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Topline results from the Phase III HERCULES study with caplacizumab in acquired thrombotic thrombocytopenic purpura (aTTP)

Webcast – 2nd October 2017

Topline results Phase III HERCULES study

Participants on the call

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Webcast 2nd October 2017

Agenda

- Welcome and introduction
- Topline results from the Phase III HERCULES study
- Conclusions & next steps
- Q&A

Topline results: Phase III HERCULES study

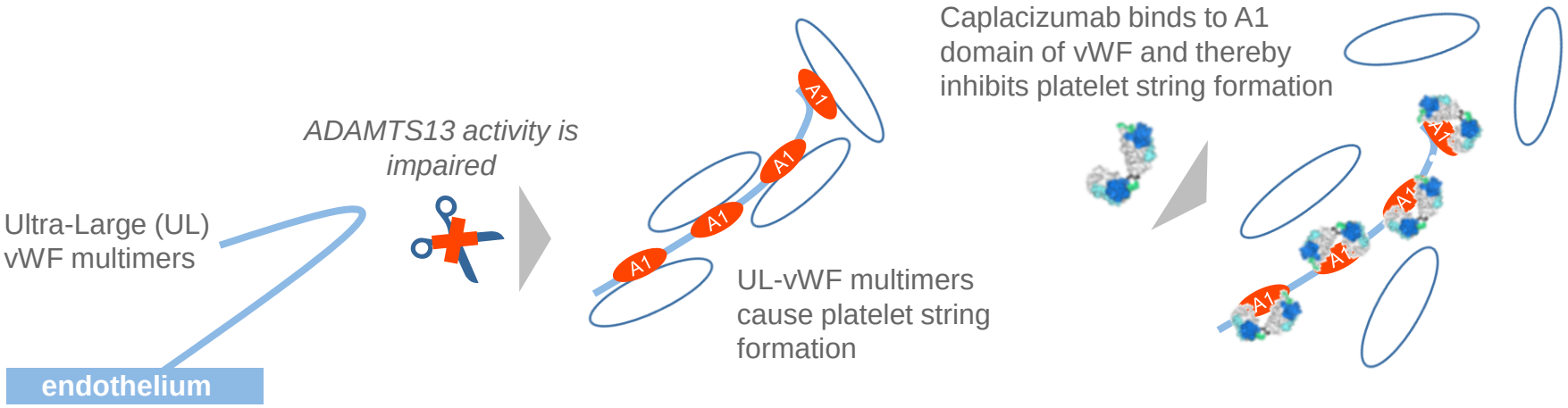
Primary endpoint and key secondary endpoints met

- *Primary endpoint*: statistically significant reduction in time to platelet count response
- *First secondary endpoint*: 74% relative reduction in patients with aTTP-related death, aTTP recurrence or a major thromboembolic event during the study drug treatment period
- *Second secondary endpoint*: 67% relative reduction in patients with aTTP recurrence during the overall study period
- *Third secondary endpoint*: no caplacizumab-treated patients had refractory disease
- *Fourth secondary endpoint*: trend to faster normalisation of organ damage markers
- Safety profile consistent with Phase II TITAN results and mechanism of action

