BCX7353 – APeX-1
Second Interim Analysis Results

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BioCryst Pharmaceuticals, Inc.

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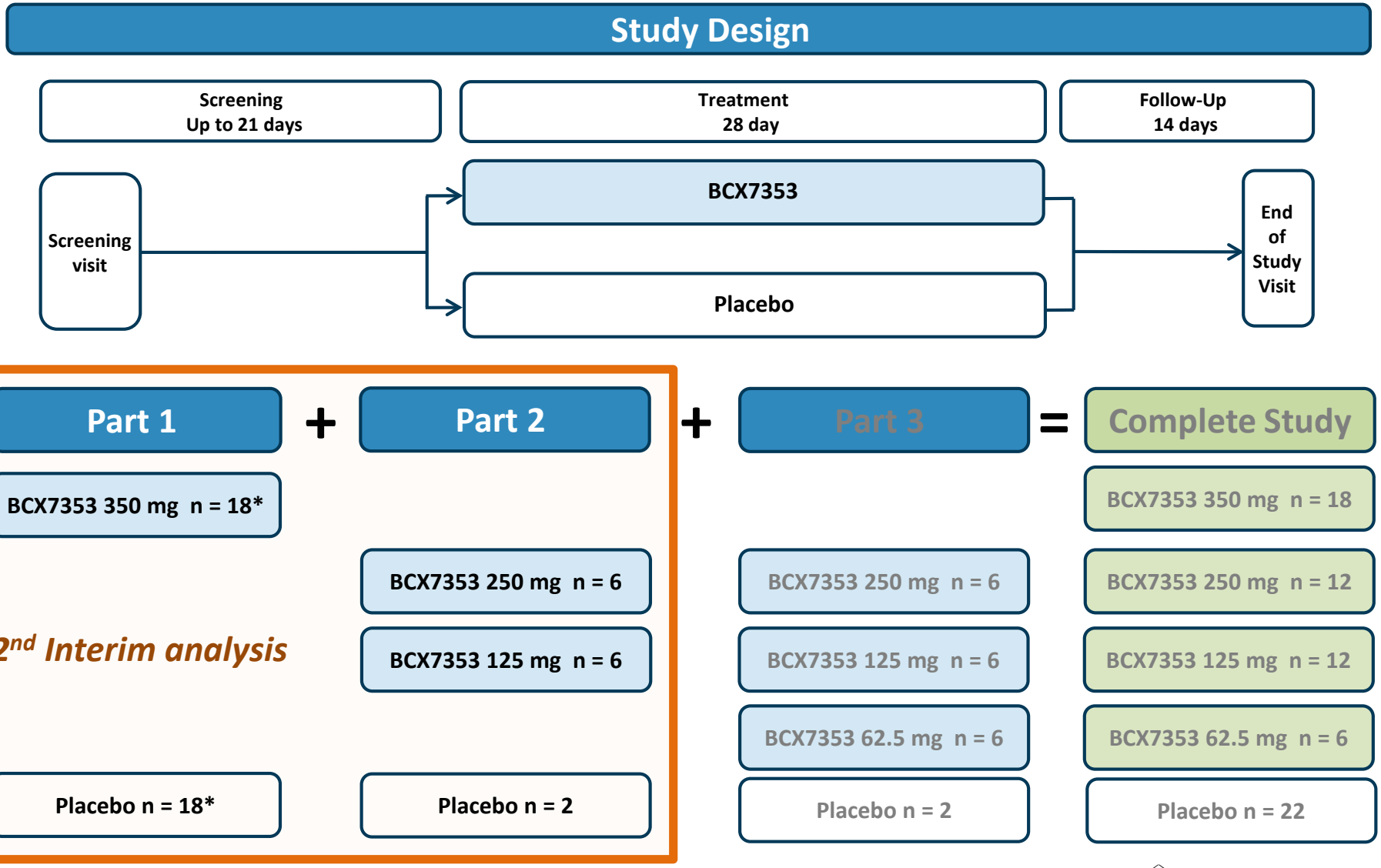
Headlines – APeX-1 Trial second interim analysis

- BCX7353 once daily for 4 weeks showed clinically meaningful and statistically significant reductions in the rate of angioedema attacks
  - 125 mg dose showed a reduction of 73% in overall attack rate (p=0.002)
- Oral BCX7353 once daily over 4 weeks was generally safe and well tolerated
- A dose related improvement in GI tolerability was observed in the 250 and 125 mg dose groups
- No significant treatment emergent abnormalities in laboratory safety parameters were observed in the 250 mg and 125 mg dose groups
- Steady state trough drug levels (24 hours after dosing) greatly exceeded the target therapeutic range at the 250 mg and 350 mg dose levels. Trough levels for the 125 mg dose were generally within the target range
- PK profile and kallikrein inhibition levels were similar to those seen at the same dose levels in Phase 1 healthy subjects

APeX-1: Trial design



*1st Interim analysis evaluated 14 subjects in each arm in Part 1

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APeX-1 second interim analysis population

	BCX7353			
	125 mg	250 mg	350 mg	Placebo
Randomized and treated	7	6	18	20
Intent to Treat (ITT) population	7	6	18	20
Per Protocol (PP) population	6	5	14	19
Excluded from PP population				
HAE Type 1 or 2 not confirmed			1	1
<28 days of dosing with study drug	1		3	
Non compliance with diary completion		1		
Study drug compliance, mean % (SD)	98% (5)	99% (1)	98% (8)	98% (6)

Age – years, mean (SD)	48.4 (14.0)	50.7 (12.1)	43.8 (11.6)	46.5 (11.7)
Sex – female, n (%)	5 (71%)	2 (33%)	11 (61%)	12 (60%)
Prior androgen use, n (%)	2 (29%)	5 (83%)	15 (83%)	11 (55%)
Qualifying attack rate, attacks/wk mean (SD)	0.90 (0.26)	0.83 (0.52)	0.84 (0.35)	0.90 (0.46)

