Avoralstat – OPuS-2 Results

February 8, 2016

BioCryst Pharmaceuticals, Inc.

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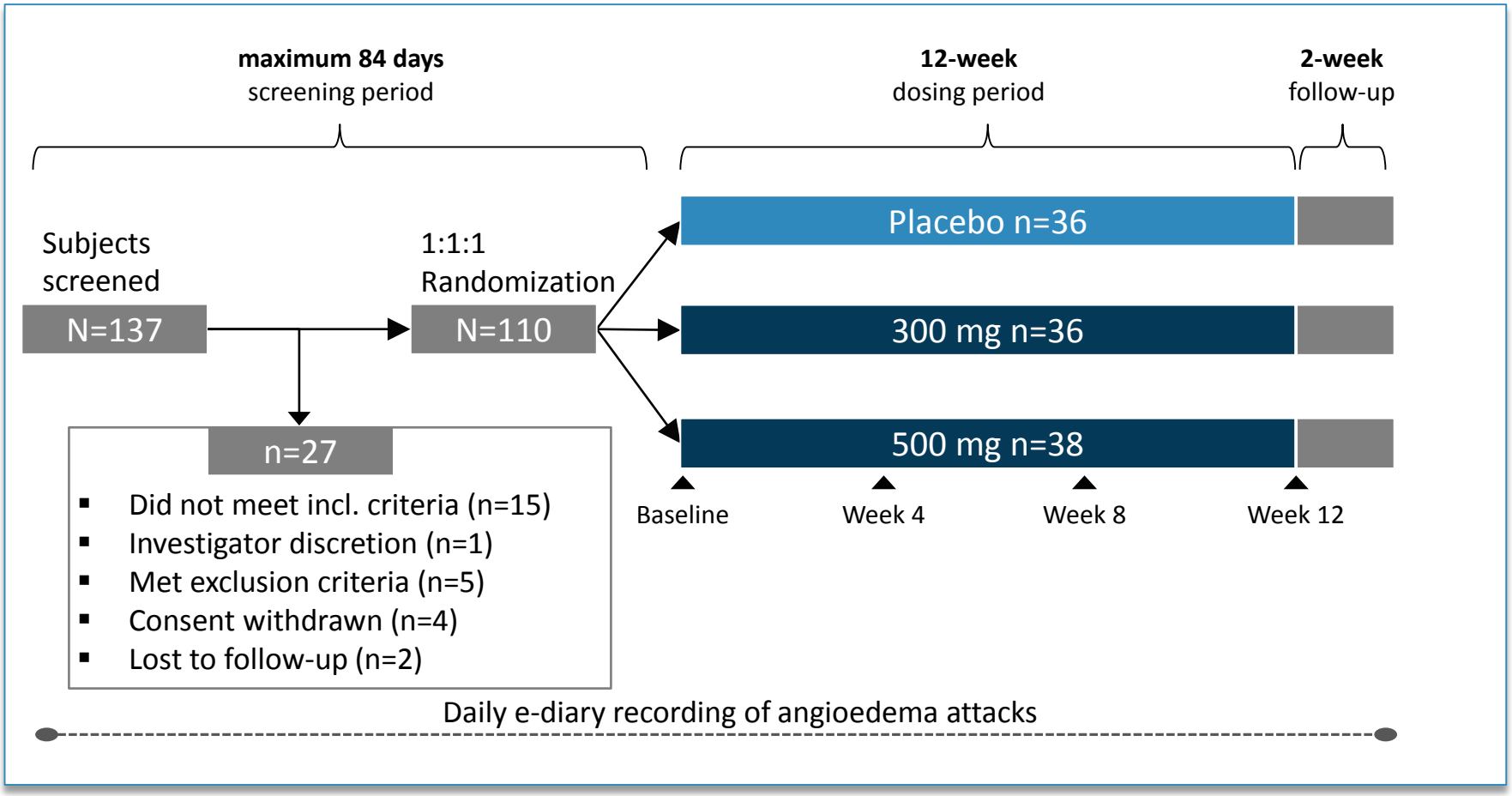
OPuS-2 study design overview