aTTP: acquired thrombotic thrombocytopenic purpura

Caplacizumab (anti-vWF Nanobody) in aTTP

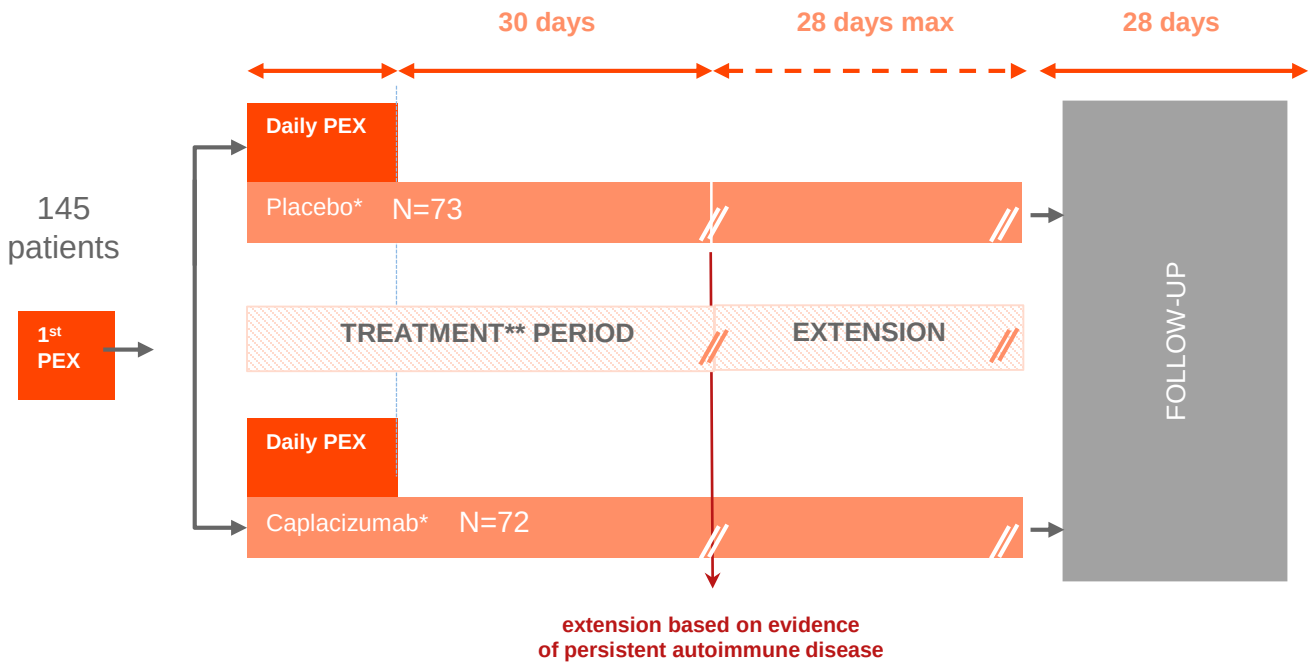
- aTTP is an acute, life-threatening autoimmune blood clotting disorder
- High unmet medical need with no approved therapeutic drug



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

Phase III HERCULES study design

Randomised, double-blind, placebo-controlled, multi-national study



** iv bolus (10mg) followed by daily sc (10mg) ** including corticosteroids at start of daily PEX until underlying disease activity resolved*

