OC 11.4: Phase 2/3 Trial of Subcutaneous Engineered FVIIa Marzeptacog Alfa (Activated) in Hemophilia A or B with Inhibitors: Efficacy, Safety and Pharmacokinetics

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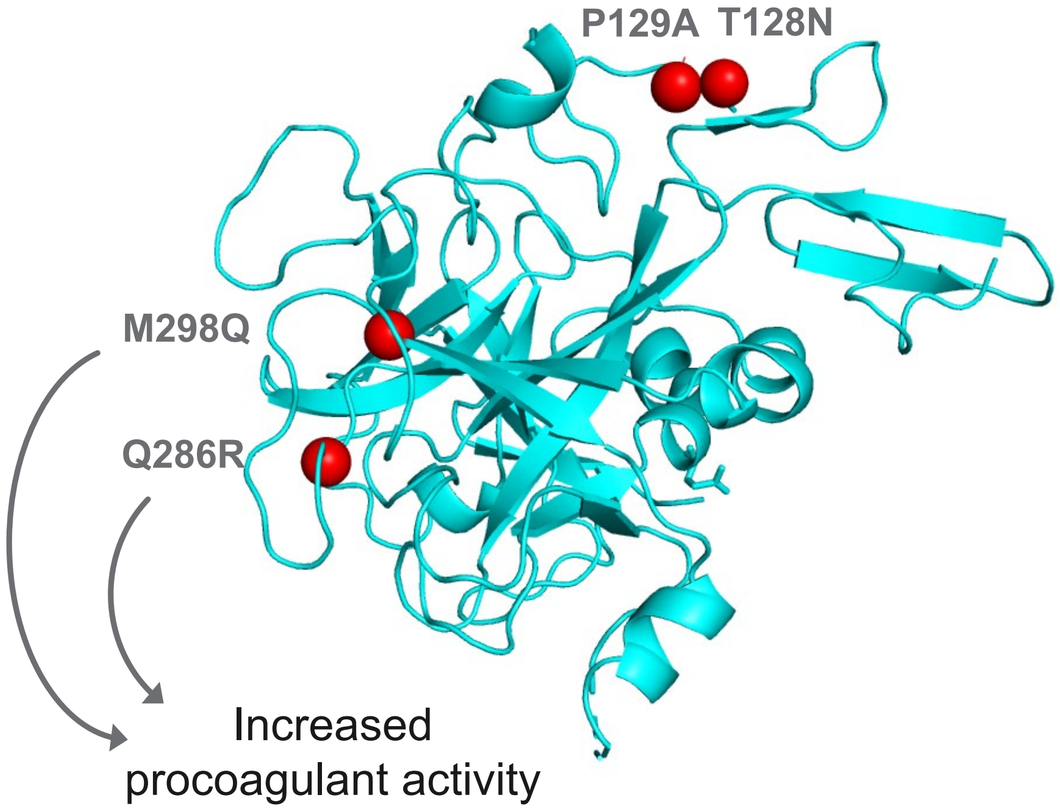
Marzeptacog alfa (activated): MarzAA

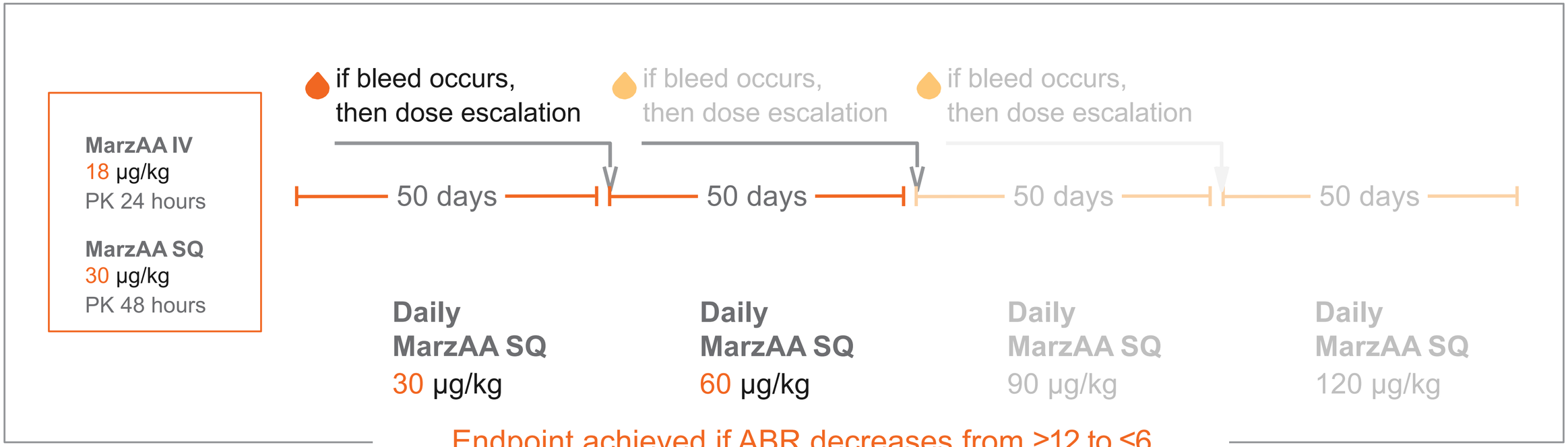
Prophylaxis is not available for patients with hemophilia B with inhibitors or hemophilia A with inhibitors who fail emicizumab