Baseline characteristics of study subjects

	Avoralstat 500 mg TID	Avoralstat 300 mg TID	Placebo
Number of subjects	*38*	*36*	*36*
Age – mean (range)	41.1 (18, 73)	40.4 (20, 71)	42.1 (20, 67)
Female gender – n (%)	30 (78.9%)	29 (80.6%)	26 (72.2%)
Caucasian ethnicity – n (%)	36 (94.7%)	32 (88.9%)	34 (94.4%)
BMI – mean (range)	26.7 (19.2 – 35.9)	28.1 (19.1, 36.0)	25.6 (19.4, 35.9)
Europe : North America – n:n	18:20	14:22	18:18
Qualifying attack rate ***mean (SD)***	0.95 (0.39)	0.93 (0.39)	0.92 (0.34)
Qualifying attack rate ≥ 1 attack/week – n (%)	12 (31.6%)	10 (27.8%)	14 (38.9%)
Concurrent androgen use – n (%)	2 (5.3%)	4 (11.1%)	4 (11.1%)

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Study conduct

Parameter	Value
Countries	US, Canada, Germany, UK, France, Italy, Hungary, Belgium
Number of sites enrolling subjects	40 sites
Number of sites enrolling subjects per region, US: EU: CA	20 : 17: 3
Subjects per Site, median (min, max)	2 subjects (1, 12)
Number of subjects with ≥ 95% compliance in daily HAE attack diary (n/n in ITT)	105/110
Number of subjects with ≥ 95% compliance in drug dosing (capsule count)	94/110
Eligibility met (n % in ITT)	110 (100%)
Early discontinuation from study drug (n % in ITT)	7 (6.4%)
Reasons for early discontinuation	Adverse Event (2) Protocol Violation (1) Study Non-Compliance (1) Lack of Efficacy (2) Pregnancy (1)

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Efficacy endpoints

Endpoint	Avoralstat 500 mg TID		Avoralstat 300 mg TID		Placebo	
Number of subjects	*38*		*36*		*36*	
Confirmed attack rate per week ***mean (SD)***	0.63	(0.57)	0.71	(0.66)	0.61	(0.41)
Subject-reported attacks ***mean (SD)***	0.66	(0.57)	0.77	(0.72)	0.67	(0.45)
Attack severity (AAS84 score) ***median [range]***	52.5	[0,372]	76	[0,463]	83	[0,381]
Angioedema Quality of Life Index Total Score § ***LS mean {SEM} change from baseline***						
Week 4	-16.6*	{2.4}	-5.1	{2.5}	-9.4	{2.1}
Week 8	-18.6*	{2.7}	-11.0	{3.0}	-9.7	{2.1}
Week 12	-17.5	{2.7}	-9.9	{3.1}	-12.1	{2.6}
Number of attacks	*263*		*288*		*252*	
Attack duration (hours) ***LS mean {SEM}***	24.3†	{1.5}	26.8	{1.5}	30.4	{1.5}

