BCX7353 – APeX-1
Final Analysis Results

September 5, 2017

BioCryst Pharmaceuticals, Inc.

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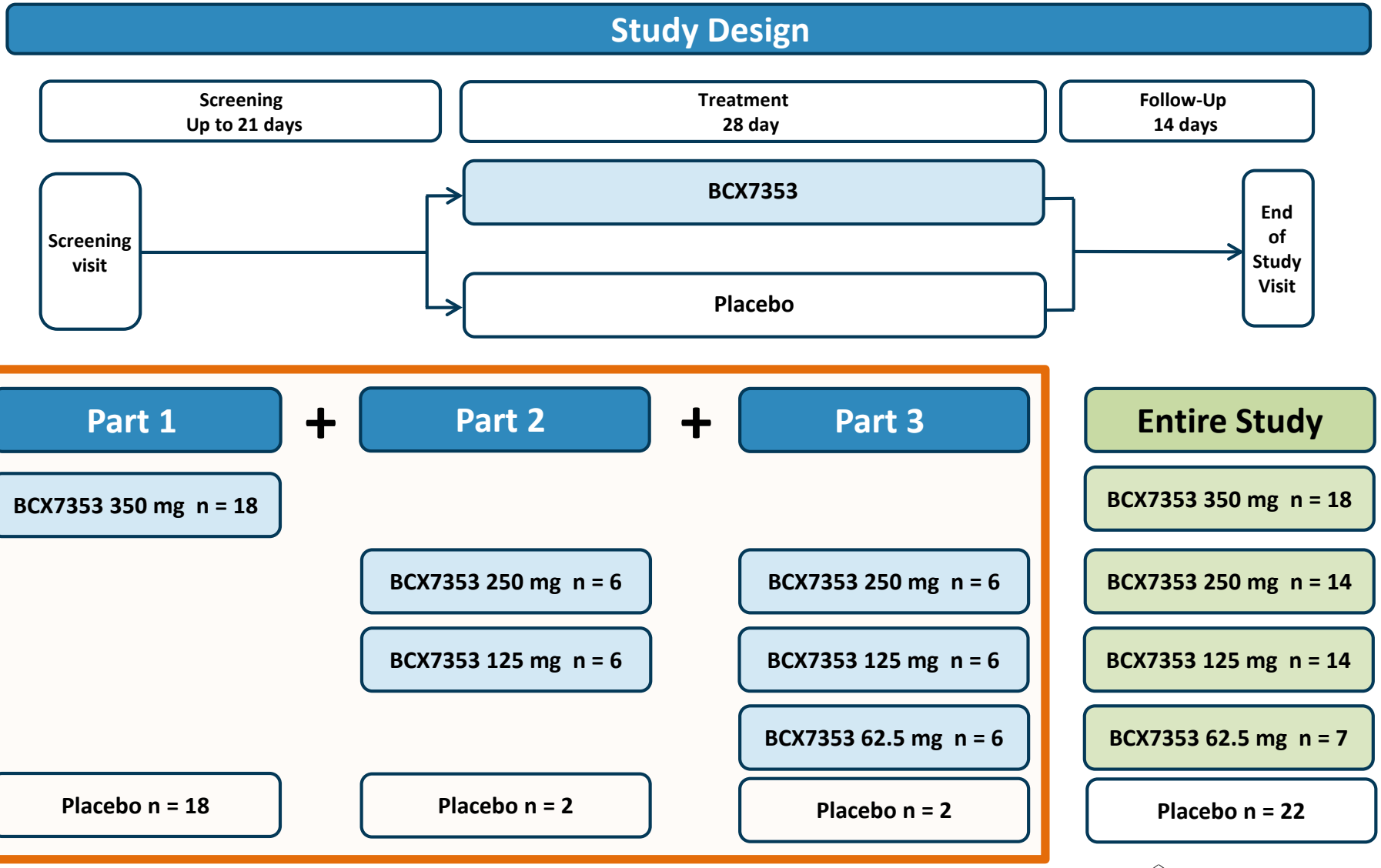
Highlights

- Attractive and competitive product profile for the prevention of HAE attacks at the 125 mg dose
  - Once-daily oral dosing
  - Competitive attack rate reductions of 73% ($p<0.001$)
  - Safety and tolerability profile similar to placebo
  - Quality of Life scores that are multiples better than the minimum clinically important difference ($p<0.001$)
- Phase 3 dose selection supported by consistent and predictable results
  - 125 mg dose is attractive based on efficacy, safety and tolerability
  - 250 mg and 350 mg doses showed dose-related AEs and drug levels far exceeded the target threshold for efficacy
  - 62.5 mg dose showed no benefit and drug levels were below the target threshold for efficacy
  - High predictability of PK and PD provides confidence in choosing 175 mg as the second dose

Trial design and final enrollment



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Final analysis population

	BCX7353				
	62.5 mg	125 mg	250 mg	350 mg	Placebo
Randomized and treated	7	14	14	18	22
Intent to Treat (ITT) population	7	14	14	18	22
Per Protocol (PP) population	7	13	12	14	21
Excluded from PP population					
HAE Type 1 or 2 not confirmed				1	1
<90% compliance dosing with study drug		1	1	3	
Non compliance with diary completion			1		
Study drug compliance, mean % (SD) [1]	99 (1.4)	99 (3.6)	100 (2.7)	98 (7.7)	99 (1.4)
Age – years, mean (SD)	38.9 (16.6)	48.1 (12.6)	40.9 (13.4)	43.8 (11.6)	46.8 (11.1)
Sex – female, n (%)	6 (86%)	10 (71%)	6 (43%)	11 (61%)	13 (59%)
Prior androgen use, n (%)	3 (43%)	4 (29%)	8 (57%)	15 (83%)	12 (55%)
Qualifying attack rate, attacks/wk mean (SD)	1.05 (0.44)	0.94 (0.40)	0.91 (0.43)	0.84 (0.35)	0.87 (0.45)
Baseline C1-INH function: % of normal, median (IQR)	9% (6-36)	12% (9-22)	13% (5-22)	9% (4-23)	8% (3-31)

[1] Study drug compliance assessed by returned capsule counts

Rate of overall confirmed angioedema 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	46	0.454	-0.478	-51%	<0.001
BCX7353 62.5 mg	7	0.865	-0.067	-7%	0.715
BCX7353 125 mg	13	0.248	-0.684	-73%	<0.001
BCX7353 250 mg	12	0.507	-0.426	-46%	0.006
BCX7353 350 mg	14	0.394	-0.538	-58%	<0.001
Placebo	21	0.932	-	-	-
Interim analysis (May 2017): Parts 1+2 combined					
BCX7353 125 mg	*6*	*0.253*	*-0.691*	*73%*	*0.002*
BCX7353 250 mg	*5*	*0.595*	*-0.349*	*37%*	*0.128*
Placebo	*19*	*0.945*			