- Four engineered amino acid substitutions within the FVIIa protein
- 9-fold more potent catalytic activity than NovoSeven RT
- Allows subcutaneous dosing
- Half-life prolonged when using subcutaneous dosing

Granted Orphan Drug Designation in the US and EU

MarzAA phase 2/3 SQ clinical trial MAA-201 design



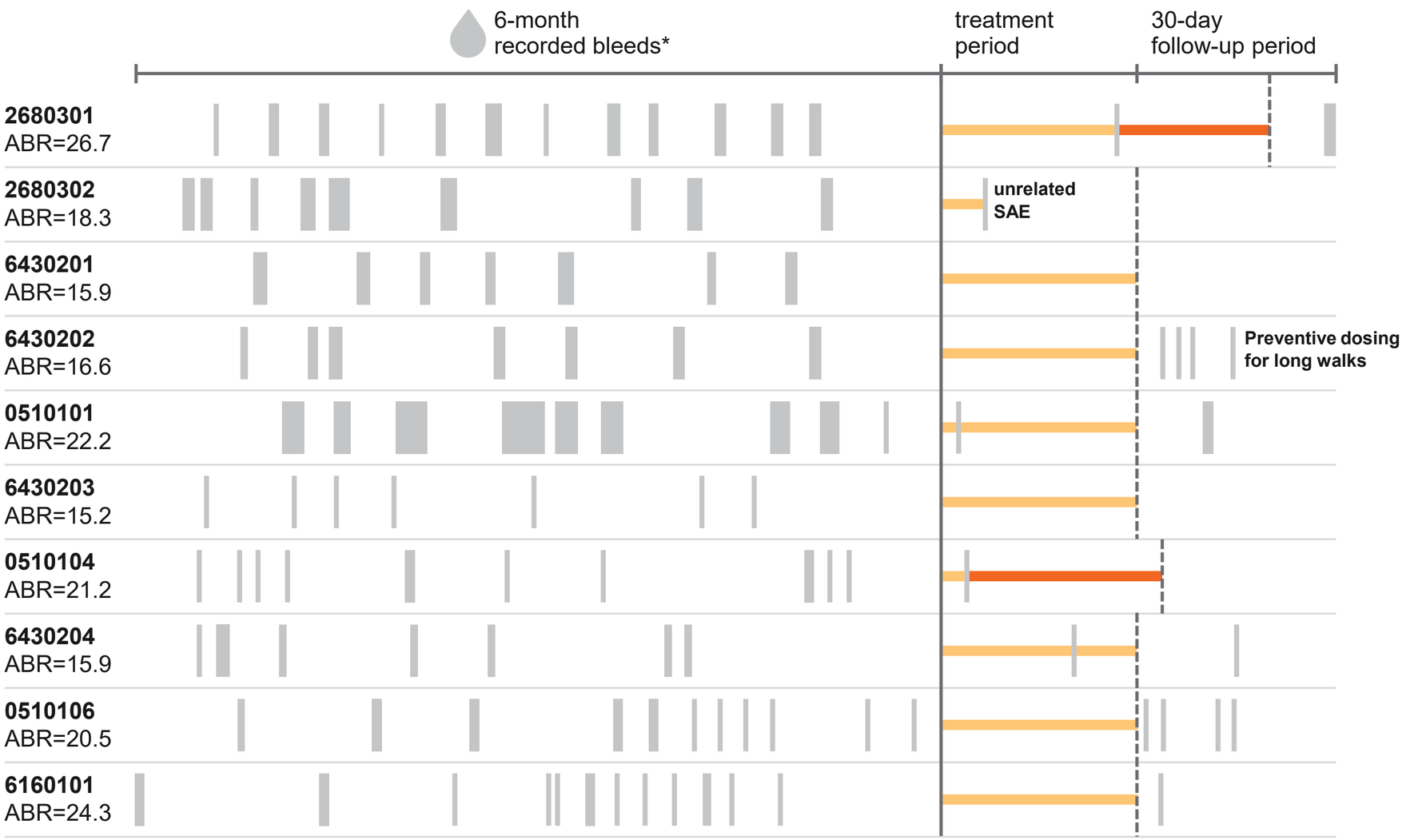
- Patients with documented annual bleeding rate (ABR) >12
- Open label SQ study with individual dose escalation if needed in Hemophilia A or B with inhibitors
- Primary endpoint: reduction in annualized bleed rate **at final dose level**
- Secondary endpoints: safety and tolerability, inhibitor formation