Rate of overall confirmed attacks: PP population

Treatment	n	LS mean[1] Attacks per Week	Difference vs Placebo	Percentage Reduction vs Placebo	p-Value vs Placebo
Effective dosing period (Week 2-4) – PP Population					
BCX7353 combined	25	0.402	-0.543	57%	<0.001
BCX7353 125 mg	6	0.253	-0.691	73%	0.002
BCX7353 250 mg	5	0.595	-0.349	37%	0.128
BCX7353 350 mg	14	0.397	-0.548	58%	0.001
Placebo	19	0.945	-	-	-
Part 1 Interim analysis:					
BCX7353 350 mg	*11*	*0.343*	*-0.572*	*63%*	*0.006*
Placebo	*13*	*0.915*			

[1] Least squares mean calculated using an ANCOVA model with qualifying attack rate as covariate

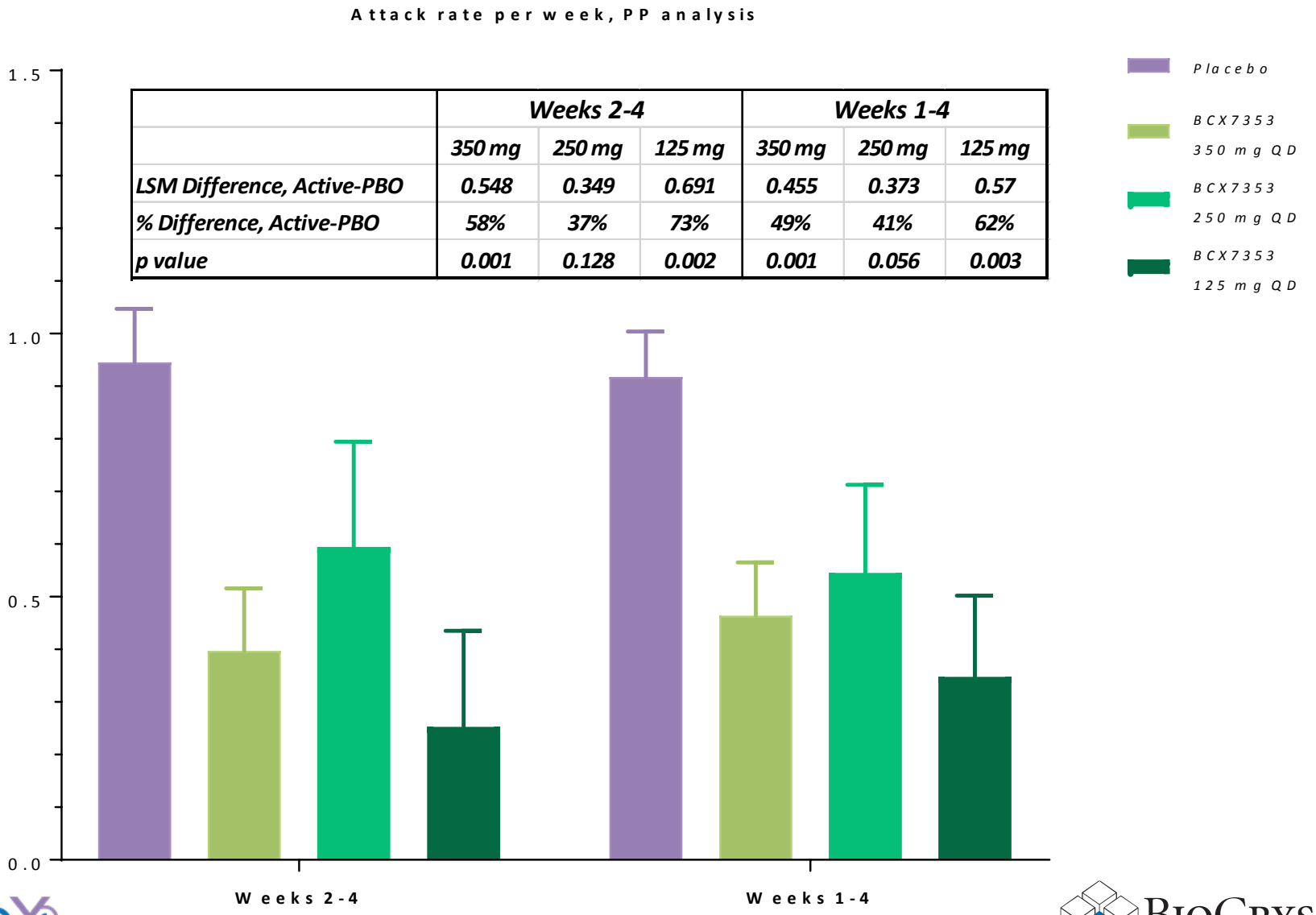
Rate of overall confirmed attacks: ITT population

Treatment	n	LS mean[1] Attacks per Week	Difference vs Placebo	Percentage Reduction vs Placebo	p-Value vs Placebo
Effective dosing period (Week 2-4) – ITT Population					
BCX7353 combined	31	0.457	-0.481	51%	0.002
BCX7353 125 mg	7	0.249	-0.689	73%	0.004
BCX7353 250 mg	6	0.526	-0.411	44%	0.090
BCX7353 350 mg	18	0.515	-0.423	45%	0.014
Placebo	20	0.938	-	-	-
Part 1 Interim analysis:					
BCX7353 350 mg	*14*	*0.436*	*-0.474*	*52%*	*0.035*
Placebo	*14*	*0.911*			

[1] Least squares mean calculated using an ANCOVA model with qualifying attack rate as covariate