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

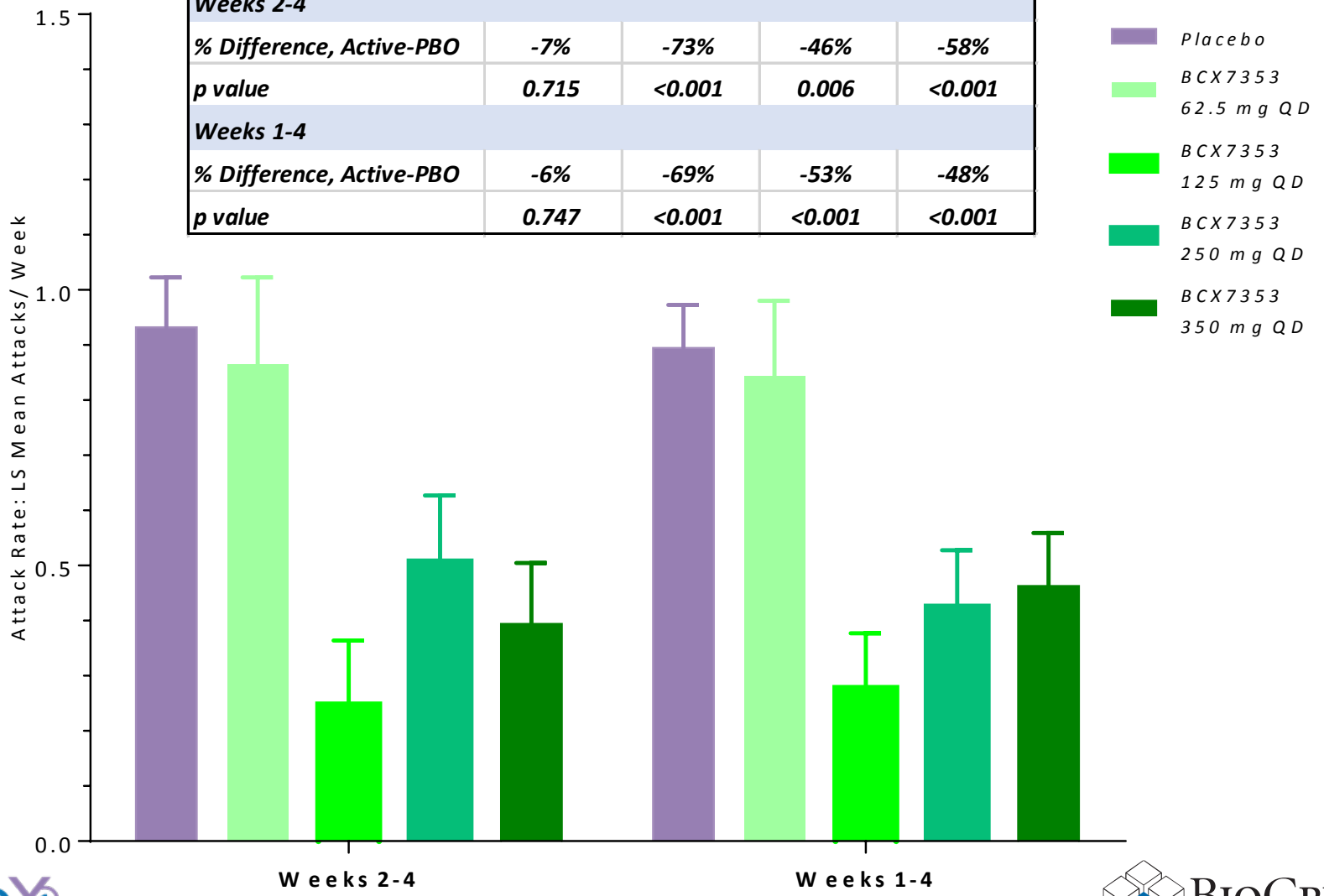
125 mg dose provided consistent reductions in attack rate

Analysis	n	LS mean[1] Attacks per Week		Difference vs Placebo	Percentage Reduction vs Placebo	p-Value vs Placebo
		BCX7353 125 mg	Placebo			
Confirmed attacks, Weeks 2-4 PP population	13	0.248	0.932	-0.684	73%	<0.001
Confirmed attacks, Weeks 2-4 ITT population	14	0.249	0.937	-0.688	73%	<0.001
Confirmed attacks, Weeks 1-4 PP population	13	0.278	0.895	-0.617	69%	<0.001
Confirmed attacks, Weeks 1-4 ITT population	14	0.270	0.890	-0.619	70%	<0.001
Confirmed attacks requiring treatment, Weeks 2-4 PP population	13	0.221	0.807	-0.585	73%	<0.001
Confirmed attacks requiring treatment, Weeks 2-4 ITT population	14	0.224	0.771	-0.546	71%	0.002
Confirmed attacks requiring treatment, Weeks 1-4 PP population	13	0.221	0.788	-0.567	72%	<0.001
Confirmed attacks requiring treatment, Weeks 1-4 ITT population	14	0.217	0.753	-0.536	71%	<0.001

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

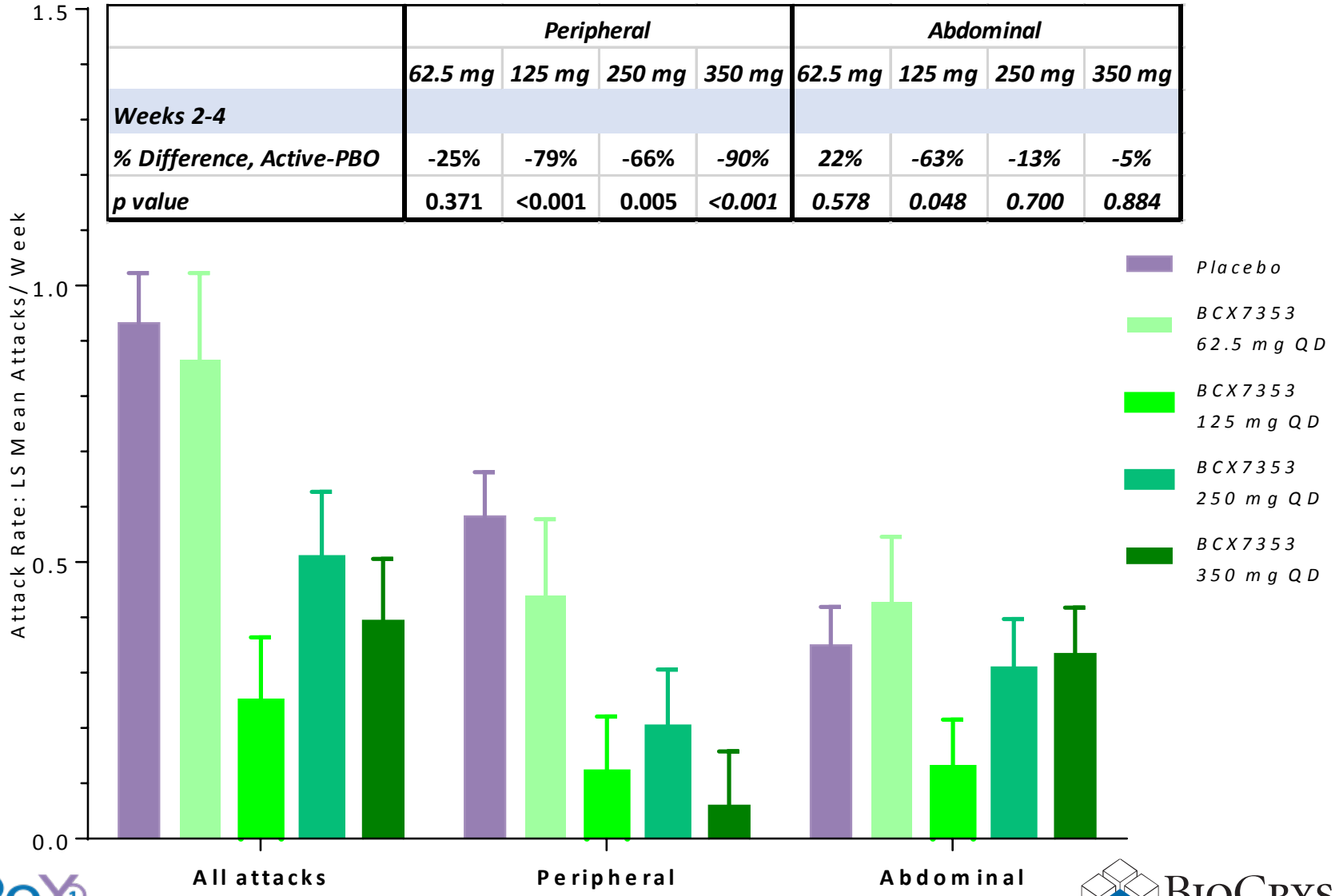
Overall angioedema attack rate per week, PP population, weeks 2-4 and 1-4

	62.5 mg	125 mg	250 mg	350 mg
Weeks 2-4				
% Difference, Active-PBO	-7%	-73%	-46%	-58%
p value	0.715	<0.001	0.006	<0.001
Weeks 1-4				
% Difference, Active-PBO	-6%	-69%	-53%	-48%
p value	0.747	<0.001	<0.001	<0.001