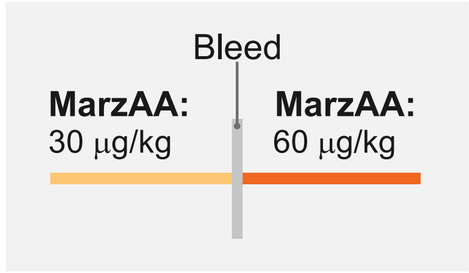
Phase 2 study patient disposition and efficacy

Clinical efficacy and tolerability demonstrated with SQ MarzAA

- 17 subjects were consented; 11 enrolled; 1 revoked consent before starting Part 2; 1 fatal SAE unrelated to MarzAA; 9 subjects completed the study
- Pre-treatment ABR: Mean 19.8; Range 12.2-26.7
- Pre-treatment Proportion of Days with Bleeding (PDB): Mean 12.3%; Range 4-22%
- Excellent compliance
  - Total of 517 subcutaneous injections
  - Exposure of 97 days of SQ dosing in one subject
  - 7 subjects remained at 30 µg/kg while 2 subjects dose escalated to 60 µg/kg per protocol due to spontaneous bleeds
- At the final dose level for all subjects:
  - 7/9 subjects had zero bleeds (traumatic or spontaneous)
  - Clinically and statistically significant reduction in ABR
  - Clinically and statistically significant reduction in proportion of days with bleeding

MarzAA demonstrated robust reduction in annualized bleed rate (ABR)