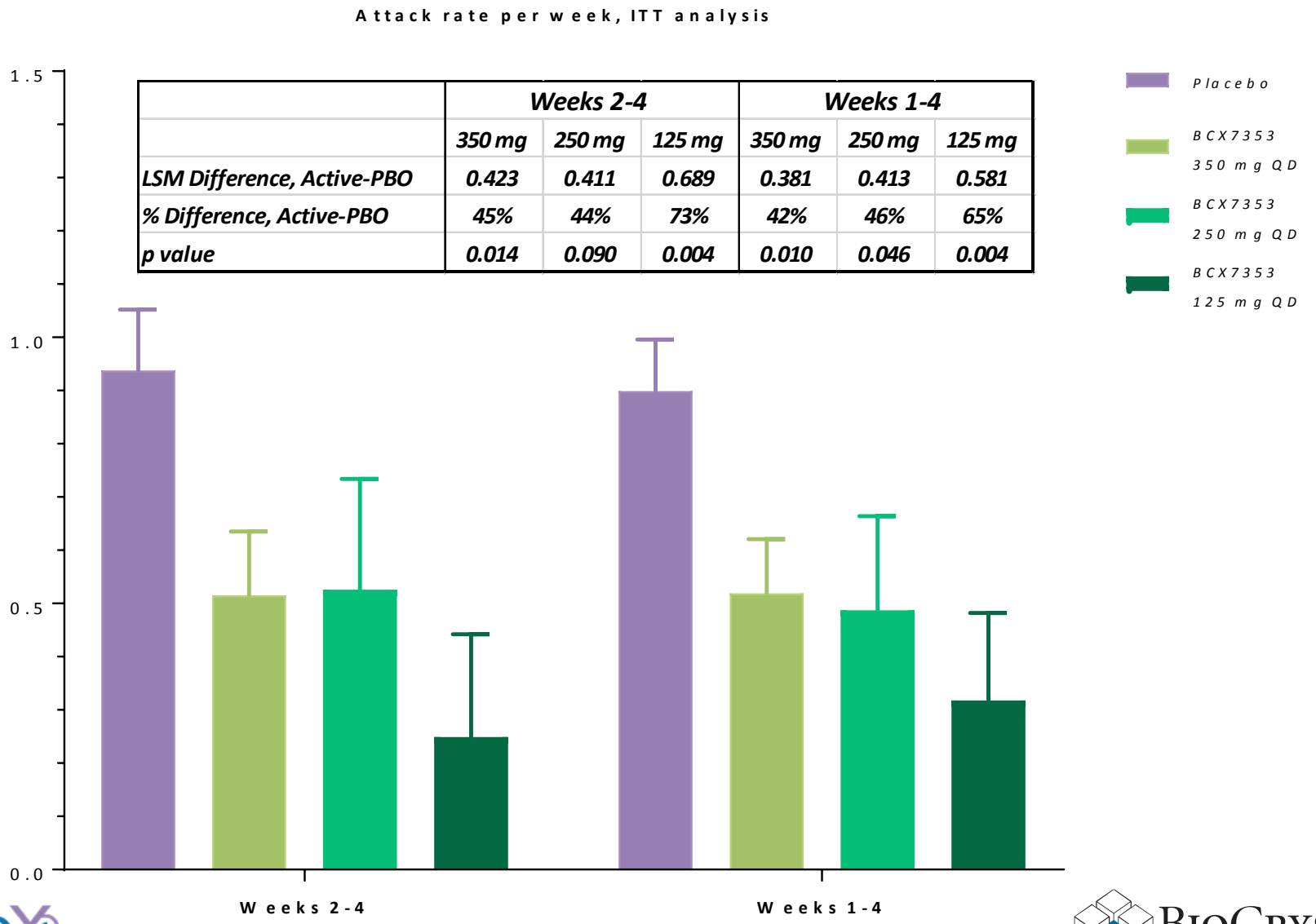
Overall attack rate, PP analysis, weeks 2-4 and 1-4

	Weeks 2-4			Weeks 1-4		
	350 mg	250 mg	125 mg	350 mg	250 mg	125 mg
LSM Difference, Active-PBO	0.548	0.349	0.691	0.455	0.373	0.57
% Difference, Active-PBO	58%	37%	73%	49%	41%	62%
p value	0.001	0.128	0.002	0.001	0.056	0.003