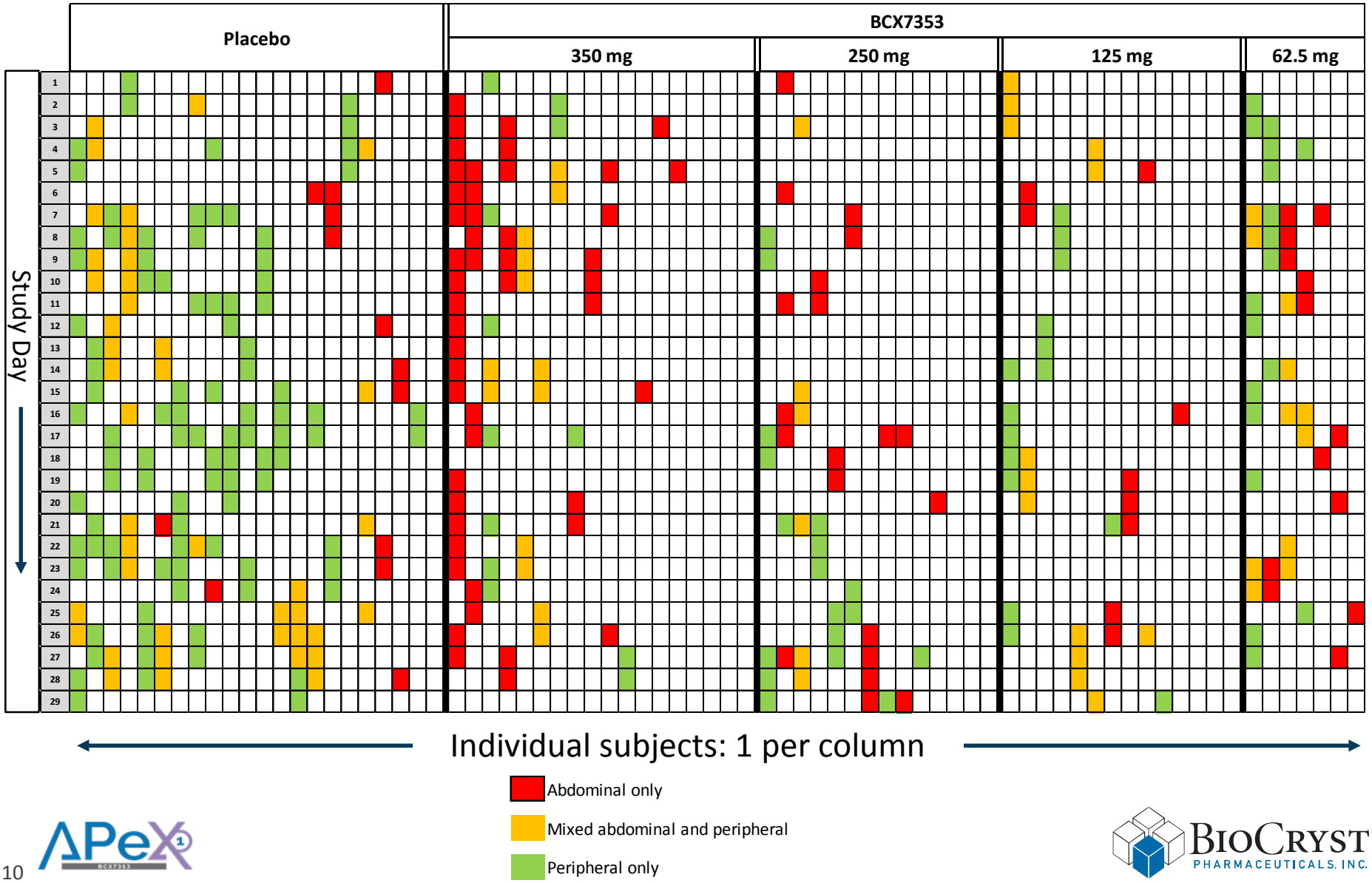


Angioedema attack rates by prespecified anatomical location, PP

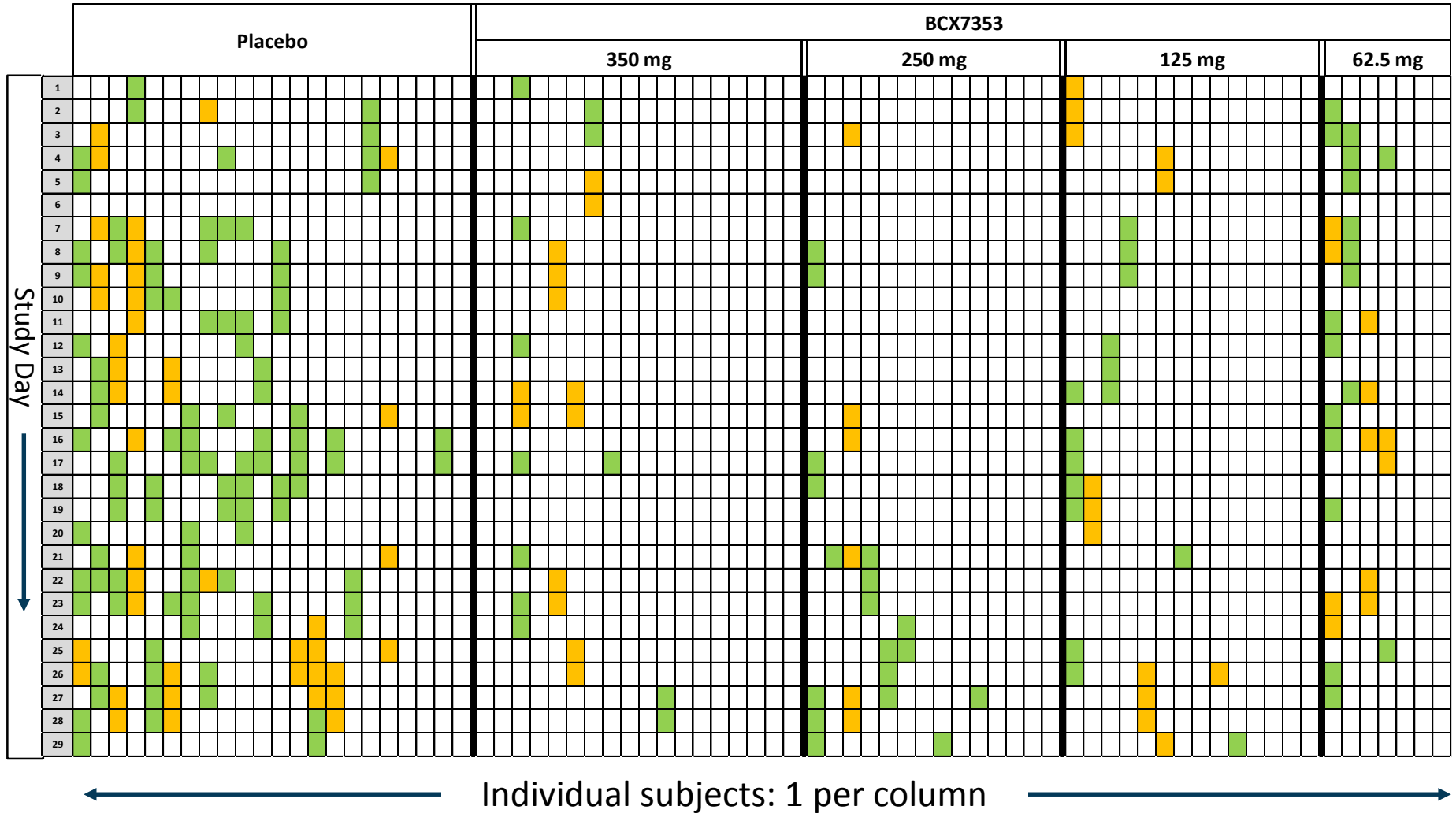
	Peripheral				Abdominal			
	62.5 mg	125 mg	250 mg	350 mg	62.5 mg	125 mg	250 mg	350 mg
Weeks 2-4								
% Difference, Active-PBO	-25%	-79%	-66%	-90%	22%	-63%	-13%	-5%
p value	0.371	<0.001	0.005	<0.001	0.578	0.048	0.700	0.884