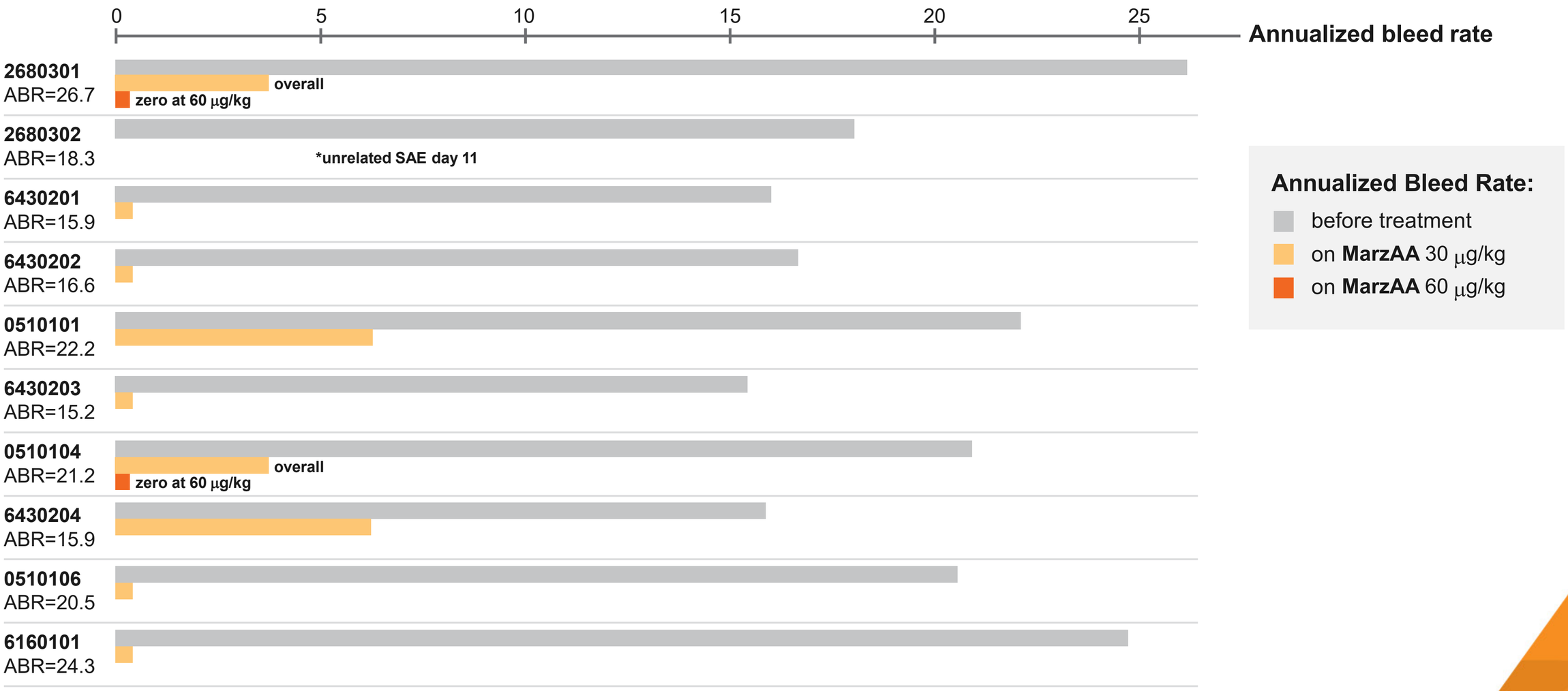




*The width of each grey bar represents bleed duration: 1 to 9 days

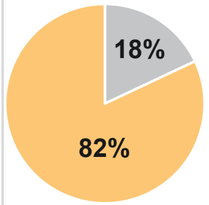
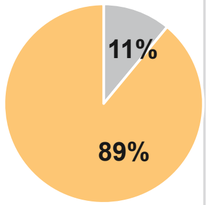
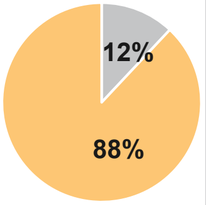
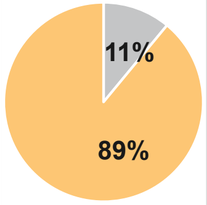
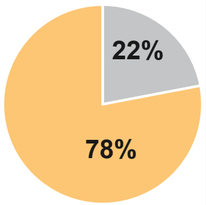
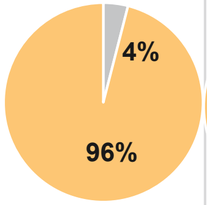
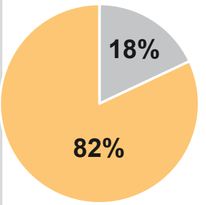
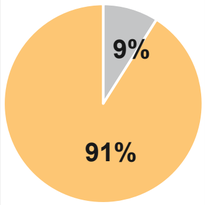
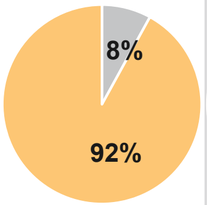
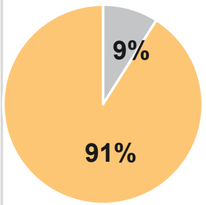
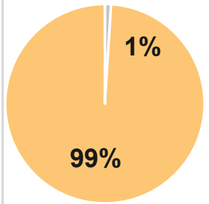
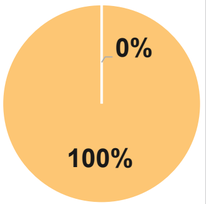
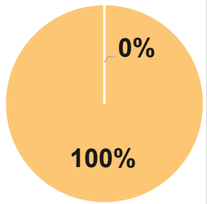
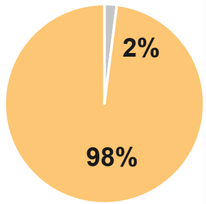
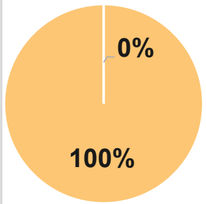
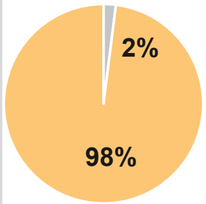
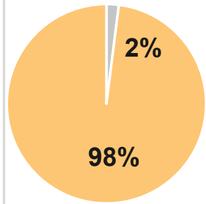
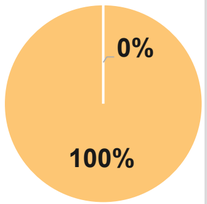
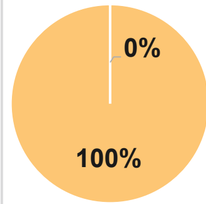
Significant reduction in ABR with treatment compared with baseline