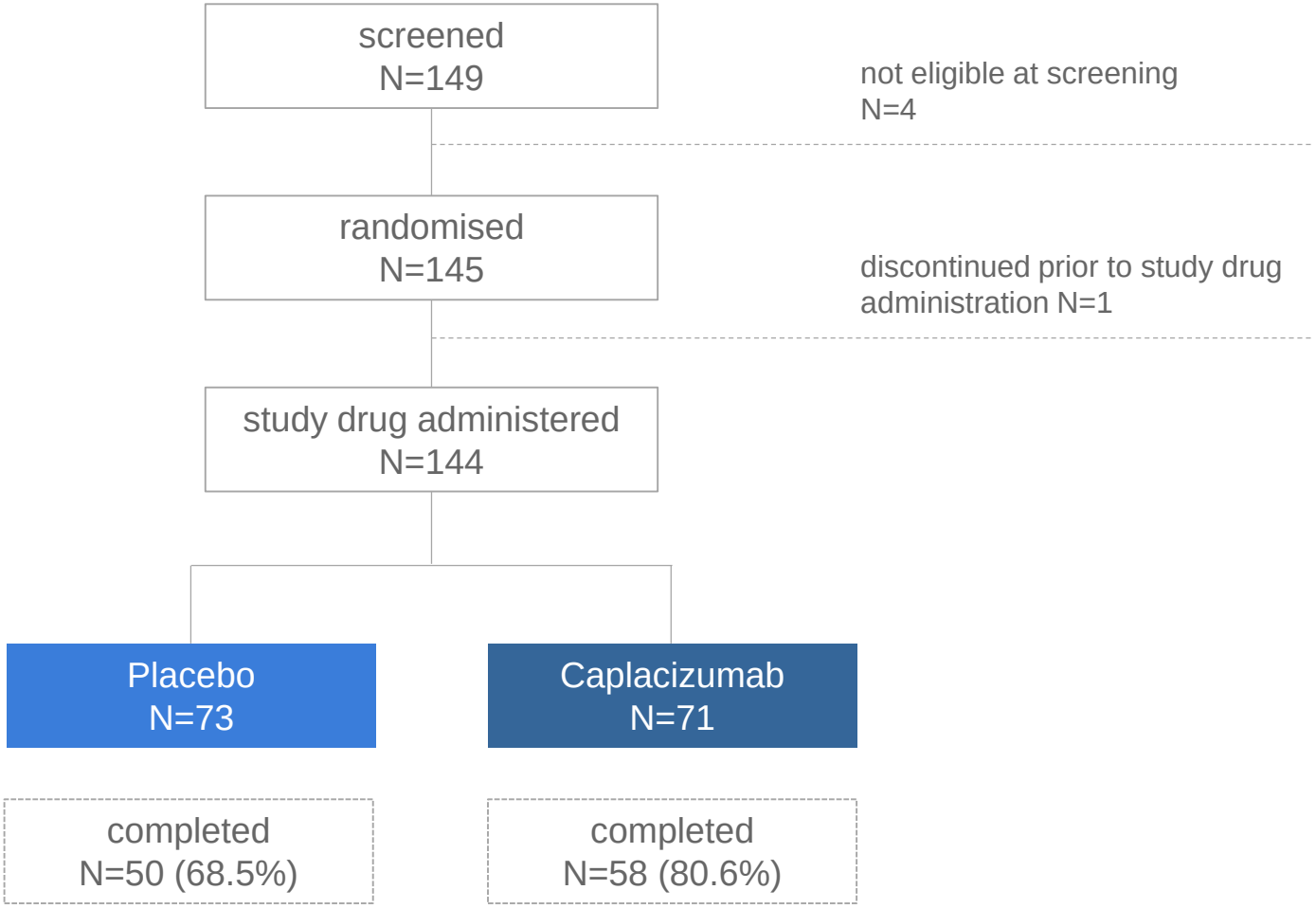
Primary endpoint: time to confirmed normalisation of platelet count response

Secondary endpoints:
- aTTP-related death, recurrence of aTTP, or at least one major thromboembolic event during the study drug treatment period
- recurrence of aTTP in the overall study period
- refractoriness to treatment
- time to normalisation of 3 organ damage markers