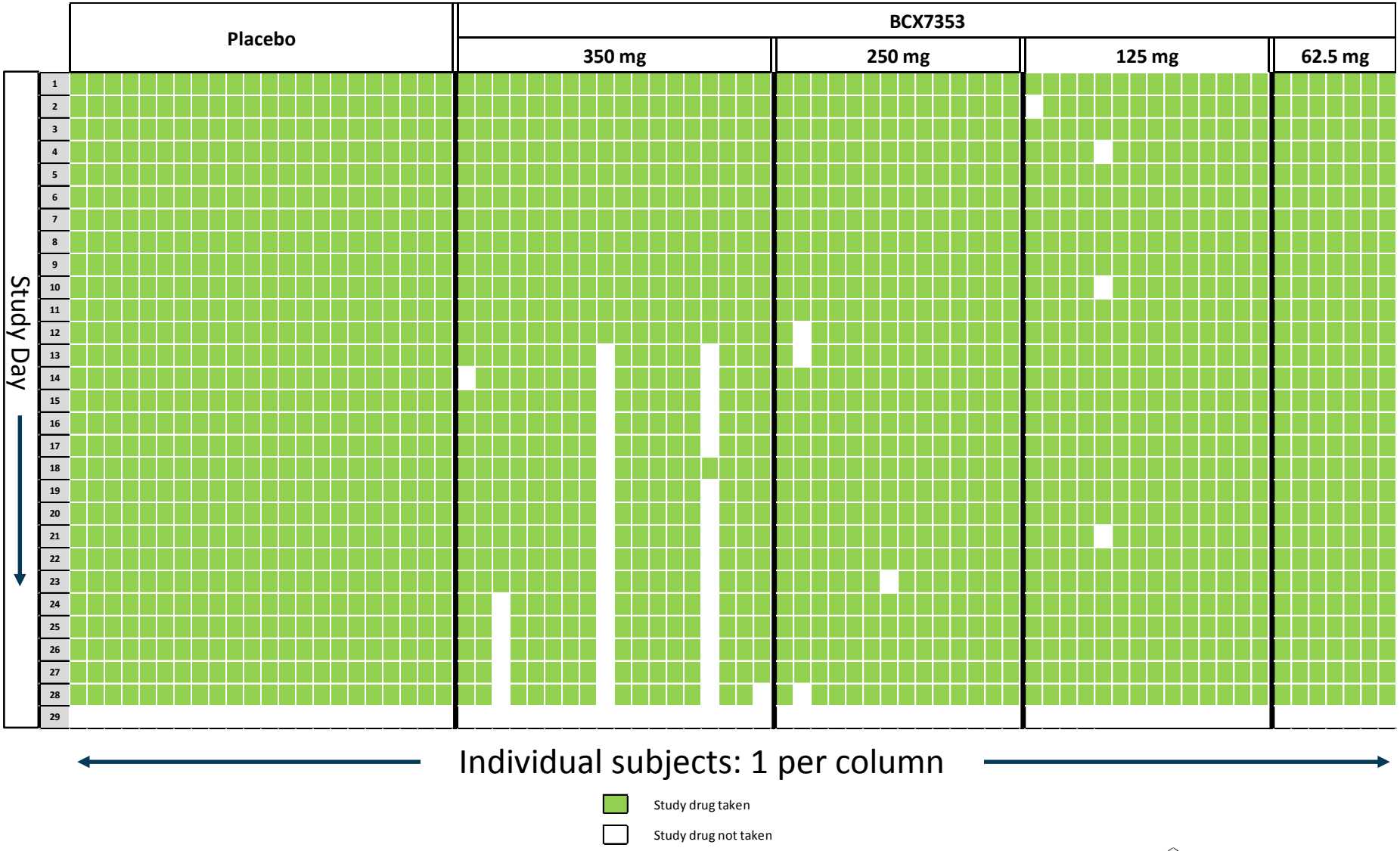
Individual subject attacks: days with any angioedema symptoms



Individual subject attacks: days with unequivocal angioedema symptoms



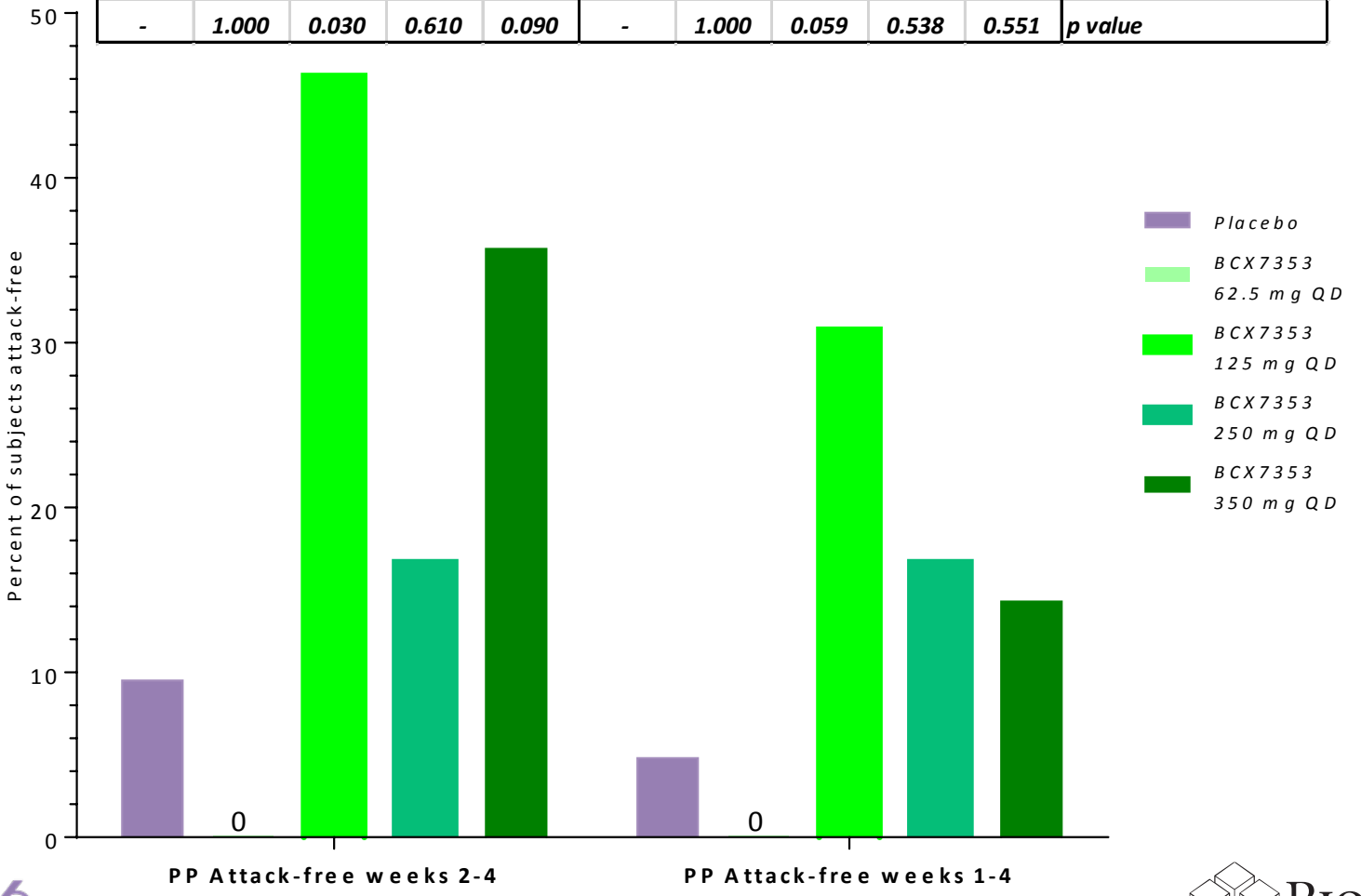
Doses of study drug recorded in the subject diary