Median ABR reduced to zero



Significant reduction in Proportion of Days with Bleeding (PDB)

Median Proportion of Days with Bleeding reduced to zero

Subject	2680301	2680302	6430201	6430202	0510101	6430203	0510104	6430204	0510106	6160101
Pre-treatment										
On-treatment		Unrelated SAE								

Grey denotes the Proportion of Days with Bleeding during period of observation

- Average **pre-treatment** percentage of days of bleeding was **12.3%** (SD 5.8%) [median = 11.0%]
- Average **on-treatment** percentage were reduced to **0.8%** (SD 0.9%) [median 0%]
- Analysis of these pairwise differences by Wilcoxon signed-rank test has p=0.009 for 93.8% reduction

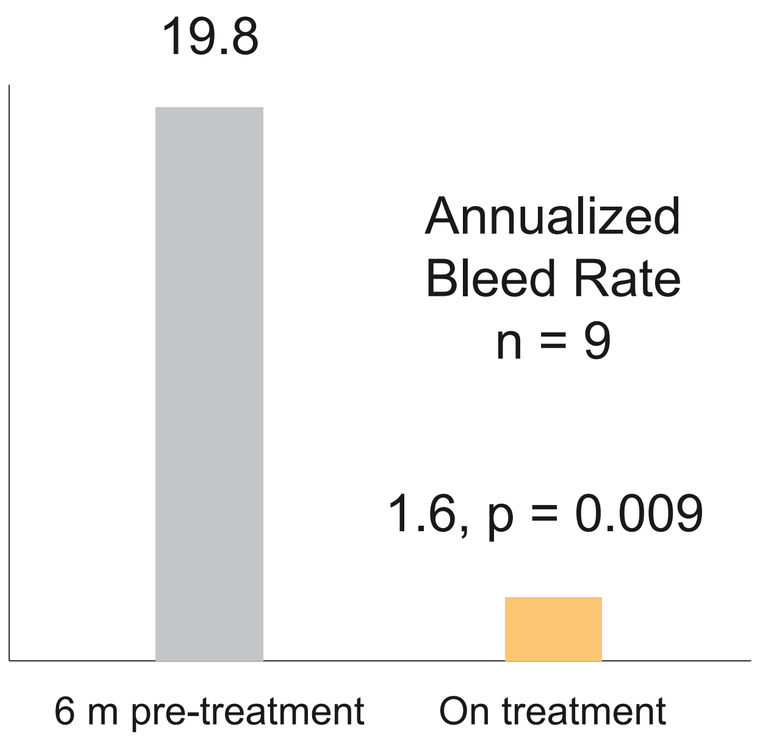
Marzeptacog alfa (activated) Phase 2 demonstrates clinical efficacy

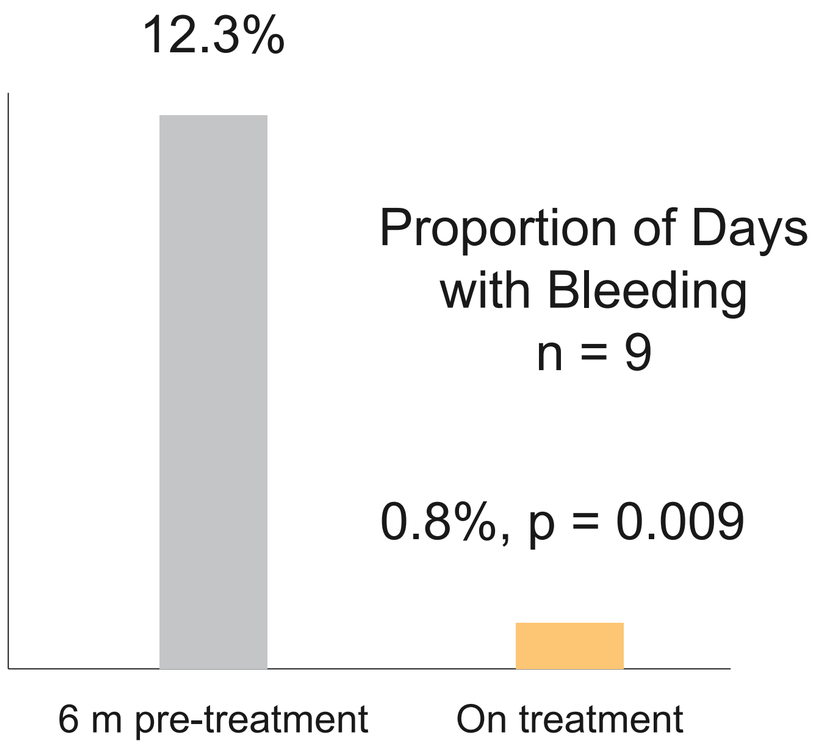
Greater than 90% reduction in all bleeding; Median ABR zero; Median bleeding days zero