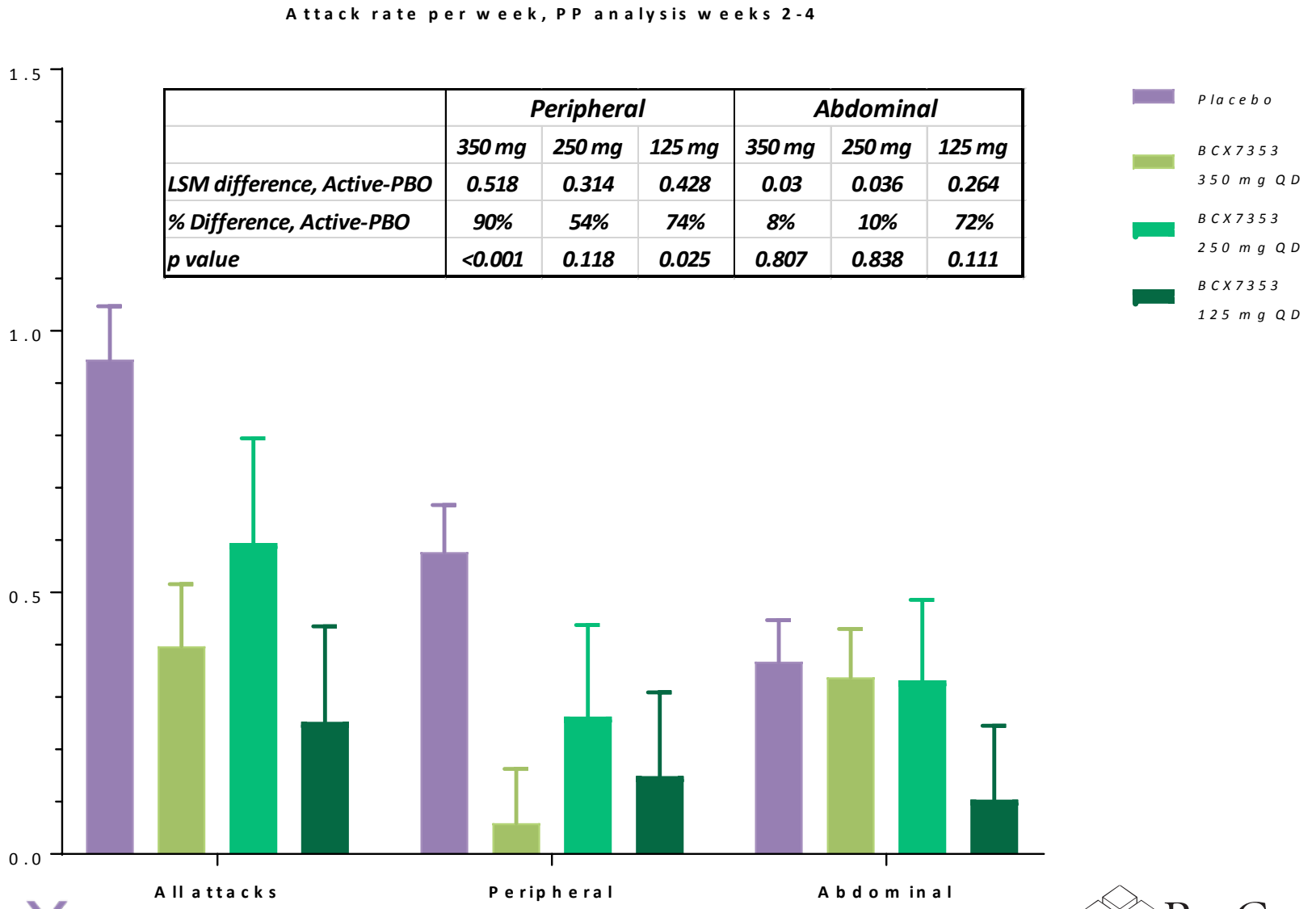


Overall attack rate, ITT analysis, weeks 2-4 and 1-4

	Weeks 2-4			Weeks 1-4		
	350 mg	250 mg	125 mg	350 mg	250 mg	125 mg
LSM Difference, Active-PBO	0.423	0.411	0.689	0.381	0.413	0.581
% Difference, Active-PBO	45%	44%	73%	42%	46%	65%
p value	0.014	0.090	0.004	0.010	0.046	0.004



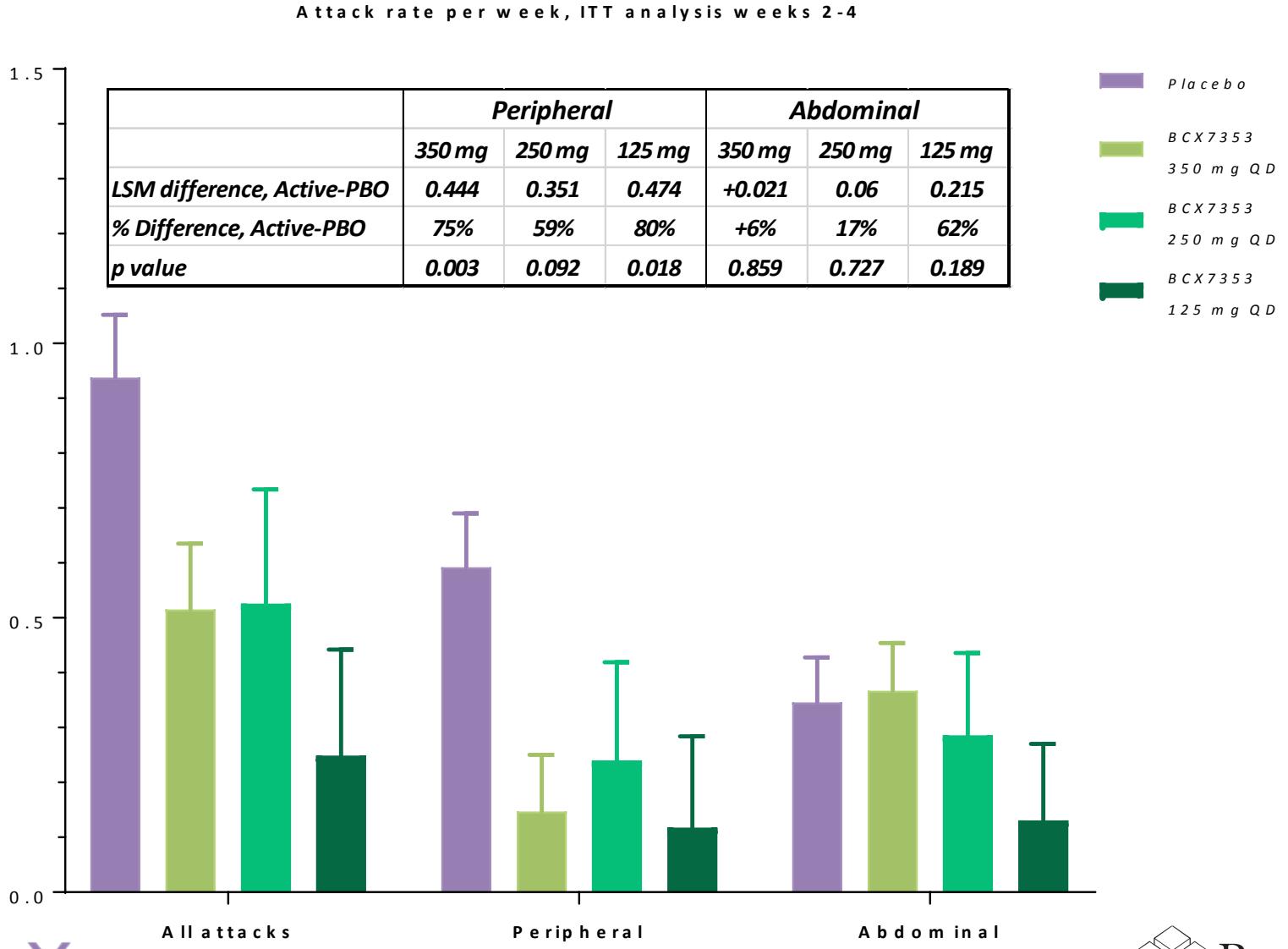
Attack rates by prespecified anatomical location, PP