**p<0.05; †p<0.005; § reduction in score from baseline indicates improvement*

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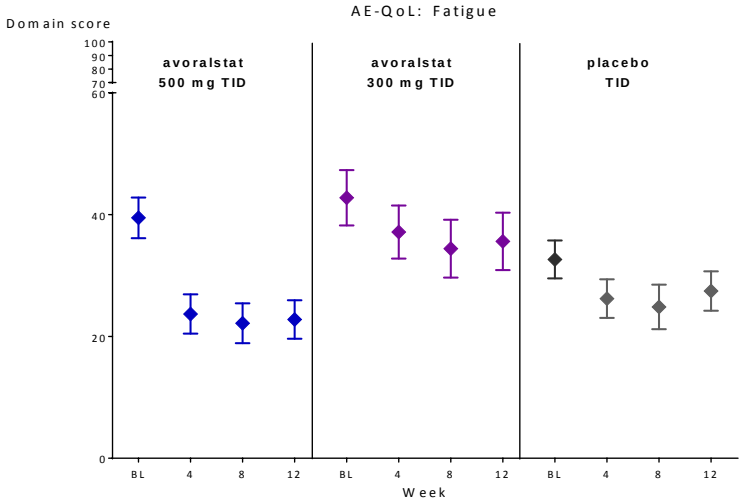
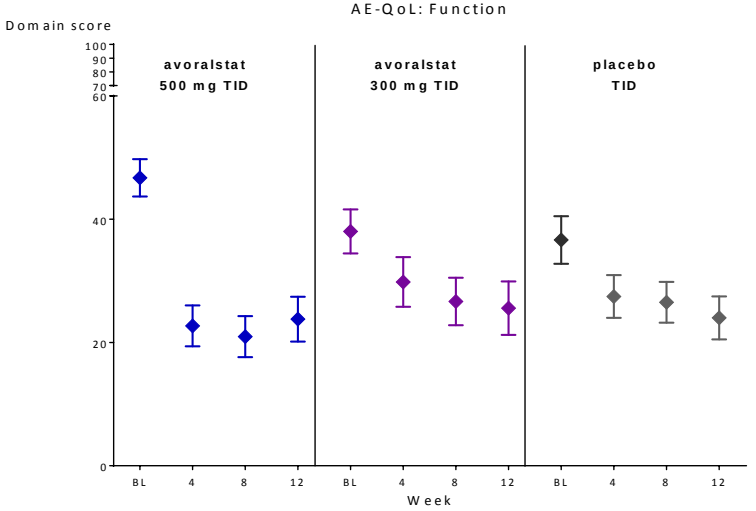
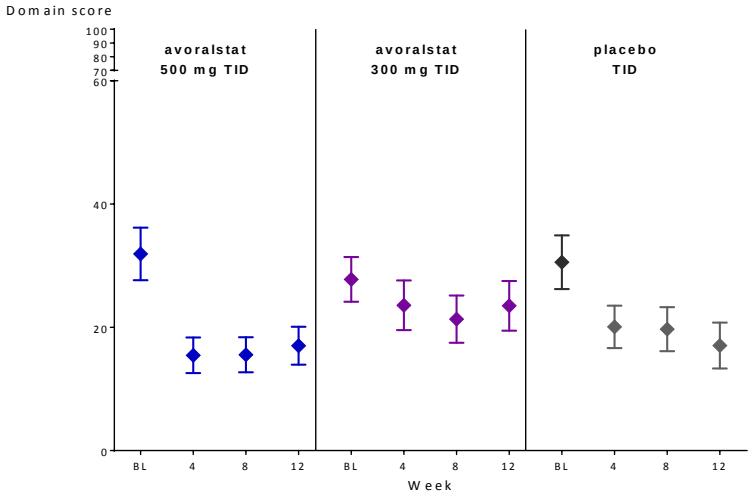
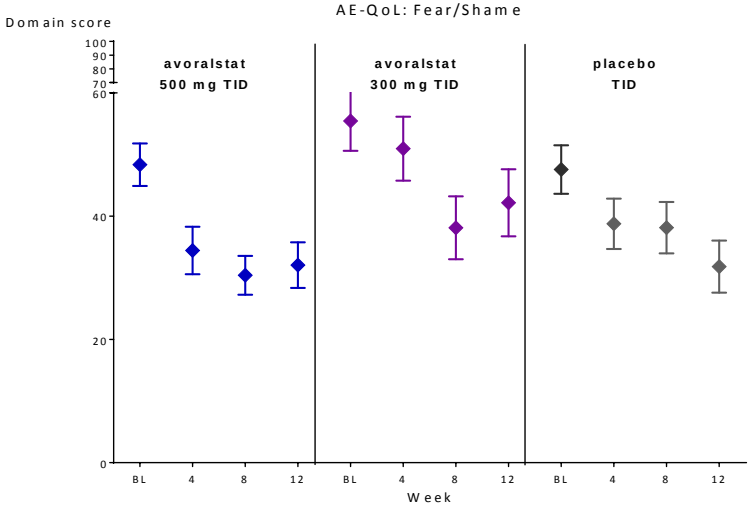
Angioedema Quality of Life domains









Mean (SEM); reduction in score from baseline indicates improvement

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Safety

Category	Avoralstat 500mg (N=38)	Avoralstat 300mg (N=36)	Placebo (N=36)
Number of subjects per group	*38*	*36*	*36*
Number of Subjects with Any Serious AE, n (%)	3 (7.9)	2 (5.6)	3 (8.3)
Number of Subjects with Any Drug-Related SAE, n (%)	0	0	0
Number of Subjects with Any AE of Grade 3 or Grade 4, n (%)	4 (10.5)	5 (13.9)	5 (13.9)
Number of Subjects with Any Drug-related AE of Grade 3 or Grade 4, n (%)	0	3 (8.3)	1 (2.8)
Number of Subjects with AE Leading to Permanent Discontinuation from Study, n (%)	2 (5.3)	0	0