Mean Annualized Bleeding Rates (ABR) significantly reduced from 19.8 to 1.6

Mean Proportion of Days with Bleeding (PDB) significantly reduced from 12.3% to 0.8%

Safe & well tolerated, ~1% ISRs (517 SQ doses) and no ADAs



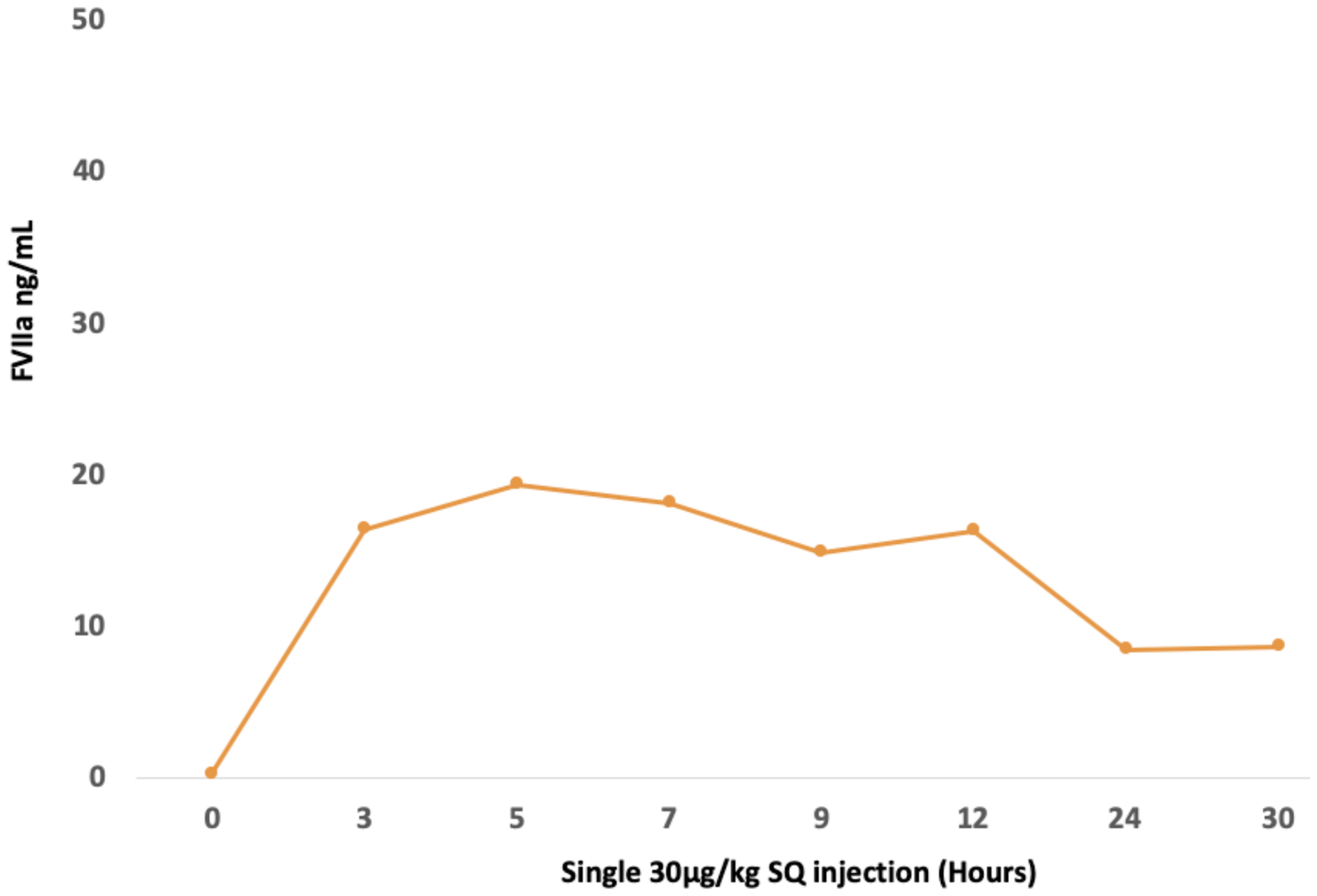


MAA-201 safety

Safe & well tolerated

+ No anti-drug antibodies were detected
+ One fatal unrelated SAE: intracerebral hemorrhage due to untreated hypertension