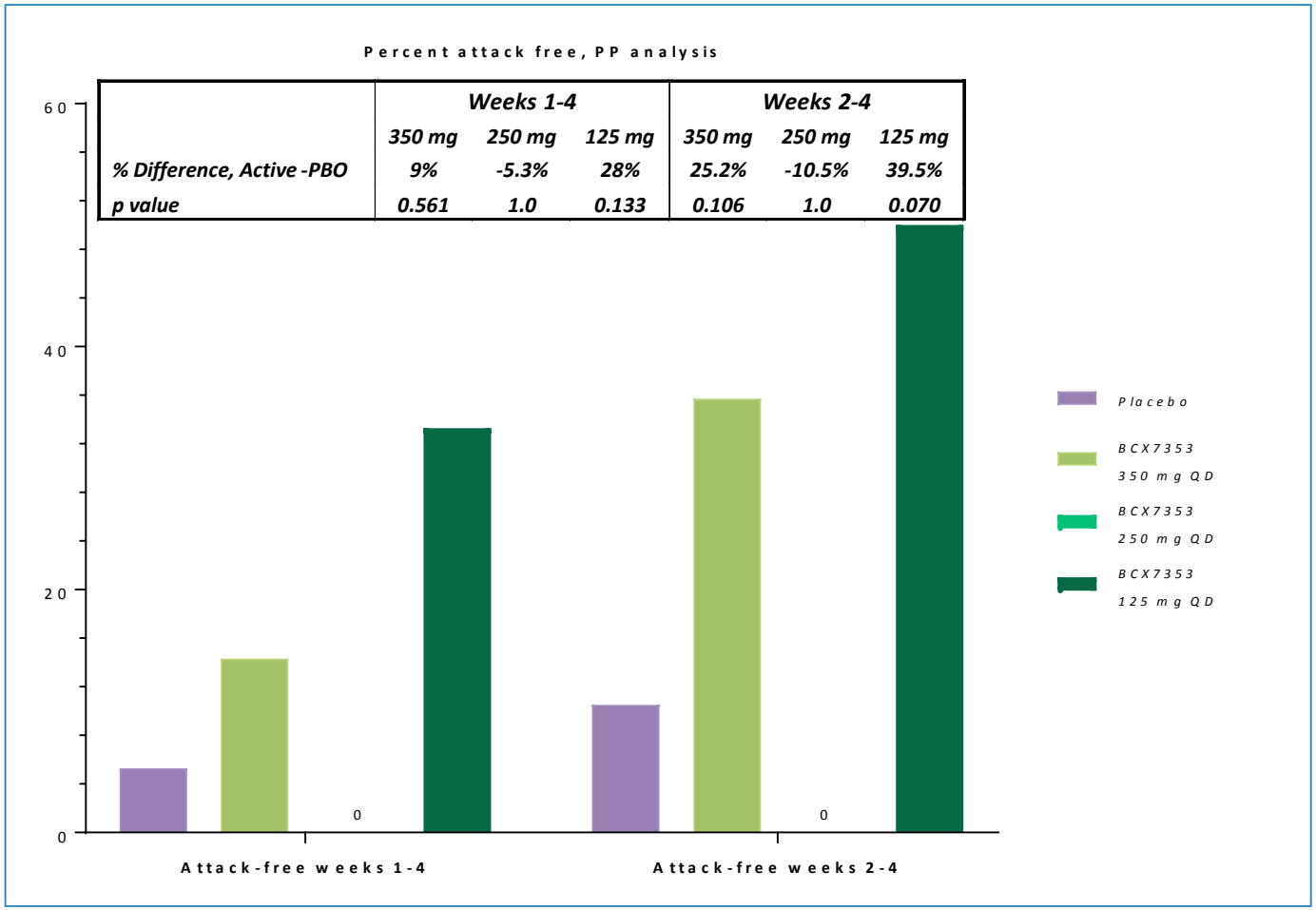
	Peripheral			Abdominal		
	350 mg	250 mg	125 mg	350 mg	250 mg	125 mg
LSM difference, Active-PBO	0.518	0.314	0.428	0.03	0.036	0.264
% Difference, Active-PBO	90%	54%	74%	8%	10%	72%
p value	<0.001	0.118	0.025	0.807	0.838	0.111

Attack rates by prespecified anatomical location, ITT

	Peripheral			Abdominal		
	350 mg	250 mg	125 mg	350 mg	250 mg	125 mg
LSM difference, Active-PBO	0.444	0.351	0.474	+0.021	0.06	0.215
% Difference, Active-PBO	75%	59%	80%	+6%	17%	62%
p value	0.003	0.092	0.018	0.859	0.727	0.189

