



## Regulatory Feedback on Context of Use Biomarker Validation for Caplacizumab



Benedicte Brackeva  
EBF Open Symposium, November 19, 2020

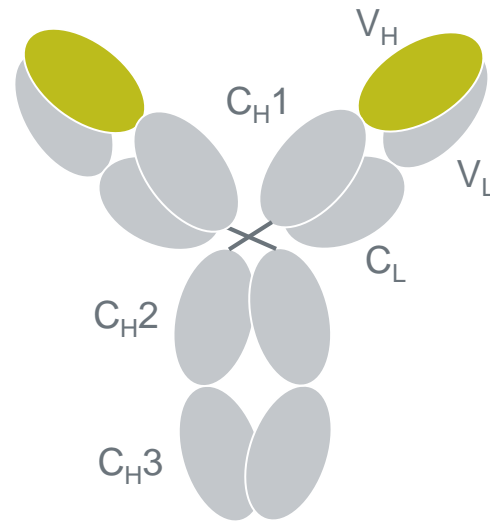
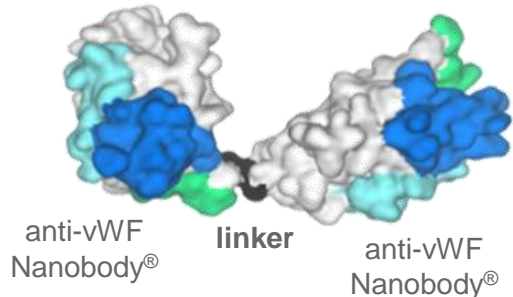
- **What is a Nanobody<sup>®</sup>?**
- **Caplacizumab clinical development program**
- **Clarification request from Health Canada**
- **Selection of biomarkers in support of late stage clinical trials in aTTP patients**
- **Take-home messages**

# What is a Nanobody<sup>®</sup>?

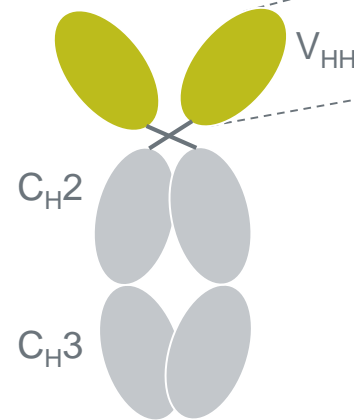
Antibody-based biotherapeutic from Ablynx, a Sanofi company