- Avoralstat was generally safe and well tolerated
- The most common adverse events were gastrointestinal (soft stool and flatus)
- Adverse event incidences were balanced across all 3 arms
- No significant laboratory abnormality differences across arms

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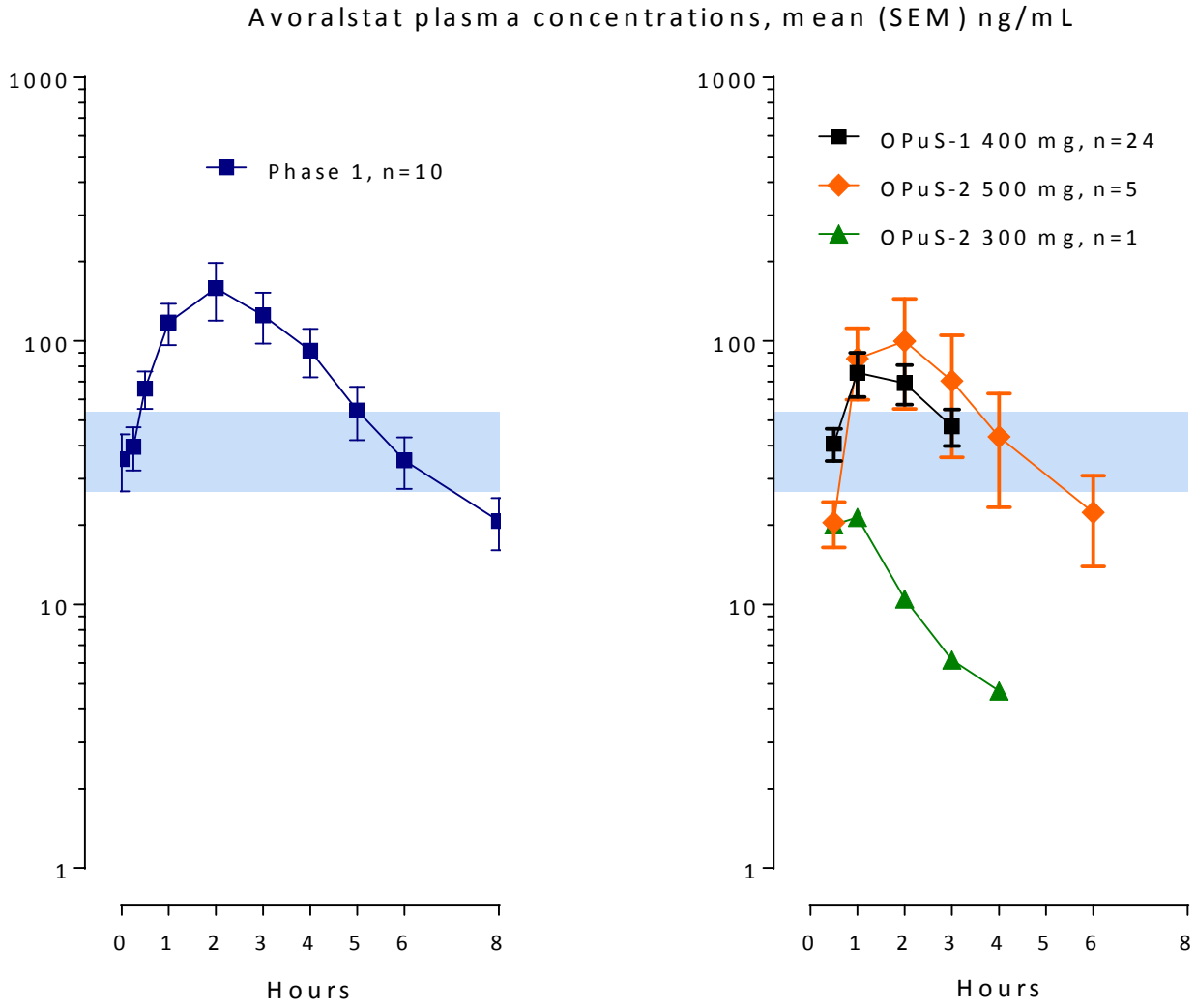