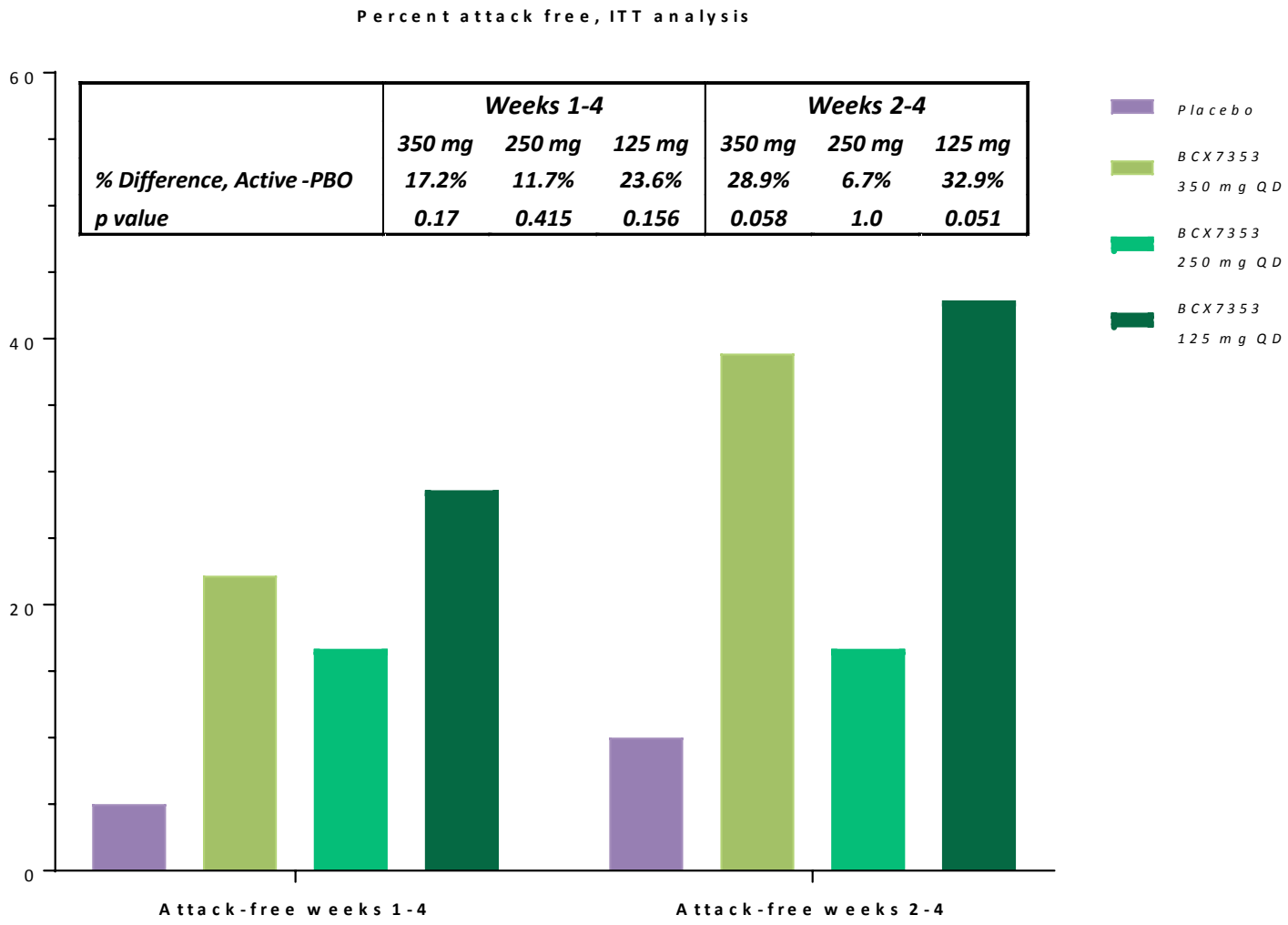


Percent of subjects attack-free, PP analysis

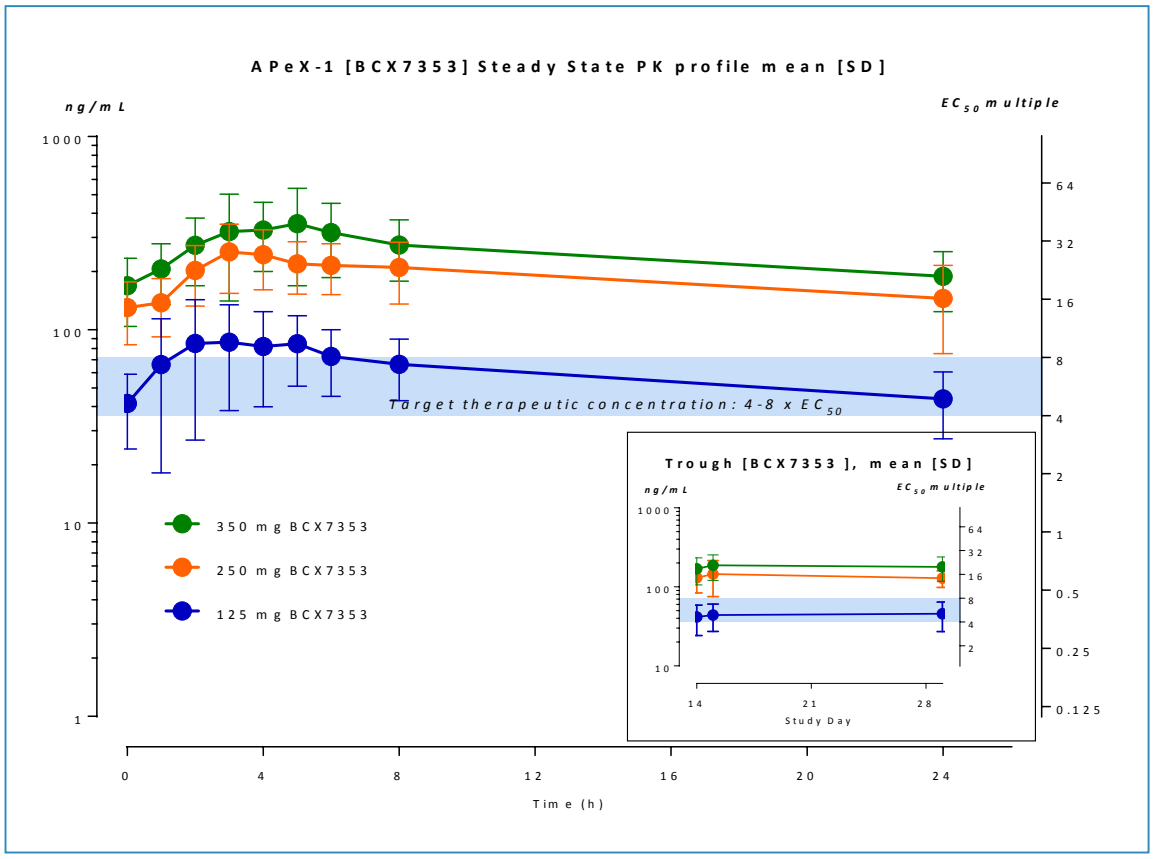


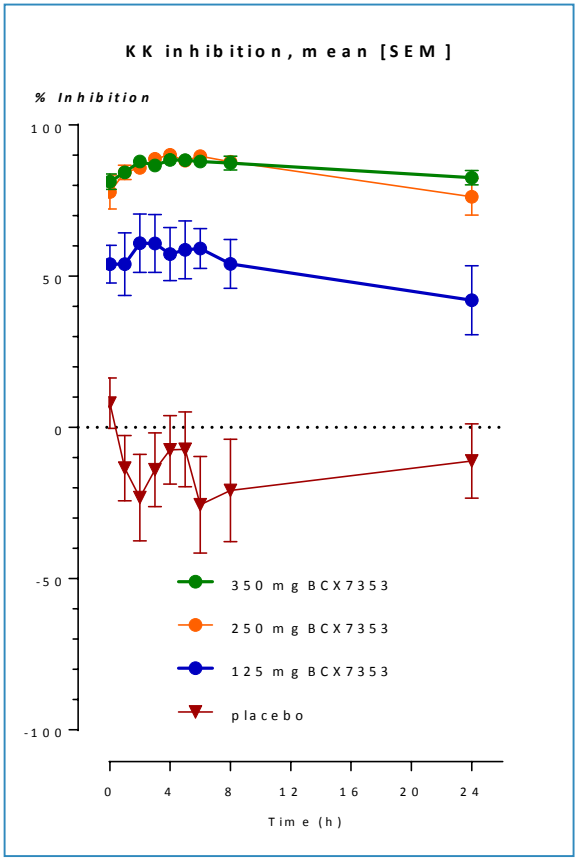
Percent of subjects attack-free, ITT analysis

	Weeks 1-4			Weeks 2-4		
	350 mg	250 mg	125 mg	350 mg	250 mg	125 mg
% Difference, Active -PBO	17.2%	11.7%	23.6%	28.9%	6.7%	32.9%
p value	0.17	0.415	0.156	0.058	1.0	0.051