PEX: plasma exchange

Phase III HERCULES study

Patient disposition



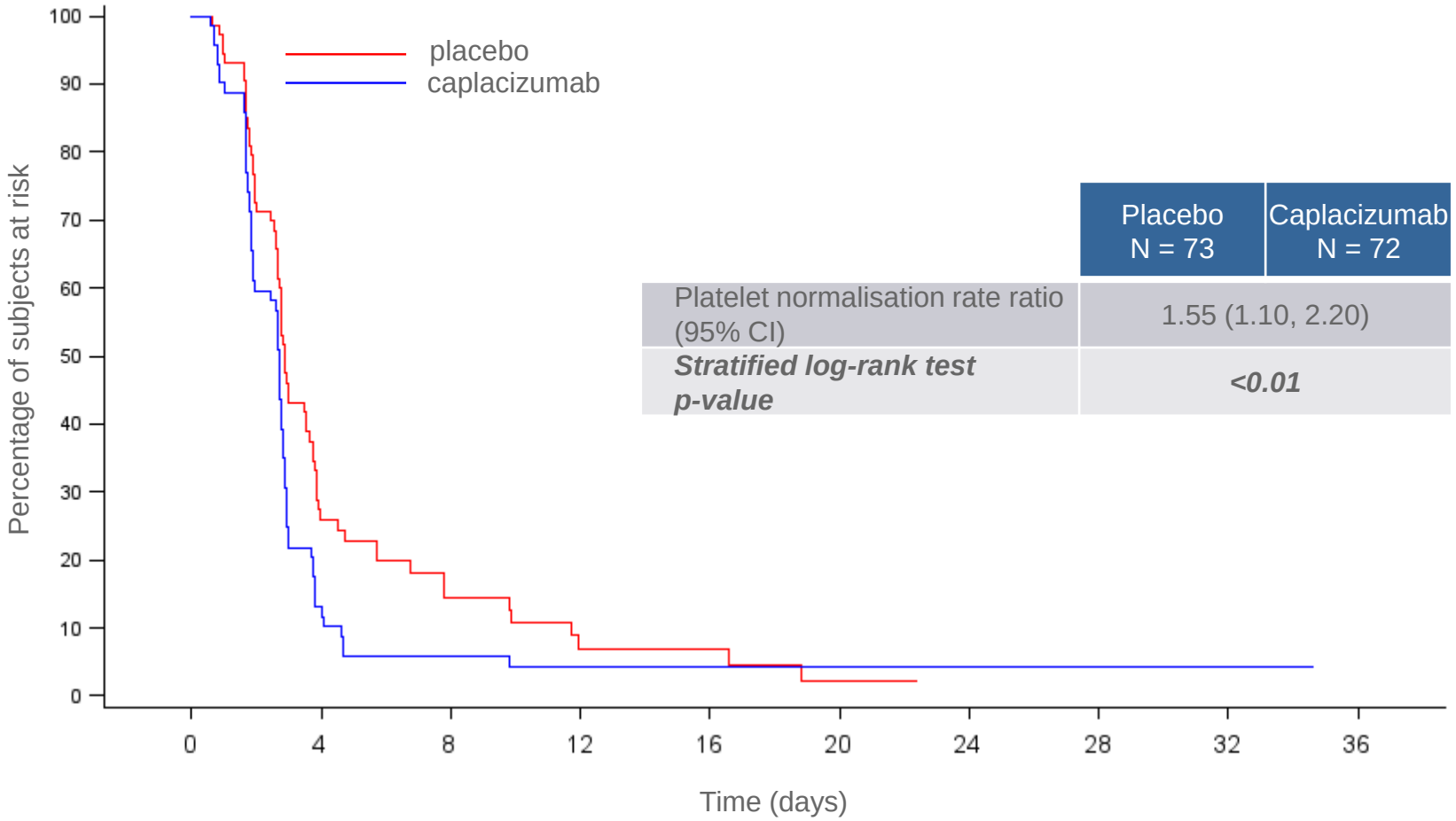
Patient demographics and baseline disease characteristics

Groups generally well balanced

	Placebo N=73	Caplacizumab N=72
Mean age (SD)	47.3 (14.1)	44.9 (13.5)
Females (%)	51 (69.9%)	49 (68.1%)
Previous aTTP episode(s) N (%) - initial - recurrent	 34 (46.6%) 39 (53.4%)	 48 (66.7%) 24 (33.3%)
ADAMTS13 activity at baseline N (%) - <10% - ≥10%	 65 (90.3%) 7 (9.7%)	 58 (81.7%) 13 (18.3%)
Baseline platelet count (10^9/L) - N - Mean (SD)	 72 39.1 (29.1)	 70 32.0 (27.2)

Primary endpoint

Statistically significant reduction in time to platelet count response



	Placebo N = 73	Caplacizumab N = 72
Platelet normalisation rate ratio (95% CI)	1.55 (1.10, 2.20)	
Stratified log-rank test p-value	***<0.01***	

First key secondary endpoint

Subjects with aTTP-related death, aTTP recurrence or at least one major thromboembolic event during the study drug treatment period