Bivalent anti-vWF Nanobody<sup>®</sup>  
(28kD) for the treatment of  
aTTP

**Cablivi**<sup>®</sup>  
caplacizumab



**Conventional antibodies**



**Heavy chain only antibodies**

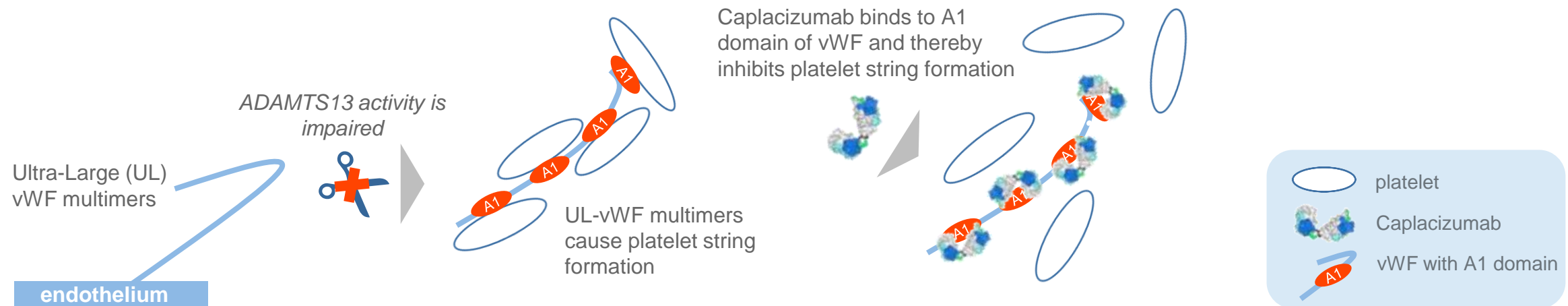
**Ablynx' Nanobody<sup>®</sup>**

- 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

# Caplacizumab

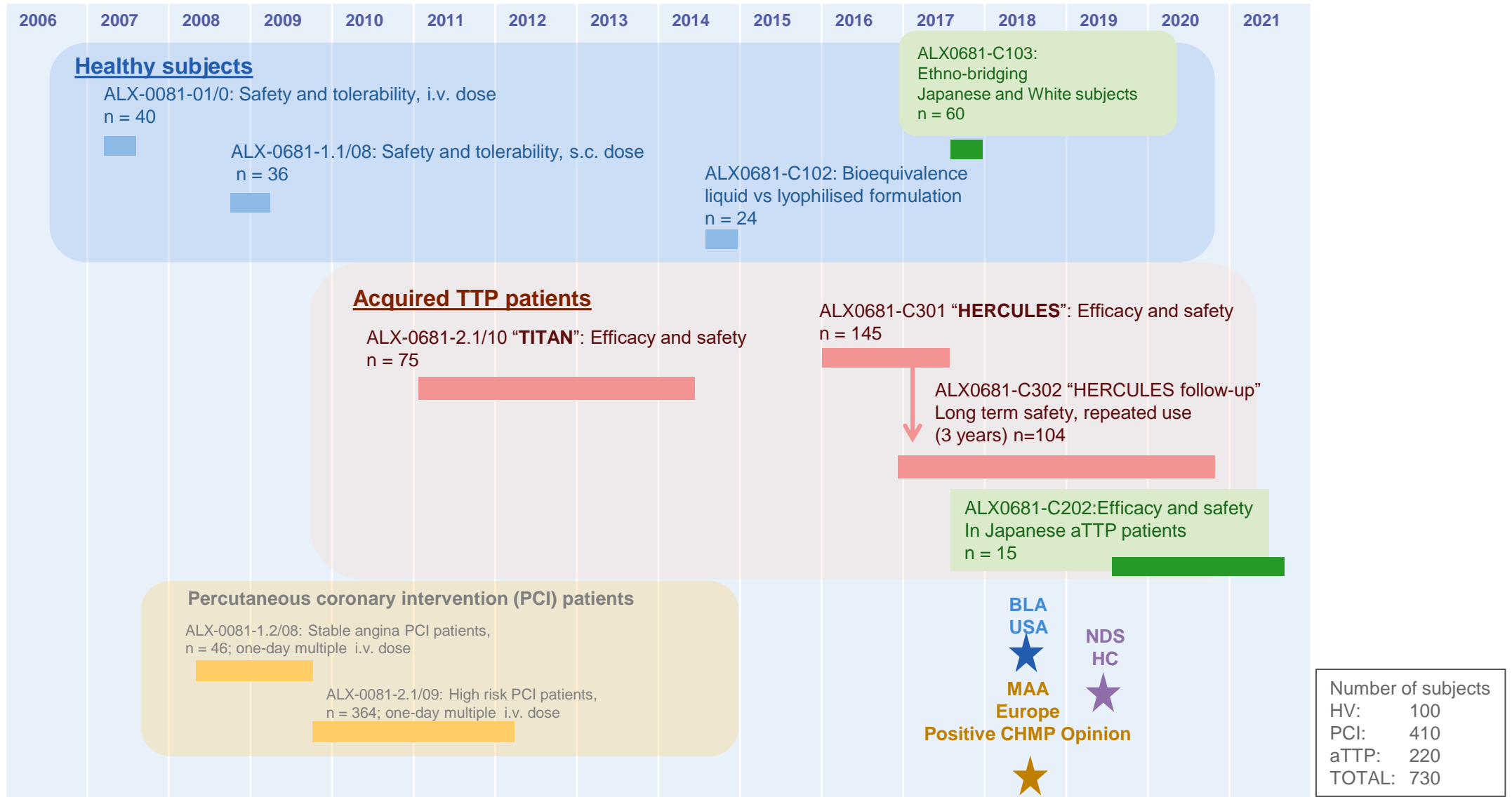
## anti-vWF Nanobody in aTTP

- 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**

# Caplacizumab clinical development program



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

# Clarification request from Health Canada

## New Drug Submission for CABLIVI, clinical clarifax#4

“Clarifax” received on November 7, 2019:



Health Canada

Santé Canada

**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.

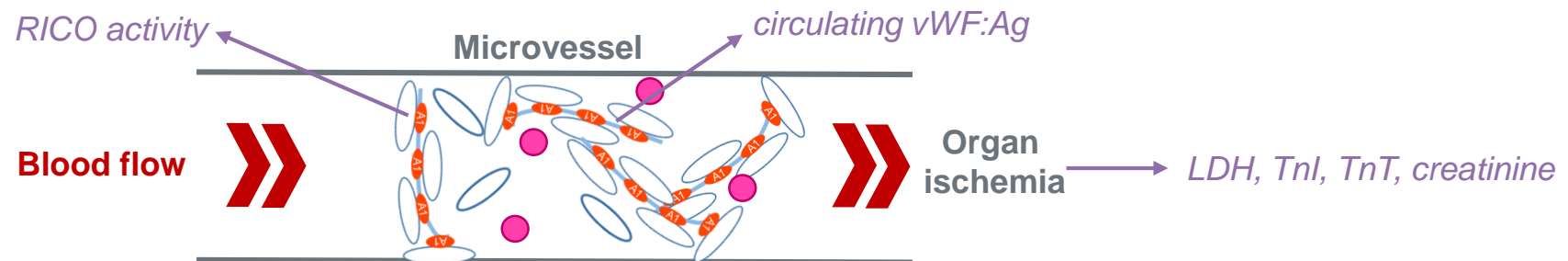
- In doing so, please list the pivotal or key studies among those submitted in this NDS, that established and validated the related detection methods, as supporting evidence for the clarification.



# Selection of biomarkers in aTTP patients

## Late-stage clinical trials

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



## 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.



## 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

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- 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