PK and KK inhibition profiles at steady state for BCX7353 dose levels 125 mg, 250 mg and 350 mg QD in HAE subjects in APeX-1

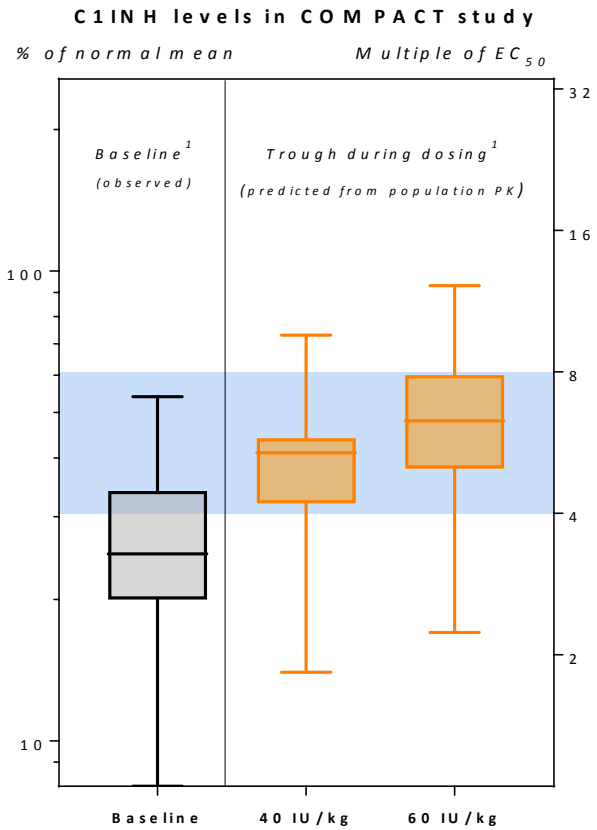




Steady state drug levels greatly exceeded the target therapeutic range for both 250 mg and 350 mg QD and trough levels for the 125 mg dose were generally within the target range