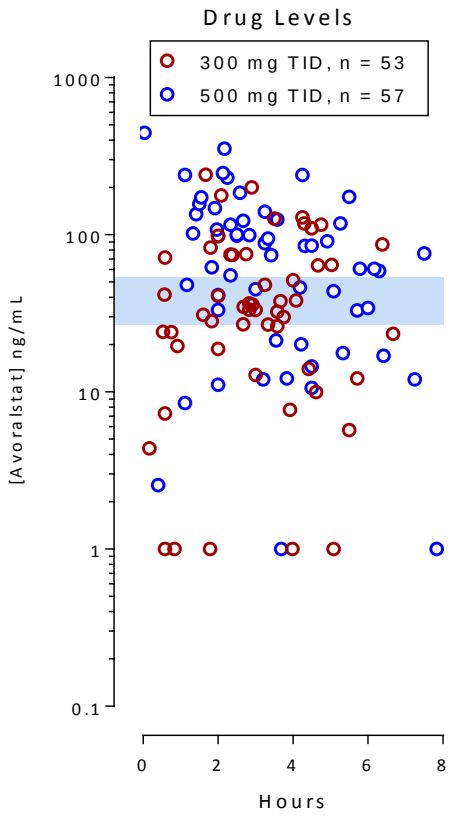
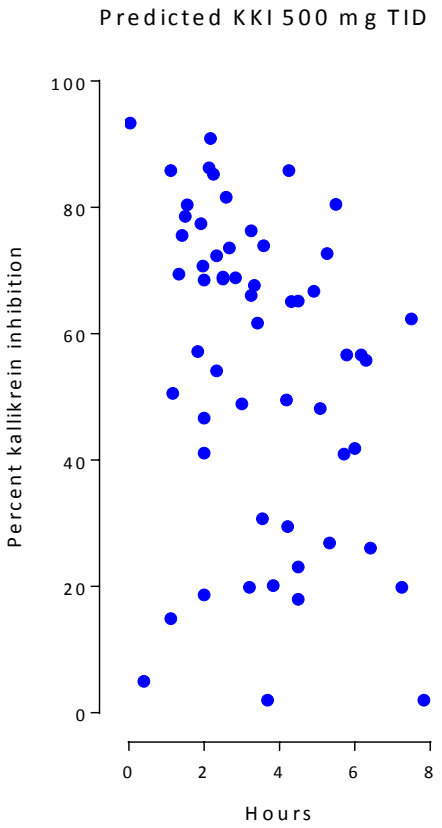
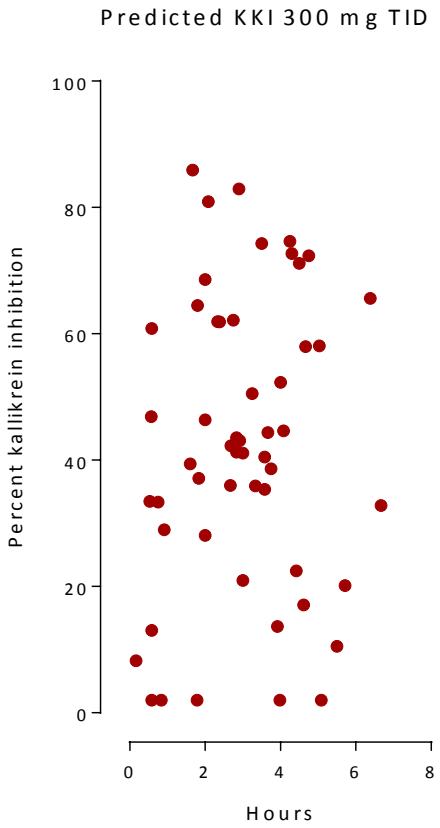
Serial avoralstat plasma concentrations after dosing of liquid formulations in healthy subjects and HAE patients



Population avoralstat plasma concentrations in OPuS-2 and predicted kallikrein inhibition