+ 517 SQ injections were administered
  - 6 injection site reactions in 2 subjects
    - 1 moderate swelling that resolved without sequelae in one subject
    - 2 mild and 3 moderate redness that resolved without sequelae in the other subject and did not occur with subsequent SQ injections

Mean First SQ dose PK; Mean Trough & Mean 7h post-dose FVIIa level by dose



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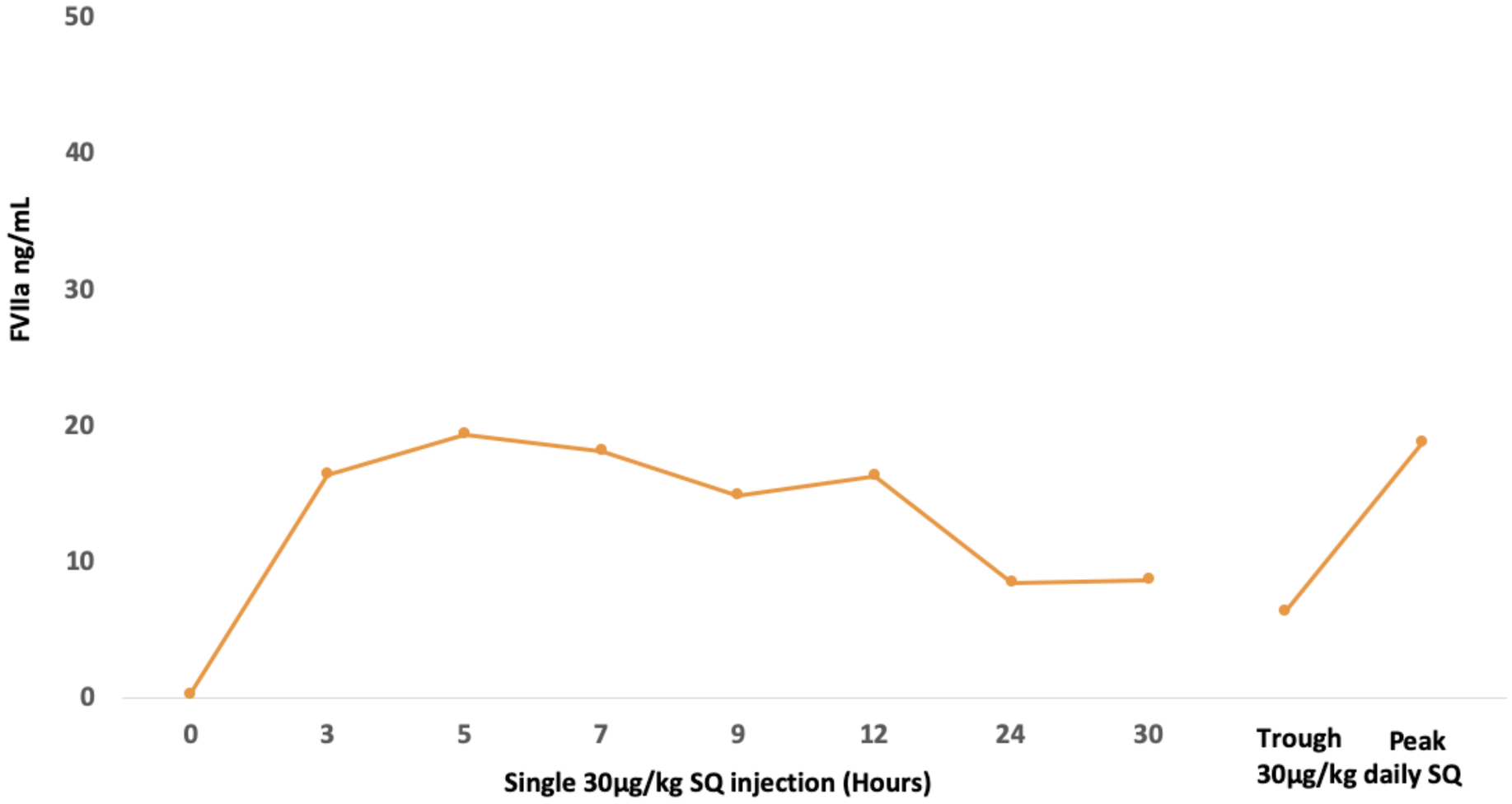

