11 May 2020

WFH COVID-19 Task Force
Radek Kaczmarek and Glenn Pierce, Co-chairs
Assad Haffar, Cedric Hermans, Barbara Konkle, Brian O'Mahony, David Page, Flora Peyvandi, Steve Pipe, Mark Skinner

In response to a request for information on the potential interaction between the coagulopathy associated with some COVID-19 cases and new hemostatic agents (in clinical development or recently approved), the WFH has received replies from the 5 companies queried. Please find below a summary of the replies received from these pharmaceutical companies. Full letters are available on the WFH website.

Collectively, the companies give us assurance they are being vigilant and there are no observations that have changed the risk : benefit assessment for these therapies. However, given the unfolding information of the effect of SARS-CoV-2 on the coagulation systems in young and old, including evidence of elevated D-dimers, and thrombosis in both large and small vessels in hospitalized patients with severe COVID-19, vigilance should remain heightened. Patients on emicizumab or any of these investigational agents, who develop COVID-19 and are hospitalized, will likely be supplemented with replacement clotting factors to maintain hemostasis, along with anticoagulant therapy to decrease thrombotic risk, creating an extremely complex situation of which we collectively have very little to no experience.

In summary, we remain concerned should a person with hemophilia on a rebalancing agent clinical trial acquire severe COVID-19 requiring hospitalization. Proactive clinical management involving the hemophilia treatment center and sponsor is advised.

Additional reading, published in Nature, 8 May 2020:
https://www.nature.com/articles/d41586-020-01403-8?utm_source=Nature+Briefing&utm_campaign=4d3d1489a2-briefing-dy-20200511&utm_medium=email&utm_term=0_c90fd39373-4d3d1489a2-43016595

Approved Non-factor Therapy
Roche, 14 April 2020, emicizumab

COVID-19 is caused by a novel coronavirus, therefore knowledge about how it may affect people with Haemophilia A is not well understood. Severe COVID-19 patients with or without haemophilia may develop COVID-19 associated coagulopathy resembling disseminated intravascular coagulation (DIC) as the condition progresses.

Importantly, Hemlibra is known to interfere with one-stage clotting assays, some of which are used to diagnose and monitor patients with DIC (table attached to original letter).
Patient safety is Roche’s highest priority. At this time, the interaction between Hemlibra and the coagulopathy secondary to COVID-19 infection is unknown. We are committed to obtaining as much information as possible. We are closely monitoring the evolving COVID-19 situation and reviewing any information regarding COVID-19 infections in patients receiving Hemlibra as it becomes available.

Rebalancing Agents in Clinical Trials

Sanofi, 9 April 2020, fitusiran (small inhibitory RNA for antithrombin)

To date there have been no reported cases of patients on fitusiran being infected by COVID-19 so it is not possible to assess the potential impact of these COVID-19 complications. We are working in partnership with our study investigators to identify and minimize potential risks to our patients.

Based on these discussions, we have implemented the following measures to support our investigators and patients. We are having regular discussions with our study sites and have encouraged increased communication between our investigators and patients. For patients in our clinical trials, we are providing support to facilitate home visits to help avoid hospital appointments required by the study protocol, following the WHO recommendation to minimize possibility of exposure. Sanofi is also communicating to our investigators on a range of topics including a reminder that key coagulation assays under fitusiran treatment are altered (e.g. low antithrombin level) and to reinforce the potential to use antithrombin replacement therapy if needed (Note: per protocol, every study site has already been provided antithrombin replacement in case needed and already have guidance to consider antithrombin replacement in certain case of e.g. sepsis).

Apicintex, 10 April 2020, SerpinPC (serine protease inhibitor to activated protein C)

Naturally we have considered the impact of COVID-19 on the safety of participants in our clinical trial. We had already tested the interaction between SerpinPC and the cytokine storm/coagulopathy with appropriate controls and demonstrated no interaction. Our preclinical toxicology work also demonstrates that SerpinPC is not prothrombotic in WT animals at high doses, well in excess of those planned for use in our clinical trial. Importantly, we have observed no increase in D-dimer in any subject on trial, either healthy volunteer or PwH.

Our clinical CRO have dedicated research clinics located across University Hospitals in Eastern Europe and have a track record in drug development that is trusted by the World’s Leading Pharmaceutical and Biotechnology organizations. We are holding weekly meetings with the clinical sites, including the hemophilia clinical staff. In line with the EMA Guidance on the Management of Clinical Trials during the COVID-19 pandemic (Version 2 - 27/03/2020) we are
continually reviewing our procedures and the situation, with the safety of the participants in our study as our primary concern.

**Pfizer, 7 May 2020, marstacimab (anti-TFPI)**

*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).

*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:*

  o Subject and study level stopping rules that have previously been reviewed and agreed with global regulatory authorities.
  o 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 (cTnI) laboratory data as well as electrocardiogram (ECG) and clinical data associated with cTnI elevations
  o 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.

Green Cross Pharma, 16 April 2020, MG1113 (anti-TFPI)

Green Cross Pharma responded to our inquiry, but did not agree to have their letter posted on the WFH website.