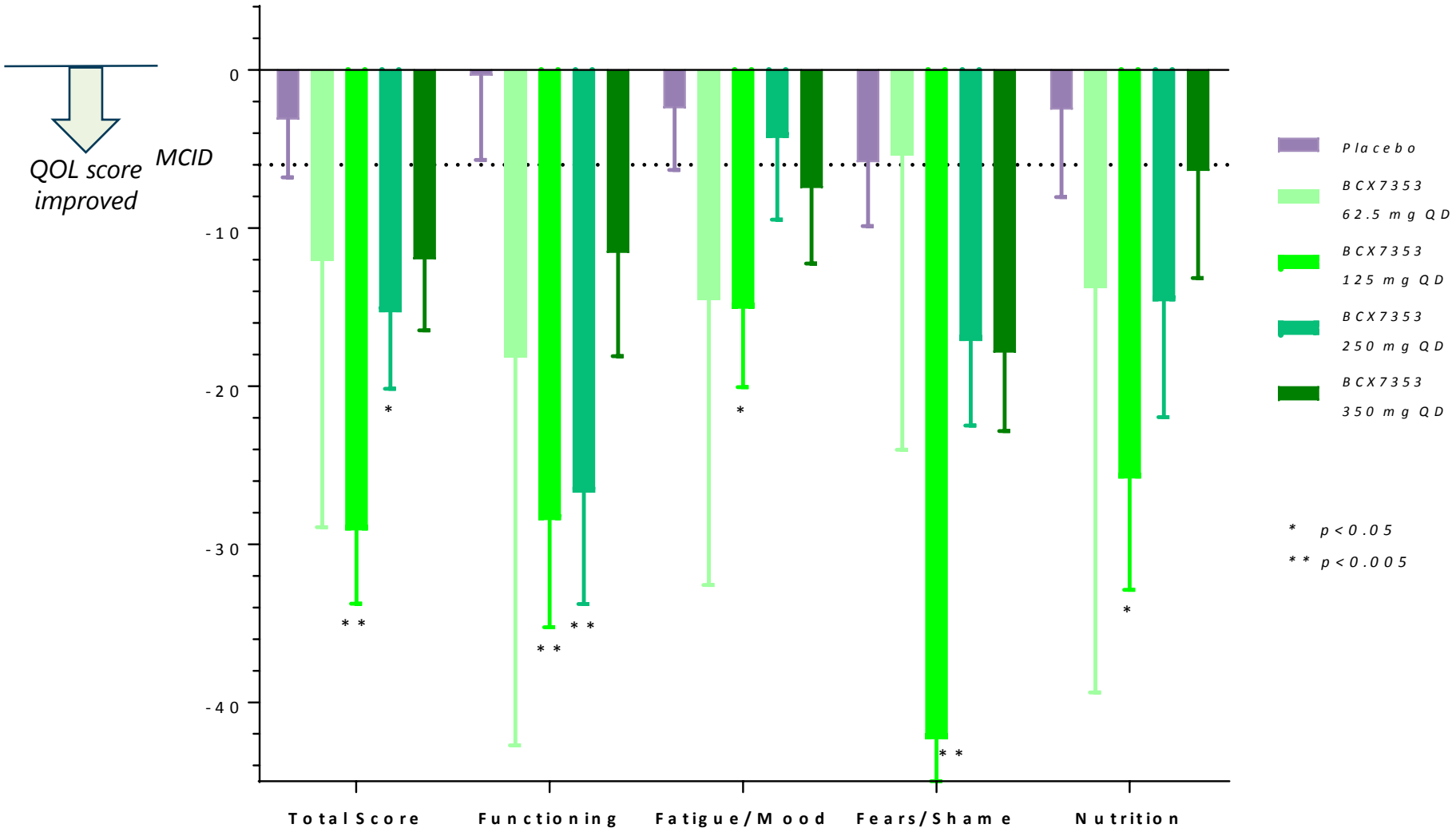
Seven subjects recorded one additional day of dosing in their diary compared to capsule count reconciliation:
Placebo- 4 subjects; 350 mg – 1 subject; 125 mg 1 subject; 62.5 mg- 1 subject
Two subjects recorded one less day of dosing in their diary compared to capsule count reconciliation:
350 mg – 1 subject; 250 mg – 1 subject

Percent of subjects attack-free, PP

PBO	62.5 mg	125 mg	250 mg	350 mg	PBO	62.5 mg	125 mg	250 mg	350 mg	
Weeks 2-4					Weeks 1-4					
9.5%	0.0%	46.2%	16.7%	35.7%	4.8%	0.0%	30.8%	16.7%	14.3%	% Attack free
-	-9.5%	36.7%	7.2%	26.2%	-	-4.8%	26.0%	11.9%	9.5%	Difference, Active-PBO
-	1.000	0.030	0.610	0.090	-	1.000	0.059	0.538	0.551	p value



Angioedema quality of life (AE-QoL): LS mean change from BL at day 29, PP



Difference in adjusted least square means are shown (Active treatment minus Placebo).
ANCOVA Model includes terms of treatment and adjusted qualifying attack rate.
Reductions (negative changes from BL) represent improvement in quality of life scores.
MCID, minimum clinically important difference, -6 points (*Weller, K. 2016. Allergy 71(8): 1203-1209.)*
BCX7353 dose level compared with placebo

Treatment-emergent adverse event summary

Category	BCX7353 62.5 mg N = 7	BCX7353 125 mg N = 14	BCX7353 250 mg N = 14	BCX7353 350 mg N = 18	Placebo N = 22
Subjects with any TEAE[1], n (%)	4 (57)	7 (50)	11 (79)	14 (78)	15 (68.2)
Subjects with any Serious AE, n (%)	0	0	1 (7)[2]	0	0
Subjects with Drug-Related Grade 3/4 AE, n (%)	0	0	0	1 (6)	0
Subjects with AE Leading to D/C from Study Drug, n (%)	0	0	0	3 (17)	0
Non- drug-related, n (%)	0	0	0	1 (6)[3]	0
Drug-related, n (%)	0	0	0	2 (11)[4,5]	0

[1] TEAE- treatment-emergent adverse event

[2] GI infection- investigator assessed as unrelated to study drug. Abdominal symptoms similar to several previous non-HAE-attack episodes occurring over past 3 years resulting in severe vomiting and diarrhea. Pt presented to ER and hospitalized for IV fluids and antiemetics as a precaution. No HAE acute attack meds given. Recovered and discharged the following day. Missed 1 day of dosing due to event.

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

[4] n=1 Gastroenteritis with liver disorder (both assessed as 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

[5] n=1 Vomiting/ abdominal cramps. Previously reported in 2nd interim analysis

Post-baseline abnormalities in ALT, AST or bilirubin

Metric	62.5 mg	125 mg	250 mg	350 mg	Placebo
N	7	14	14	18	22
Prior Androgen, N	*3*	*4*	*8*	*15*	*12*
ALT ≥3xULN	0	0	1 (12.5)	3 (20)	0
AST ≥3xULN	0	0	0	0	0
Bili ≥2xULN	0	0	0	0	0
No Prior Androgen, N	*4*	*10*	*6*	*3*	*10*
ALT ≥3xULN	0	0	0	0	0
AST ≥3xULN	0	0	0	0	0
Bili ≥2xULN	0	0	0	0	0

Post-baseline abnormalities in liver function tests were confined to subjects with prior exposure to androgens and were confined to 250 mg and 350 mg doses

Three of the four subjects with post-baseline ALT > 3xULN also had baseline values > 3xULN

Most frequent treatment-emergent adverse events, other than gastrointestinal events

Category	BCX7353 62.5 mg N=7	BCX7353 125 mg N=14	BCX7353 250 mg N=14	BCX7353 350 mg N=18	Placebo N=22
Treatment-Emergent Adverse Events occurring in ≥2 subjects overall, subject incidence n (%) in descending order System Organ Class (SOC) *Preferred Term*					
Infections and Infestations					
Nasopharyngitis	2 (29%)	0	1 (7%)	5 (28%)	6 (27%)
Upper Respiratory Tract Infection	0	0	1 (7%)	0	1 (5%)
Pharyngitis	0	0	1 (7%)	1 (6%)	0
Gastrointestinal infection	0	0	1 (7%)	1 (6%)	0
Nervous system disorders					
Headache	2 (29%)	2 (14%)	1 (7%)	1 (6%)	4 (18%)
Migraine	0	1 (7%)	0	1 (6%)	0
Musculoskeletal and connective tissue disorders					
Arthralgia	0	0	0	1 (6%)	1 (5%)
General disorders					
Fatigue	1 (14%)	0	0	2 (11%)	1 (5%)
Injury, poisoning and procedural complications					
Contusion	0	0	1 (7%)	0	1 (5%)
Investigations*					
Liver function tests	0	0	1 (7%)[1]	2 (11%)[2,3]	0

* Clinically significant changes and/or reported by investigator. Event in 250 mg group not reported as AE by investigator.