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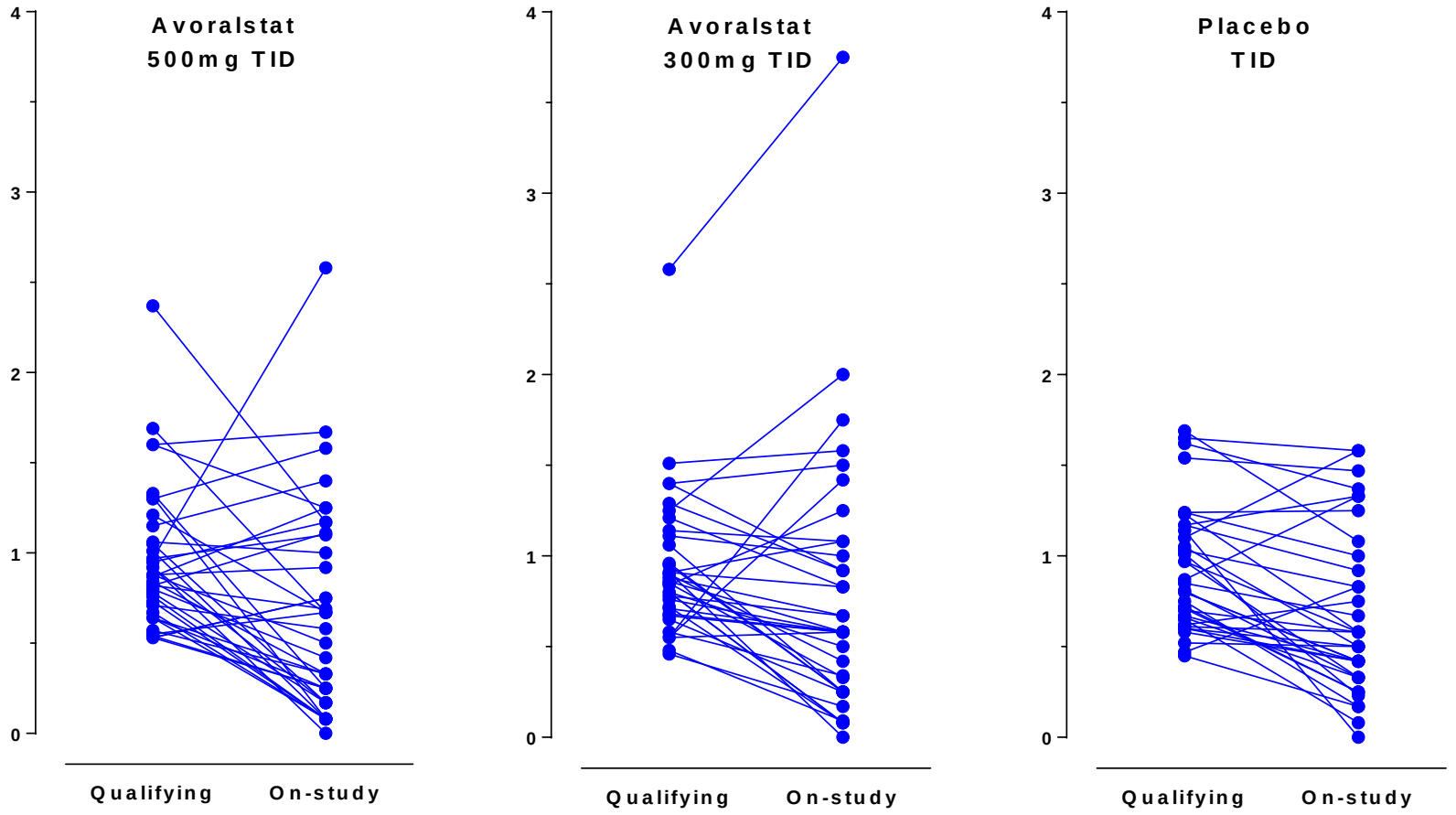
Patient-reported attack rates per week in OPuS-2



