable safety profile, consistent with the noninhibitor cohort and earlier studies.

Keywords: Research, Human, Diseases, Study Population, Hemophilia, Bleeding and Clotting, Clinical Research

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Palladino: Pfizer, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: No, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: Yes, Current Employment: Yes, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Johnny Mahlangu: CSL Behring, Consultancy (Includes expert testimony): Yes, Patents & Royalties: No, Ended employment in the past 24 months: No, Research Funding: Yes, Divested equity in a private or publicly-traded company in the past 24 months: No, Current equity holder in publicly-traded company: No, Current Employment: No, Current holder of stock options in a privately-held company: No, Current equity holder in private company: No, Honoraria: No, Sanofi, Consultancy (Includes expert testimony): No, Patents & Royalties: No, Ended employment in the 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