Number of subjects (%)	Placebo N=73	Caplacizumab N=72*
Total number of subjects with at least one of the events below[1]	**36 (49.3)**	**9 (12.7)**
aTTP-related death[2]	3 (4.1)	0
recurrence[3] of aTTP	28 (38.4)	3 (4.2)
at least one treatment emergent major thromboembolic event[2]:	6 (8.2)	6 (8.5)
- cerebrovascular accident	*3 (4.1)*	*2 (2.8)*
- myocardial infarction	*1 (1.4)*	*1 (1.4)*
- pulmonary embolism	*0*	*1 (1.4)*
- deep venous thrombosis (spontaneous)	*1 (1.4)*	*0*
- deep venous thrombosis (catheter-associated)	*2 (2.7)*	*3 (4.2)*
p-value	***<0.0001***	

** percentages are based on 71 subjects entering the study drug treatment period*

[1] patients can have more than 1 event
[2] adjudication of aTTP-related death and major thromboembolic events by a blinded independent committee
[3] recurrence = recurrent thrombocytopenia after initial recovery of platelet count, requiring re-initiation of daily PEX

Second key secondary endpoint

Subjects with aTTP recurrence during the overall study period

Number of subjects (%)	Placebo N=73	Caplacizumab N=72*
aTTP recurrence[1]	**28 (38.4)**	**9 (12.7)**
during the study drug treatment period	28 (38.4)	3 (4.2)
during the follow-up period	0	6 (9.1)[2]
p-value	***<0.001***	

** percentages are based on 71 subjects entering the study drug treatment period and 66 subjects in the follow-up period*

[1] recurrence = recurrent thrombocytopenia after initial recovery of platelet count, requiring re-initiation of daily PEX

[2] ADAMTS-13 activity levels were <10% at the end of the study drug treatment period in all of these patients

Third key secondary endpoint

Percentage of subjects with refractory aTTP

Number of subjects (%)	Placebo N=73*	Caplacizumab N=72
Refractory aTTP[1]	3 (4.2)	0
p-value	*0.0572*	

** one subject discontinued prior to day 5 and is not included in the analysis*

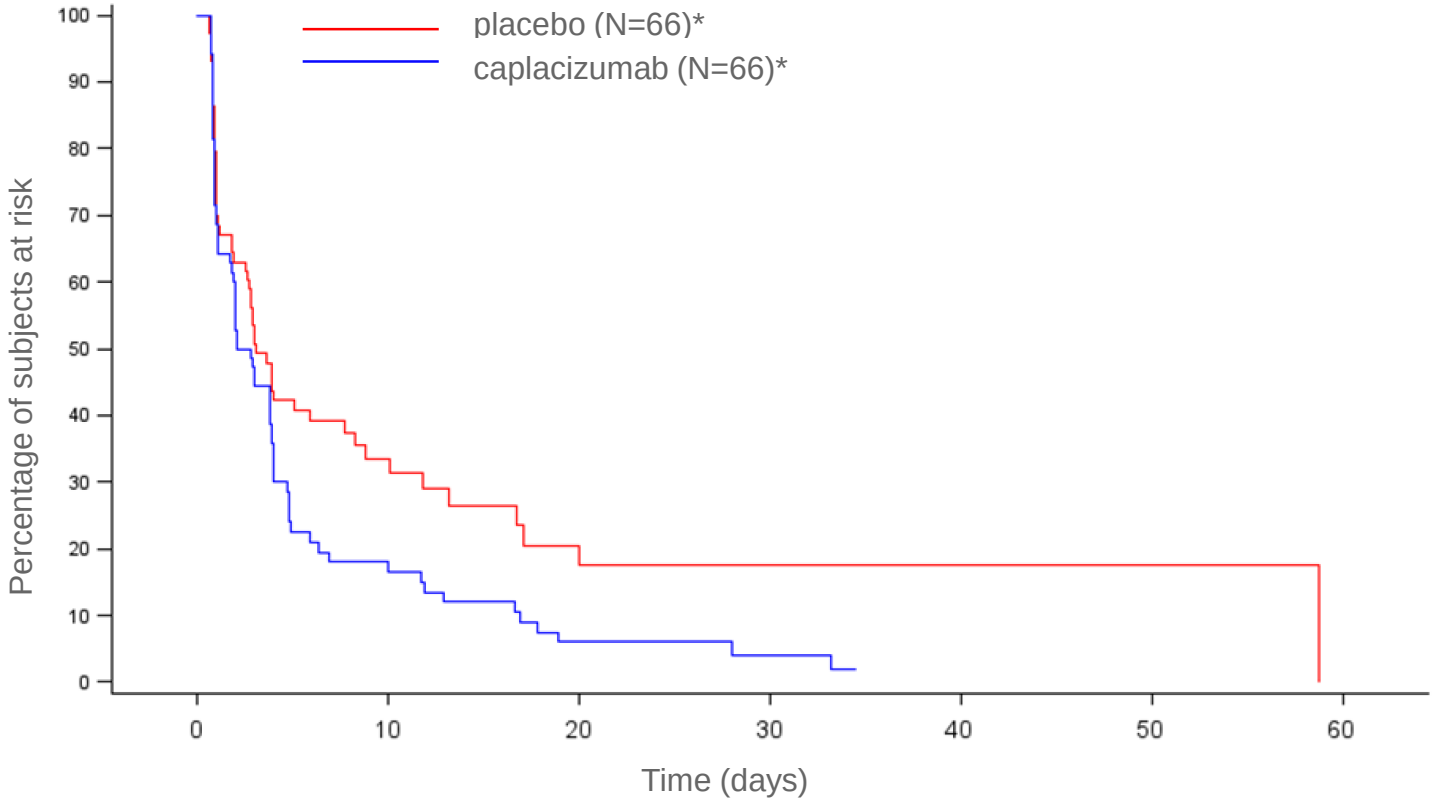
[1] refractory TTP = absence of platelet count doubling after 4 days of standard treatment and LDH > ULN