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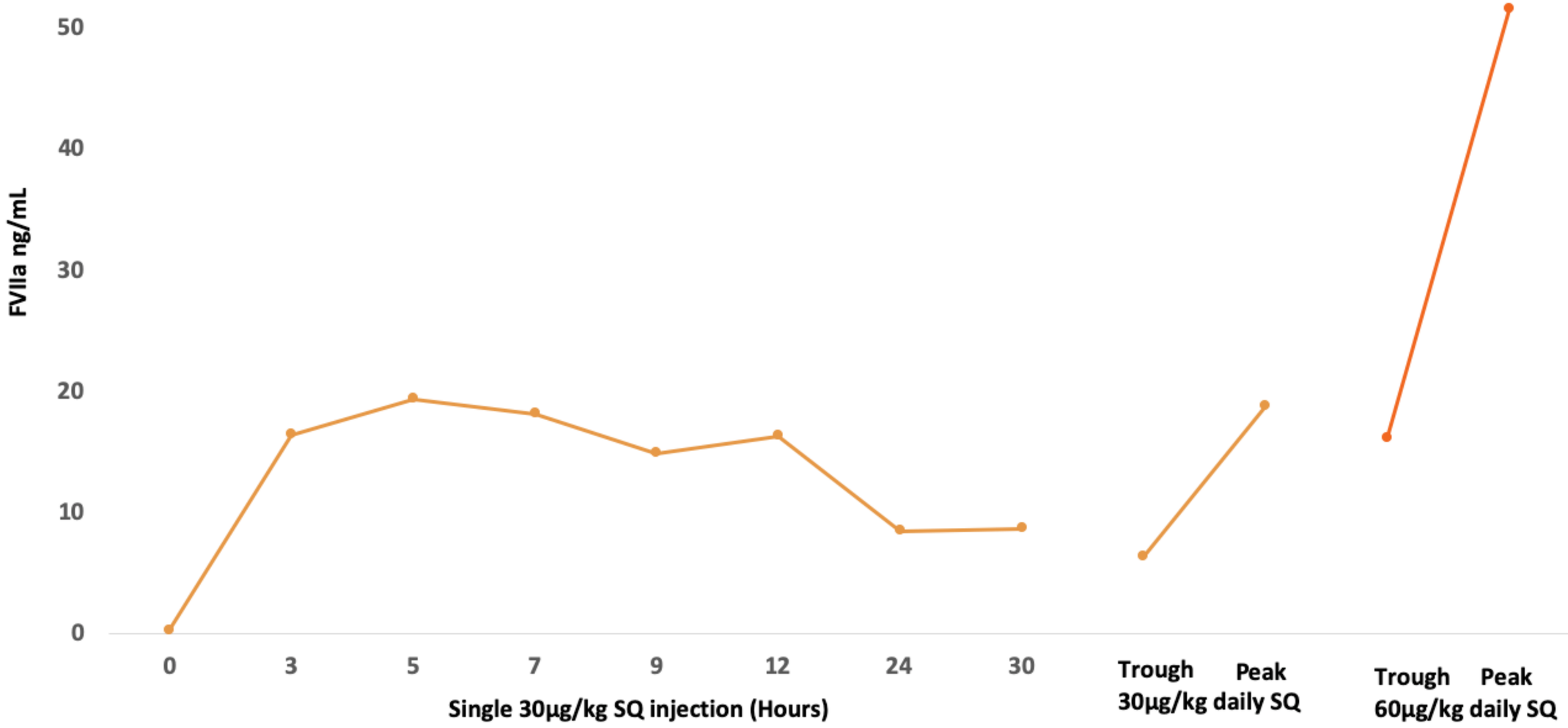

Conclusions on the marzeptacog alfa (activated) program

Moving forward in clinical development

- Clinical efficacy demonstrated
- Safe and well tolerated
- Moving forward with Phase 3 study planning
- No anti-drug antibodies detected
- Exploring the use of MarzAA in additional indications