[1] Event previously reported: ALT elevation to >3X ULN (ALT 4.1 x ULN, AST 1.9 x ULN). Baseline increase in LFTs.*20 years androgen use*

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

[3] Investigator reported Grade 1 ALT elevation. *Prior androgen use.*

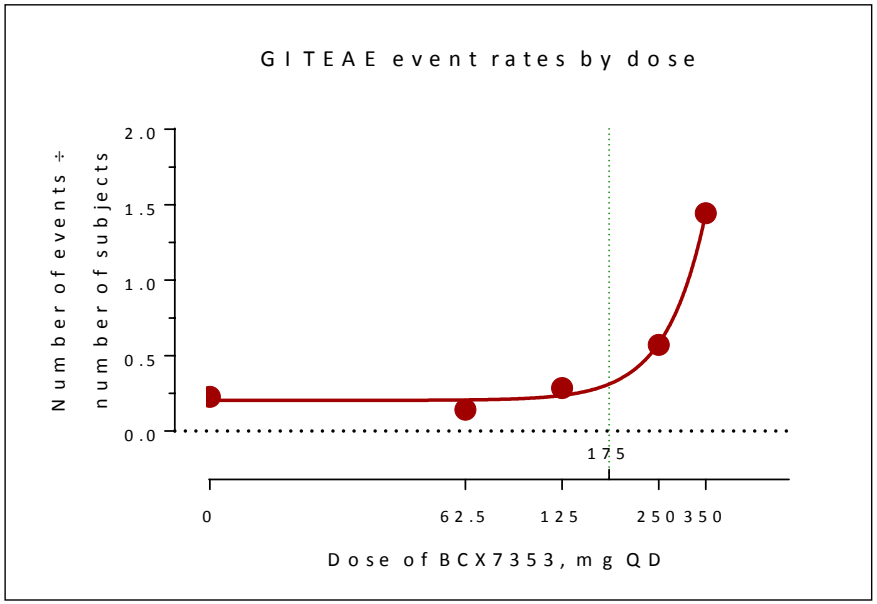
All gastrointestinal treatment-emergent adverse events

Category	BCX7353				Placebo
	62.5 mg	125 mg	250 mg	350 mg	
	N=7	N=14	N=14	N=18	N=22
Treatment-Emergent Adverse Events, subject incidence n (%), [number of events] in descending order SOC *Preferred Term*					
Gastrointestinal disorders					
Diarrhea	0	0	2 (14.3) [3]	4 (22.2) [6]	2 (9.1) [3]
Nausea	0	0	3 (21.4) [3]	3 (16.7) [5]	0
Abdominal pain	0	1 (7.1) [1]	1 (7.1) [1]	3 (16.7) [5]	0
Abdominal pain upper	1 (14.3) [1]	1 (7.1) [1]	0	1 (5.6) [1]	0
Gastroesophageal reflux disease	0	1 (7.1) [2]	0	0	1 (4.5) [1]
Flatulence	0	0	0	2 (11.1) [2]	0
Vomiting	0	0	0	2 (11.1) [2]	0
Constipation	0	0	0	1 (5.6) [1]	1 (4.5) [1]
Abdominal pain lower	0	0	0	1 (5.6) [2]	0
Abdominal discomfort	0	0	0	1 (5.6) [1]	0
Abdominal distension	0	0	0	1 (5.6) [1]	0
Dyspepsia	0	0	1 (7.1) [1]	0	0
Gingival erosion	0	0	0	1 (5.6) [1]	0
Toothache	0	0	1 (7.1) [1]	0	0
Breath odor	0	0	0	0	1 (4.5) [1]
Dental caries	0	0	0	0	1 (4.5) [2]

Exploratory analysis of gastrointestinal treatment-emergent adverse event rates

Dose group	Events n	Subjects N	Rate n/N
Placebo	5	22	0.23
62.5 mg	1	7	0.14
125 mg	4	14	0.29
250 mg	8	14	0.57
350 mg	26	18	1.44

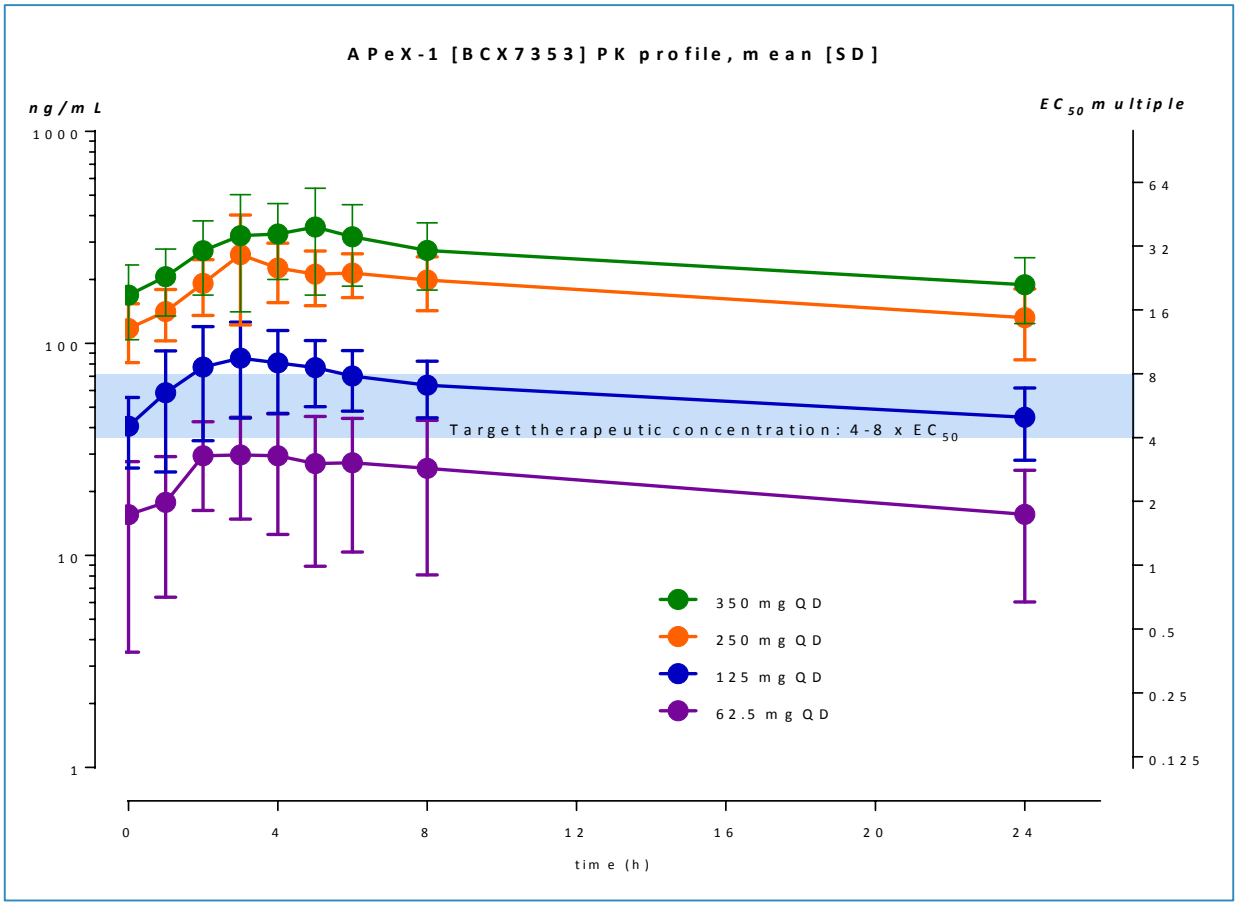
Events of gingival erosion, toothache, breath odor and dental caries were excluded from analysis

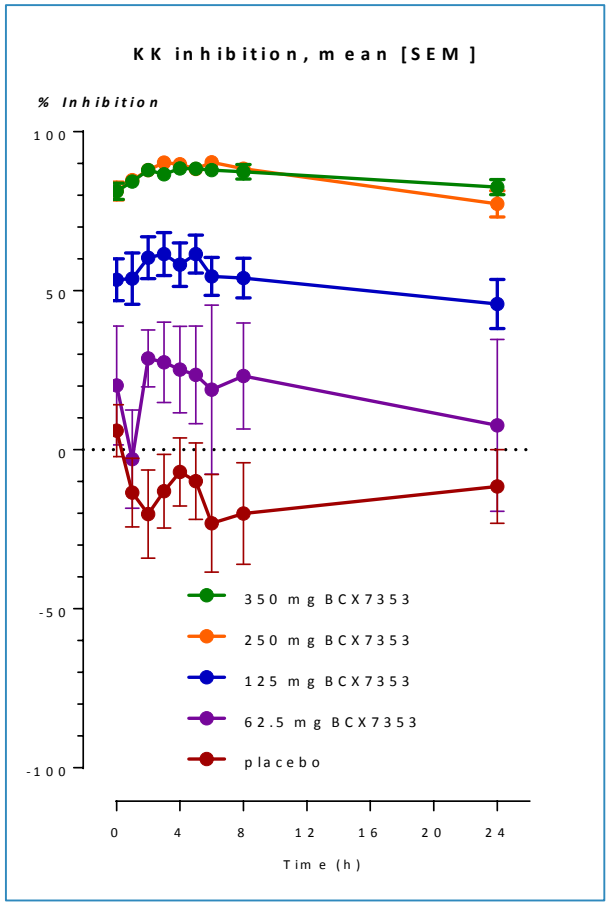


The rate of GI SOC adverse events was similar in 125 mg, 62.5 mg and placebo dose groups.

