Regulatory Feedback on Context of Use Biomarker Validation for Caplacizumab

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Presentation Overview

- What is a Nanobody®?
- Caplacizumab clinical development program
- Clarification request from Health Canada
- Selection of biomarkers in support of late stage clinical trials in aTTP patients
- Take-home messages
What is a Nanobody®?

Antibody-based biotherapeutic from Ablynx, a Sanofi company

Bivalent anti-vWF Nanobody® (28kD) for the treatment of aTTP

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Conventional antibodies

Heavy chain only antibodies

Ablynx’ Nanobody®
- small and robust
- easily linked together
- sequence homology comparable to humanized/human mAbs
- nano- to picomolar affinities
- able to bind and block challenging targets
- multiple administration routes
- manufactured in microbial cells

aTTP, acquired thrombotic thrombocytopenic purpura; vWF, von Willebrand factor

Figure adapted from company slide deck
Caplacizumab

anti-vWF Nanobody in aTTP

- aTTP is an ultra-rare, life-threatening autoimmune blood clotting disorder
- High unmet medical need with no previously approved therapeutic drug

Caplacizumab’s unique mode of action blocks binding of vWF to platelets which has an immediate effect on platelet aggregation and the ensuing micro-clot formation

ULvWF, Ultra-large von Willebrand Factor; ADAMTS13, a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13

Figure adapted from M.L. Sargentini-Maier et al. 2019
Caplacizumab clinical development program

**Healthy subjects**
- ALX-0081-01/0: Safety and tolerability, i.v. dose
  - n = 40
- ALX-0681-1.1/08: Safety and tolerability, s.c. dose
  - n = 36
- ALX-0681-2.1/0: Safety and tolerability, i.v. dose
  - n = 40
- ALX-0681-C102: Bioequivalence liquid vs lyophilised formulation
  - n = 24
- ALX0681-C103: Ethno-bridging Japanese and White subjects
  - n = 60

**Acquired TTP patients**
- ALX-0681-2.1/10 "TITAN": Efficacy and safety
  - n = 75
- ALX0681-C301 "HERCULES": Efficacy and safety
  - n = 145
- ALX0681-C302 “HERCULES follow-up”
  - Long term safety, repeated use (3 years) n=104
- ALX0681-C202: Efficacy and safety in Japanese aTTP patients
  - n = 15

**Percutaneous coronary intervention (PCI) patients**
- ALX-0081-1.2/08: Stable angina PCI patients
  - n = 46; one-day multiple i.v. dose
- ALX-0081-2.1/09: High risk PCI patients
  - n = 364; one-day multiple i.v. dose

*Study timelines: first subject in – last patient out*

Number of subjects
- HV: 100
- PCI: 410
- aTTP: 220
- TOTAL: 730
The comments outlined below must be addressed by November 19, 2019 3PM EST.

1. Please clarify whether caplacizumab at the concentration range in the serum of the caplacizumab-treated patients in the clinical trials interferes with the bioanalytical methods for quantitative assessment of vWF:Ag or vWF propeptide, serum LDH, troponin I or T and creatinine in human serum used in the TITIAN and HERCULES studies.

- In doing so, please list the pivotal or key studies among those submitted in this NDS, that established and validated the related detection methods, as supporting evidence for the clarification.
## Selection of biomarkers in aTTP patients

### Late-stage clinical trials

<table>
<thead>
<tr>
<th>Type of biomarker</th>
<th>Biomarker</th>
<th>Type of assay</th>
<th>Context of use</th>
<th>TITAN, PhII</th>
<th>HERCULES, PhIII</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PD biomarkers</strong> (target disposition)</td>
<td>vWF:Ag and/or vWF:pp</td>
<td>Automated immunoturbidimetric assay</td>
<td>Custom developed, qualified and validated</td>
<td>Central lab X</td>
<td>Central lab Y</td>
</tr>
<tr>
<td></td>
<td>RICO</td>
<td>In vitro aggregation assay</td>
<td>Custom developed, qualified and validated</td>
<td>Specialty lab</td>
<td></td>
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<tr>
<td><strong>Safety biomarkers</strong> (organ damage)</td>
<td>LDH (nonspecific)</td>
<td>Automated biochemistry analysis</td>
<td>Off-the-shelf clinical chemistry</td>
<td>Clinical sites</td>
<td>Central lab Y</td>
</tr>
<tr>
<td></td>
<td>Creatinine (kidney)</td>
<td>Automated chemiluminescent immunoassay</td>
<td>Off-the-shelf immunoassay</td>
<td>Clinical sites</td>
<td></td>
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<tr>
<td></td>
<td>Troponins (heart)</td>
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</tbody>
</table>

*PD, pharmacodynamics; vWF:Ag, von Willebrand factor antigen; vWF:pp, von Willebrand factor propeptide; RICO, ristocetin cofactor activity; LDH, lactate dehydrogenase; TnI, Troponin I; TnT, Troponin T*
Response for PD biomarkers

- 2 methods were custom developed and qualified in-house for the detection of vWF:Ag and vWF:pp.

- Both methods transferred to the central labs for clinical validation and sample analysis in support of TITAN and HERCULES. The CoU required drug interference assessment.
  - During validation of the vWF:Ag assay, drug interference at 10 µg/mL was observed. The method was then modified to improve drug interference and re-validated.
  - During validation of vWF:pp assay, no drug interference was observed at levels up to 10 µg/mL caplacizumab during validation. (The vWF:pp assay was used in TITAN, but not in support of HERCULES.)

- CoU indicated drug interference should be evaluated in the analytical methods for the detection of vWF:Ag and vWF:pp. Validation results showed drug tolerance above the measured plasma concentrations in samples from both TITAN and HERCULES.
Clarification request from Health Canada

Response for safety biomarkers

- For the organ damage biomarkers validations were performed at clinical sites or at central lab, and covered general performance of the methods for use in analysis of clinical trial samples.

- No additional validation of drug interference on these methods was performed. These safety biomarkers were implemented as accepted off-the-shelf clinical methods as their CoU.

- Time to normalization of organ damage biomarkers was performed in a post hoc analysis in support of TITAN. For HERCULES, this was a key secondary endpoint to enable the assessment of the full clinical benefit of caplacizumab. HERCULES was considered as the pivotal clinical study for establishing and validating these biomarkers.

- Context of Use for these methods and purposes was accepted by regulatory authorities without comment.
Take-home messages

• A panel of PD and safety biomarker methods were validated to various levels for CoU to support late-stage development and pivotal trials of caplicizumab.

• During a rolling review, Health Canada requested clarification on possible drug interference in selected biomarker methods and information on which key clinical trials established and validated the related methods.

• A response was provided highlighting the different context of use for the methods incl. link to the development and validation reports in the submission dossier.

• We received approval from Health Canada on February 28, 2020. Caplacizumab is approved for the treatment of adults with acquired thrombotic thrombocytopenic purpura (aTTP), in combination with plasma exchange and immunosuppressive therapy.

• A big thank you to the whole Caplacizumab team and to all clinical study participants.
THANK YOU