No caplacizumab-treated patients were refractory to therapy

LDH: lactate dehydrogenase; **ULN:** upper limit of normal

Fourth key secondary endpoint

Time to normalisation of organ damage markers[1]



** only subjects with at least one abnormal organ damage marker value at baseline were included in this analysis*

[1] time to LDH ≤ 1 x ULN and cardiac Troponin I ≤ 1 x ULN and serum creatinine ≤ 1 x ULN

LDH: lactate dehydrogenase; **ULN:** upper limit of normal

Safety profile

Treatment emergent adverse events (TEAEs)

Number of subjects (%) with TEAE	Placebo N=73	Caplacizumab N=71
At least one TEAE	71 (97.3)	69 (97.2)
At least one study drug-related TEAE	32 (43.8)	41 (57.7)
At least one TEAE leading to study drug discontinuation	9 (12.3)	5 (7.0)
At least one SAE	39 (53.4)	28 (39.4)
At least one study drug-related SAE	4 (5.5)	10 (14.1)
At least one SAE leading to death	3 (4.1)	1 (1.4)[1]

[1] adverse event occurred during the follow-up period of the study and was assessed by the investigator as not related to study drug treatment

Safety data consistent with Phase II TITAN study

Phase III HERCULES study – conclusions

Confirmation and extension of Phase II TITAN study results

- Significant reduction in time to platelet count response consistent with halting consumption of platelets in microthrombi
- Highly clinically meaningful reduction in aTTP-related death, aTTP recurrences or major thromboembolic events
- Extended treatment with caplacizumab until resolution of underlying disease prevents aTTP recurrences
- Caplacizumab has the potential to prevent refractory disease
- More evidence of the positive impact of caplacizumab on faster normalisation of organ damage markers
- Safety profile in line with previous results and mechanism of action

