3rd May 2020

Dear Dr Pierce and Dr Kaczmarek,

Thank you for your request for information relating to the marstacimab clinical development program on behalf of the World Federation of Hemophilia. We are aware that there is interest in our ongoing clinical programs among the hemophilia community, particularly at the present time, and we welcome the opportunity to share in response to your queries information that may be helpful for the community. The global health challenge we all face from the COVID-19 pandemic is unprecedented. We have an important responsibility to the patients currently in our clinical trials and are committed to doing all we can to support them during this public health crisis.

Marstacimab has not been investigated in any preclinical models in the setting of ongoing disseminated intravascular coagulopathy (DIC) in humans and we have not observed DIC in animals treated with marstacimab. We also have not observed any thrombotic events in the marstacimab clinical program to date.

Our clinical trial protocols enable clinicians to treat patients with local standard of care for coagulopathy or thromboembolic event should they occur. For example, there are no restrictions to use of anti-coagulants or other therapies to address DIC or coagulopathy should they be deemed as needed by clinicians.

The human experience with marstacimab in which we have seen no thrombotic episodes includes:
- 58 subjects have received marstacimab, including 32 subjects first in human Phase 1 study (reference attached), and 26 subjects Phase 1b/2 study
- In our ongoing Phase 2 program, subjects have received up to a total of 15 months of marstacimab prophylaxis (NCT02974855 & NCT02531815).

There are currently 2 active marstacimab trials:
- Phase 2 Study – NCT02974855 - recruitment status – fully recruited
- Phase 3 Study – NCT03938792 - recruitment status – active

In late March, Pfizer paused the recruitment portion of certain ongoing global interventional clinical studies including the Phase 3 marstacimab study above (NCT03938792). We took this action so that clinical site partners and Pfizer could concentrate on care for participants in our ongoing clinical trials and to avoid adding to the demands on the healthcare system during the peak of the COVID-19 crisis.

While the pandemic continues to challenge us all, we have been continuously monitoring the situation and are seeing that not every site, region and country is impacted in the same way. I wanted to share that we are beginning to re-start recruitment across all therapeutic areas in our portfolio, including new studies. We will do so on a site by site basis as they are ready and where health authorities allow recruitment to continue. Our guideposts continue to be the safety of participants already in our studies, the safety of new participants being entered into our studies, and the wellness of all our investigators. We will work closely with our investigator sites to confirm their readiness before new study participants are enrolled.

With regard to the Phase 2 clinical trial, NCT02974855, Pfizer are working with trial clinicians to ensure that the small number of participants who have yet to complete the trial are being managed in collaboration with their local trial centre in a manner that ensures their safety while receiving marstacimab. The clinical team is proactively arranging calls with the investigators to discuss any concerns and any potential mitigation strategies.
With regard to the Phase 3 clinical trial, NCT0393879, this trial initiates with a 6 month observational phase where subjects receive their current haemophilia regimen and are not treated with marstacimab. To date no subjects have reached the end of this observational stage of the study and therefore, no patients are currently receiving marstacimab in this trial. This study is subject to any further announcements Pfizer may make regarding its global clinical trials during the COVID-19 pandemic. Additional details are available at: https://www.pfizer.com/health/coronavirus/how-pfizer-is-responding.

Based on the observed clinical trial data to date, preclinical data, and the designs of the Phase 2 and Phase 3 clinical trials with marstacimab: Pfizer believes the benefit-risk profile remains favorable for continued development in participants with hemophilia.

Risk mitigation procedures related to the development of thrombotic events have also been proactively added to the Phase 3 protocol which too have been reviewed and agreed with the appropriate regulatory authorities. These procedures include:

- Subject and study level stopping rules that have previously been reviewed and agreed with global regulatory authorities.
- An external Data Monitoring Committee (eDMC) will monitor all safety information within the phase 3 program. In addition to overall safety review, the eDMC will focus on the evaluation of thrombotic events, injection site reactions and abnormal cardiac troponin I (cTnl) laboratory data as well as electrocardiogram (ECG) and clinical data associated with cTnl elevations.
- Ongoing internal safety assessment of the benefit/risk profile of marstacimab as the clinical trial program progresses. In addition to the standard assessments of adverse events and review of routine hematology and chemistry, physical examination vitals and ECGs, blood samples will also be collected for measurement of FVIII & FIX activity assay, FVIII & FIX Inhibitor Assay, Serology including tests for HepB & C, cardiac troponin I, TFPI (total and free), thrombin generation, prothrombin fragment 1+2, D dimer and dilute prothrombin time as well as for analysis of Anti-Drug Antibodies and Neutralizing Antibodies to marstacimab.

Additionally, the Phase 3 protocol has exclusion criteria that exclude subjects with current or history of coronary artery diseases, venous or arterial thrombosis or ischemic disease, any hemostatic defect other Hemophilia A or B, abnormal hematology, coagulation activity, renal or hepatic function or ECG that demonstrates clinically relevant abnormalities. Likewise, the phase 2 protocol has similar exclusion criteria and safety assessments as the phase 3 program. Although the eDMC is not providing oversight of the phase 2 program the safety data from both the Phase 1 and Phase 2 program will be shared with them.

We hope that this letter has answered your outstanding questions relating to marstacimab. As part of our commitment to ensure public health and safety during this challenging time we are sharing information on how Pfizer is responding to Coronavirus as well as additional information and resources at: https://www.pfizer.com/health/coronavirus. You can visit this for the latest information on what we are doing, including decisions regarding our clinical trials.

We are grateful for your partnership and look forward to continuing to work together on behalf of the patients we serve. We will continue to stay in close communication throughout this challenging time.
Please do not hesitate to contact us should further questions arise, and we would be pleased to discuss any of the above in a virtual meeting.

Sincerely

[Signature]

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References
4 Choi et al Blood (2016) 128 (22): 14