The 250 mg and 350 mg dose groups had higher rates of GI SOC events compared with placebo.

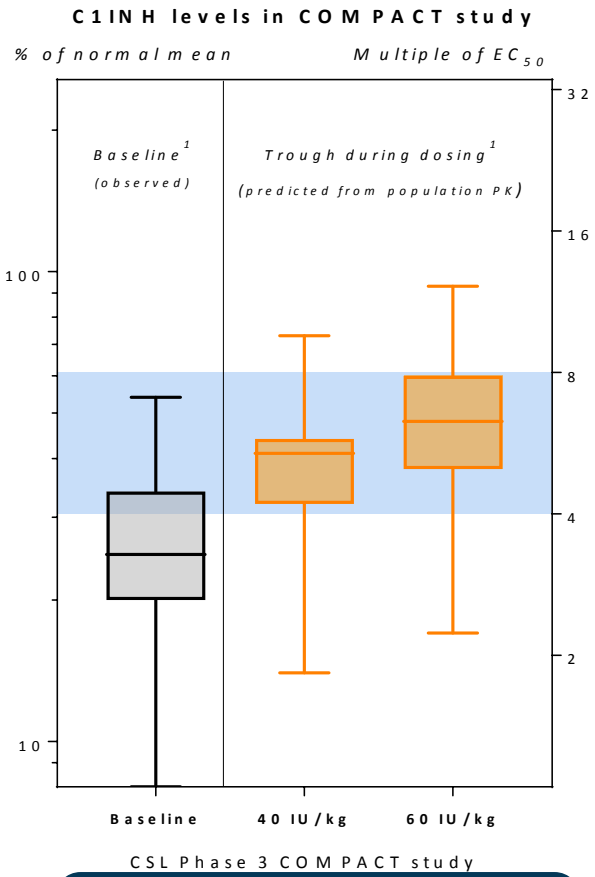
PK and KK inhibition profiles at steady state





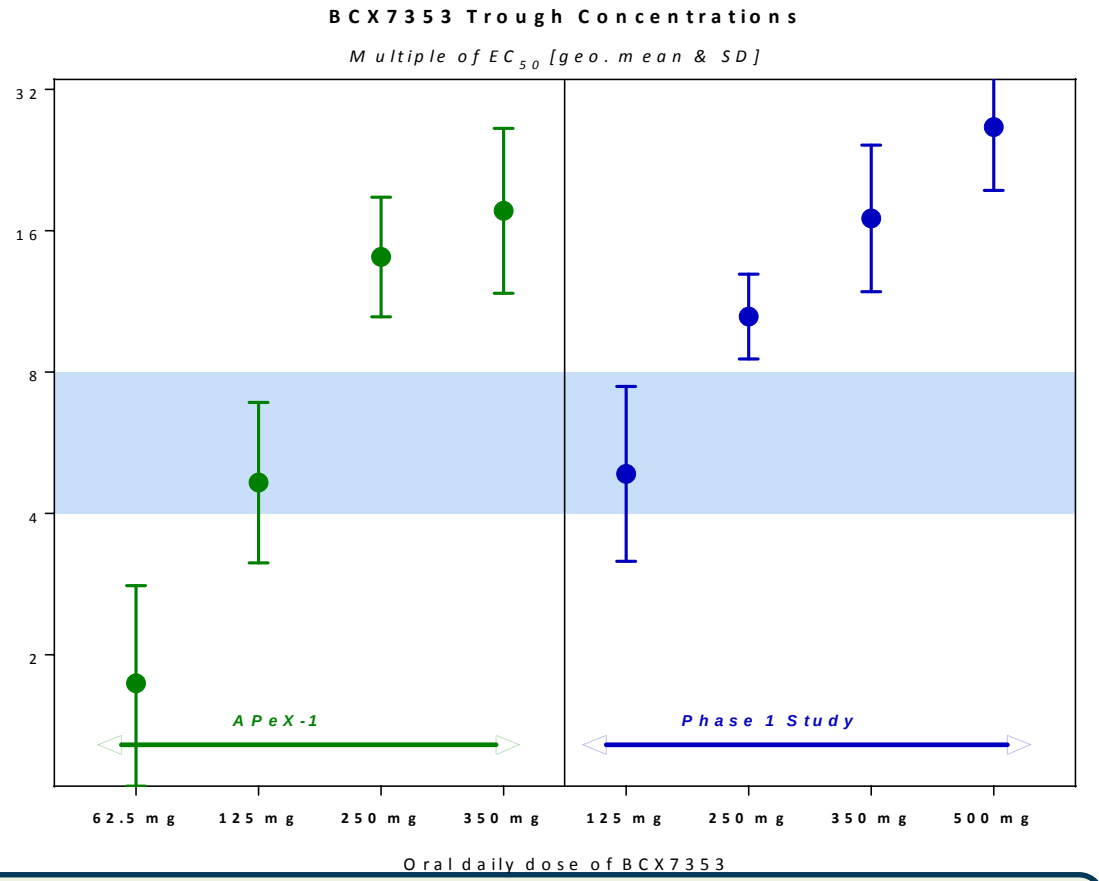
Exposure comparisons of BCX7353 and SC C1INH

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

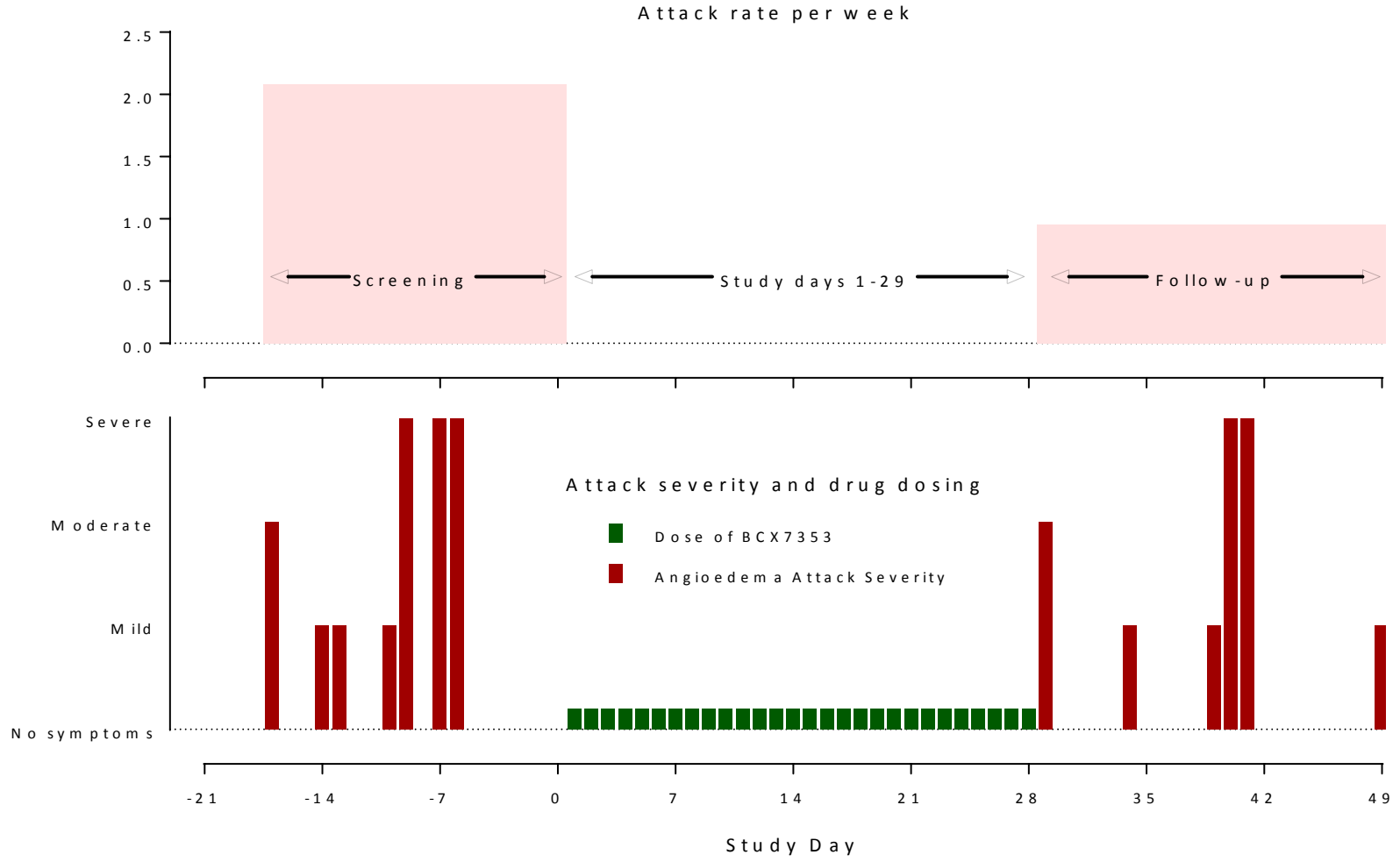
[1] Longhurst, H. et al. N Engl J Med 376, 1131-1140 (2017). Box plots represent median, 25th and 75th percentiles, minimum and maximum values. CSL-830 and BCX7353 data are from distinct clinical trials and no head to head study has been conducted.