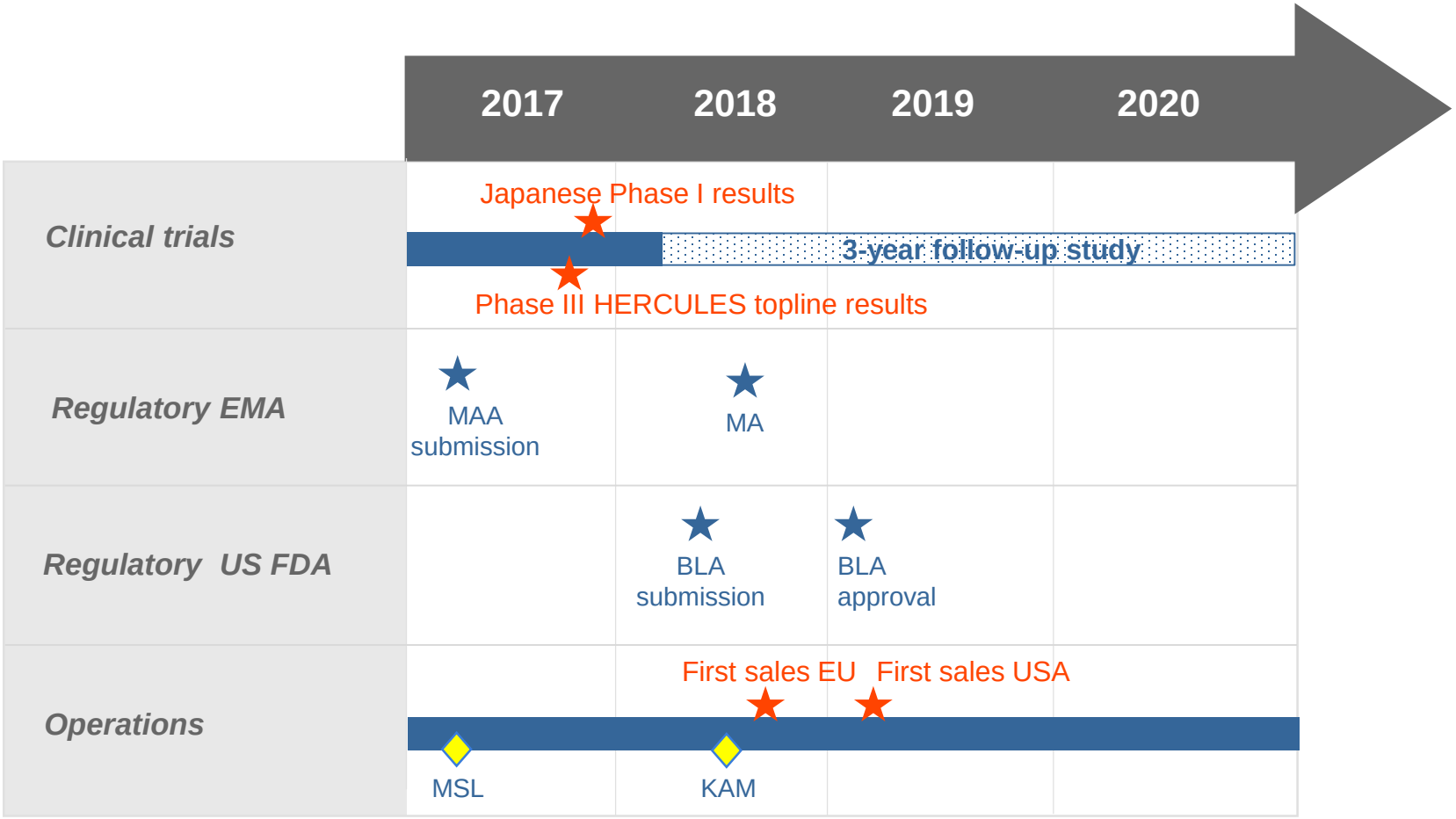
Next steps

All communicated timelines remain on track

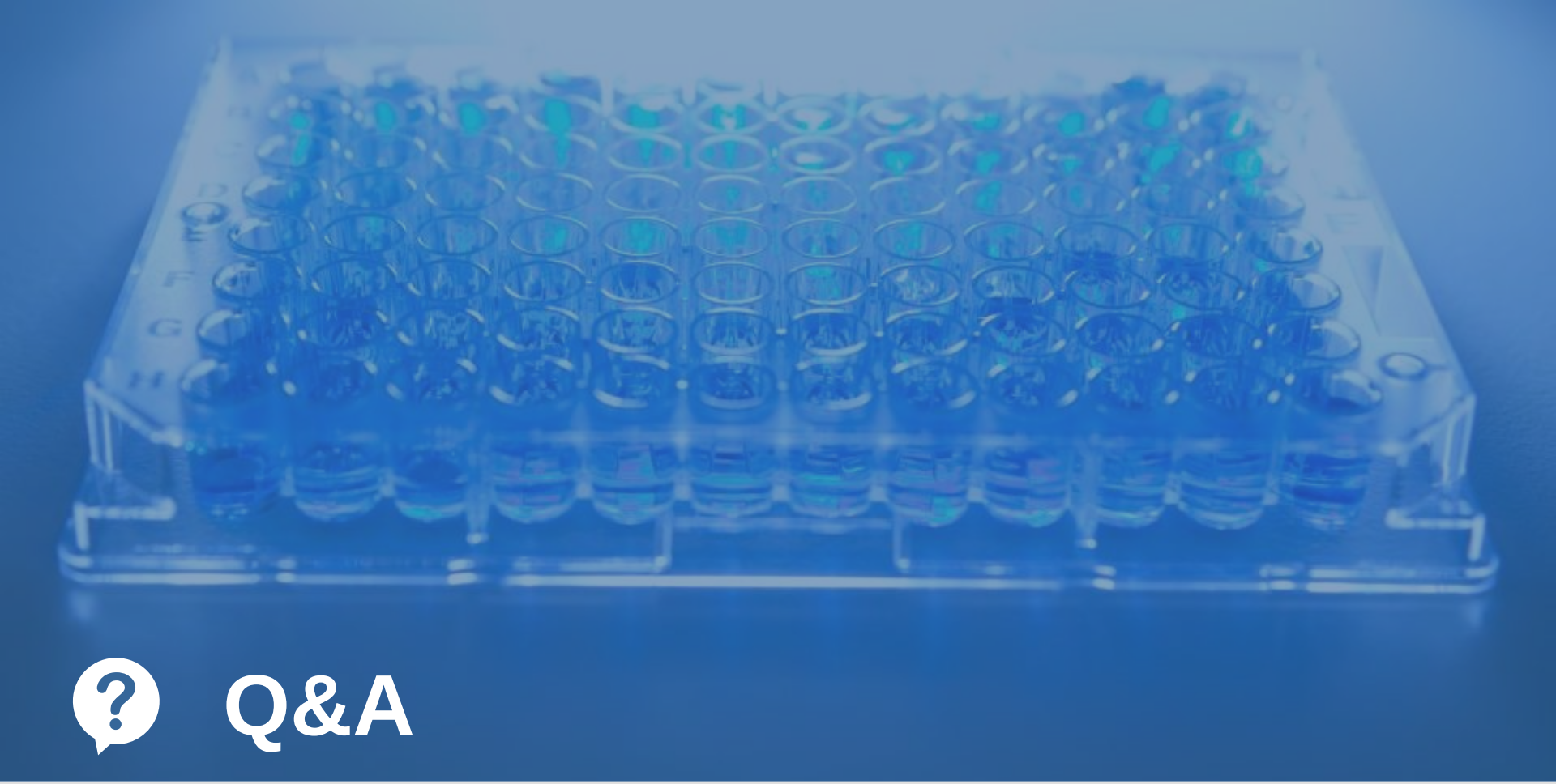
- Complete full analysis of Phase III HERCULES results and present at a key scientific conference and submit to a peer-reviewed journal
- Submit Phase III HERCULES results to EMA to support the MAA filed in February 2017
- Prepare BLA for USA FDA, filing planned in H1 2018
- Continue the 3-year follow-up study for eligible patients who participated in the Phase III HERCULES study
- Continue preparations for commercialisation of caplacizumab which is wholly-owned

Caplacizumab in aTTP

Key anticipated milestones



MAA: marketing authorisation application; **MA**: marketing authorisation; **BLA**: biologic license application; **MSL:** medical science liaison; **KAM**: key account manager



Q&A

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