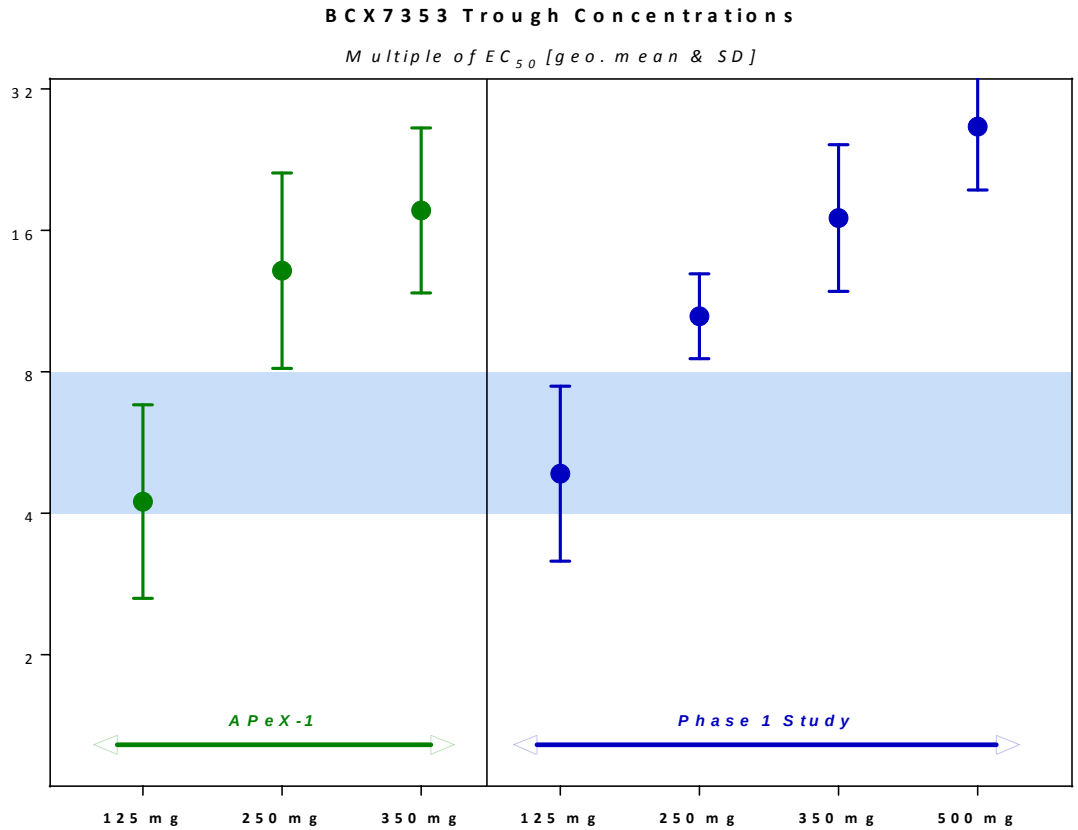
Exposure in APeX-1 and Phase 1 BCX7353 trials, and SC C1INH

CSL-830 Phase 3 study



C1INH levels at baseline and after SC dosing with CSL-830[1]

BCX7353 APeX-1 & Phase 1



BCX7353 plasma concentrations at 24 hours post-dose

[1] Longhurst, H. et al. N Engl J Med 376, 1131-1140 (2017). Box plots represent median, 25th and 75th percentiles, minimum and maximum values. CSL-830 and BCX7353 data are from distinct clinical trials and no head to head study has been conducted.

APeX-1 Second interim analysis safety summary

Category	BCX7353			
	125 mg n=7	250 mg n=6	350 mg n=18	Placebo n=20
Subjects with any Serious AE, n (%)	0	0	0	0
Subjects with Drug-Related Grade 3/4 AE, n (%)	0	0	1	0
Subjects with AE Leading to D/C from Study Drug, n (%)	0	0	3	0
Non- drug-related, n (%)	0	0	1[1]	0
Drug-related, n (%)	0	0	2[2]	0

[1] -Pre-existing liver disorder (improved from baseline, but persisting). Previously reported in 1st interim analysis

[2] -Gastroenteritis (unrelated) with liver disorder (related) (elevated ALT 1.9x ULN, GGT 5.4x ULN and ALP 1.6x ULN, with normal AST and bilirubin). Previously reported in 1st interim analysis
- Vomiting/ abdominal cramps concurrent with menses

APeX-1 Second interim analysis safety summary

Category	BCX7353 125 mg n=7	BCX7353 250 mg n=6	BCX7353 350 mg n=18	Placebo n=20
Treatment-Emergent Adverse Events occurring in ≥2 subjects overall, n (%)				
Nasopharyngitis	0	0	5 (28%)	6 (30%)
Diarrhoea	0	1 (17%)	4 (22%)	2 (10%)
Abdominal pain	0	0	3 (17%)	0
Nausea	0	2 (33%)	3 (17%)	0
Fatigue	0	0	2 (11%)	1 (5%)
Flatulence	0	0	2 (11%)	0
Vomiting	0	0	2 (11%)	0
Constipation	0	0	1 (6%)	1 (5%)
Headache	2 (29%)	0	1 (6%)	3 (15%)
Constipation	0	0	1 (6%)	1 (5%)
Migraine	1 (14%)	0	1 (6%)	0
Pharyngitis	0	1 (17%)	1 (6%)	0
Clin. significant changes in clin. chem., hematology or urinalysis, n (%)	0	1[1]	1[2]	0

[1] Treatment-emergent ALT elevation to >3X ULN (ALT 4.1 x ULN, AST 1.9 x ULN). *20 years androgen use, Baseline increase in liver enzymes*

[2] 1 event previously reported: ALT elevation > 3X ULN (ALT 3.9 x ULN, AST 1.8 xULN, GGT10.7 X ULN) *Pre-existing colitis, hepatic steatosis (fatty liver), > 20 years androgen use, Baseline increase in liver enzymes*

Conclusions

- BCX7353 once daily for 4 weeks showed clinically meaningful and statistically significant reductions in the rate of angioedema attacks
  - 125 mg dose showed a reduction of 73% in overall attack rate (p=0.002)
- Oral BCX7353 once daily over 4 weeks was generally safe and well tolerated
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- PK profile and kallikrein inhibition levels were similar to those seen at the same dose levels in Phase 1 healthy subjects
- Completion of Part 3 will help to round out the dose response data necessary to select doses for Phase 3