Comparison of OPuS-1 and OPuS-2

Parameter	OPuS-1, n = 24 400 mg TID	OPuS-2, n = 110
Study Design	4 week, crossover, placebo-controlled	12 week, parallel group, placebo-controlled, stratification by attack rate
Countries / sites	Germany, UK 5 sites total	US, Canada, Germany, UK, France, Italy, Hungary, Belgium 40 sites total
Subjects per sites, median (min, max)	4 subjects (2,8)	2 subjects (1, 12)
Attack rate qualification eligibility source	Historical	Historical OR run-in
Attacks/week study eligibility criterion	≥ 1.0	≥ 0.45
Actual qualifying attack rate mean (SD) attacks/week	1.5 (0.60)	0.93 (0.37)
Capsule compliance, mean % (SD)	Avoralstat: 98 (4.0) Placebo: 98 (3.9)	Avoralstat 300 mg: 100 (5.1) Avoralstat 500 mg: 97 (6.3) Placebo: 99 (5.8)
Interval between last dose of day→ first dose of next day (mean hours, SD) Avoralstat	9.1 (1.5)	300 mg: 11 (4.5) 500 mg: 12 (5.7)
Interval between first dose of day→ second dose of day (mean hours, SD) Avoralstat	7.3 (1.3)	300 mg: 6.8 (2.4) 500 mg: 7.2 (2.5)
Interval between second dose of day→ last dose of day (mean hours, SD) Avoralstat	7.6 (1.3)	300 mg: 6.1 (4.2) 500 mg: 5.3 (5.8)
Difference in qualifying attack rate and on-study attack rate for placebo, mean (SD)	-0.18 % (40%)	-28 % (39%)

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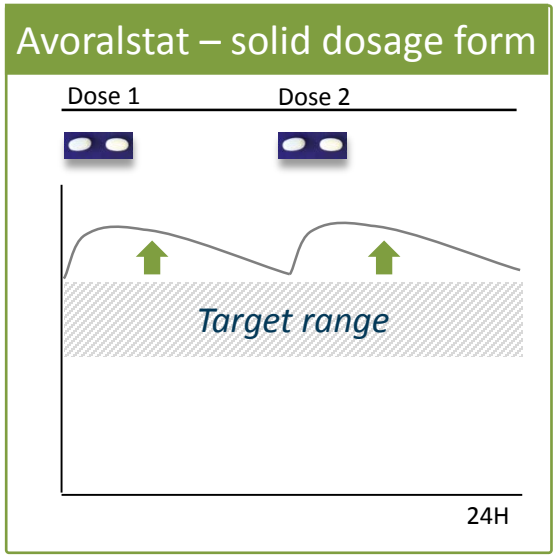
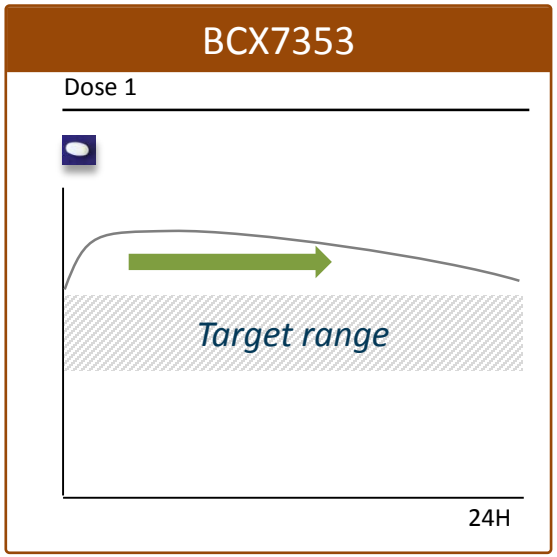
Conclusions

- Avoralstat was safe and well tolerated over 12 weeks in patients with hereditary angioedema
- The primary endpoint of HAE attack rate was not met
- Duration of attacks, severity scores, and quality of life scores showed evidence of benefit of avoralstat
- The exposure profile achieved by the liquid formulation of avoralstat was insufficient for efficacy in this study, and is not suitable for further development
- The avoralstat development program will focus on a solid dosage formulation
  - NHP studies show superior exposure and longer absorption time
  - Results of a healthy subject PK study will be available by mid-year
- In order to proceed with a new efficacy study of avoralstat in HAE patients using the solid dosage formulation, exposure in healthy subjects will need to be meaningfully better than with the liquid

Revised strategy





Goal: Conveniently dosed, highly effective, oral drug

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Key HAE Program 2016 Milestones

Avoralstat

- PK study of solid dose form (mid-2016)

BCX7353

- Complete APeX-1 proof of concept trial (end of 2016)

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