Predictable PK supports 175 mg as second dose in Phase 3

Dose, mg QD	% >4 x EC_{50}		% > 6 x EC_{50}		% > 8 x EC_{50}	
	Predicted	Actual	Predicted	Actual	Predicted	Actual
62.5	**0**	***0***	0	*0*	0	*0*
125	**70**	***64***	38	*43*	17	*0*
175	**93**		80		58	
200	97		88		73	
225	98		93		83	
250	**100**	***100***	97	*100*	93	*100*

- Given the predictable PK of BCX7353, simulations are helpful in selecting an intermediate dose of BCX7353 to study that is between 125 mg and 250 mg.
- A relatively small increase in dose above 125 mg should achieve a significant increase in the proportion of subjects achieving trough levels above the therapeutic target.
- 175 mg dose should maintain trough drug levels > 4 x EC_{50} in > 90% of patients.
- Doses ≥ 200 mg offer little additional increment in proportions achieving target level.

Study subject example, 125 mg QD BCX7353 – subject with highest qualifying attack rate in the trial



Conclusions and next steps

- Conclusion: APeX-1 results strongly support Phase 3 development
  - 125 mg dose level combines highly attractive attack frequency reductions of 73% ($p<0.001$) with a generally safe and well tolerated profile
  - PK, PD and lack of clinical benefit at 62.5 mg dose rounds out dose response
  - Exposures at 250 mg and 350 mg are not necessary for efficacy and were associated with increased AE rates
  - 175 mg dose may get more patients above the target threshold
- Next Steps
  - Finalize the design of the Phase 3 and Long Term Safety trials after End of Phase 2 meeting with FDA and Scientific Advice procedure with EMA in Q4'17
  - Initiate Phase 3 and long term safety trial in Q1'18
  - Complete all other supporting activities for NDA and MAA filing (CMC, preclinical, clinical pharmacology, etc.)
  - Expand launch preparation activities over course of next year

Back-up

BioCryst Pharmaceuticals, Inc.

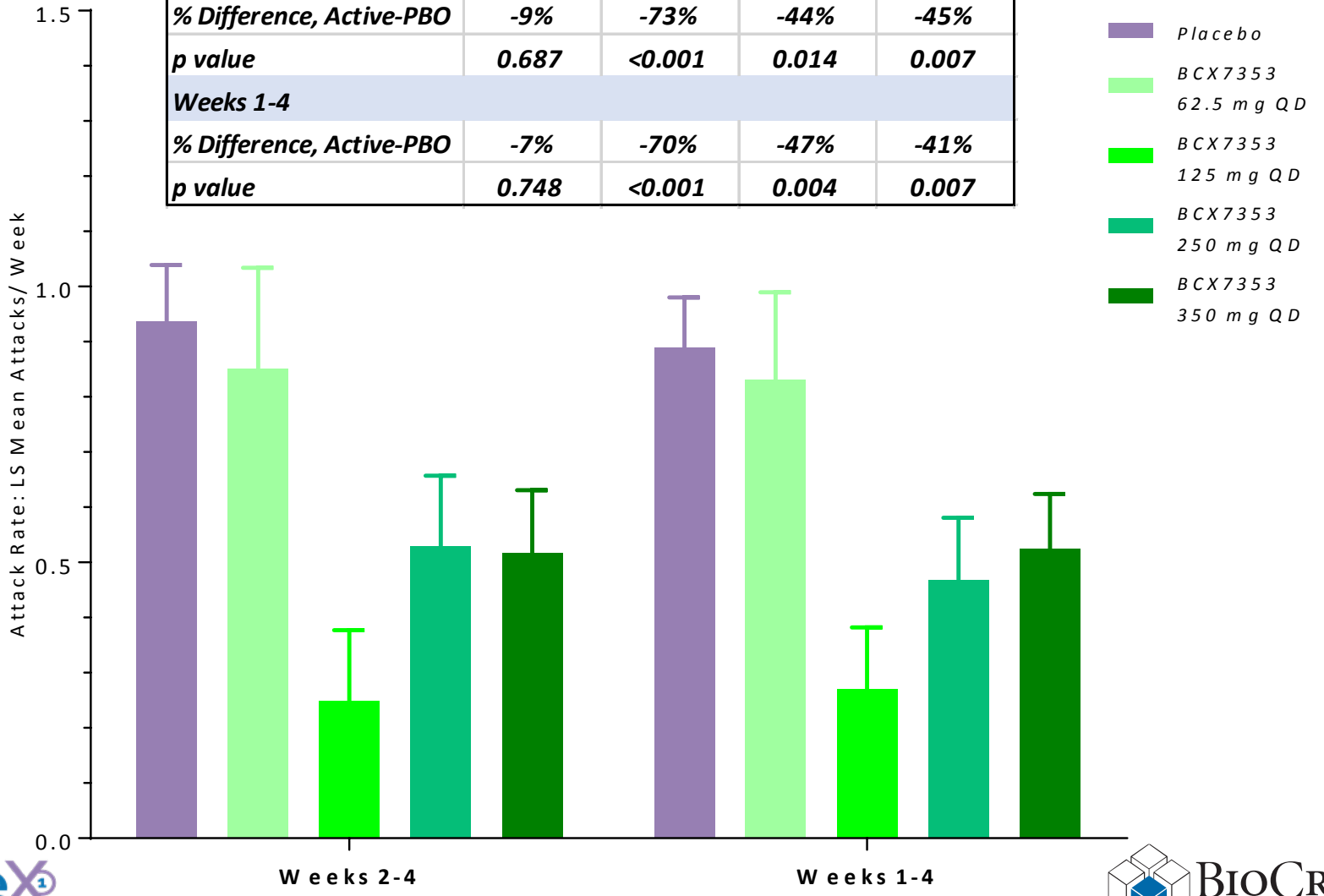
Rate of overall confirmed angioedema attacks: ITT population

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	53	0.494	-0.443	-47%	<0.001
BCX7353 62.5 mg	7	0.852	-0.084	-9%	0.687
BCX7353 125 mg	14	0.249	-0.688	-73%	<0.001
BCX7353 250 mg	14	0.529	-0.408	-44%	0.014
BCX7353 350 mg	18	0.518	-0.418	-45%	0.007
Placebo	22	0.937	-	-	-
Part 2 Interim analysis					
BCX7353 125 mg	*7*	*0.249*	*-0.689*	*73%*	*0.004*
BCX7353 250 mg	*6*	*0.526*	*-0.411*	*44%*	*0.090*
Placebo	*20*	*0.938*			

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

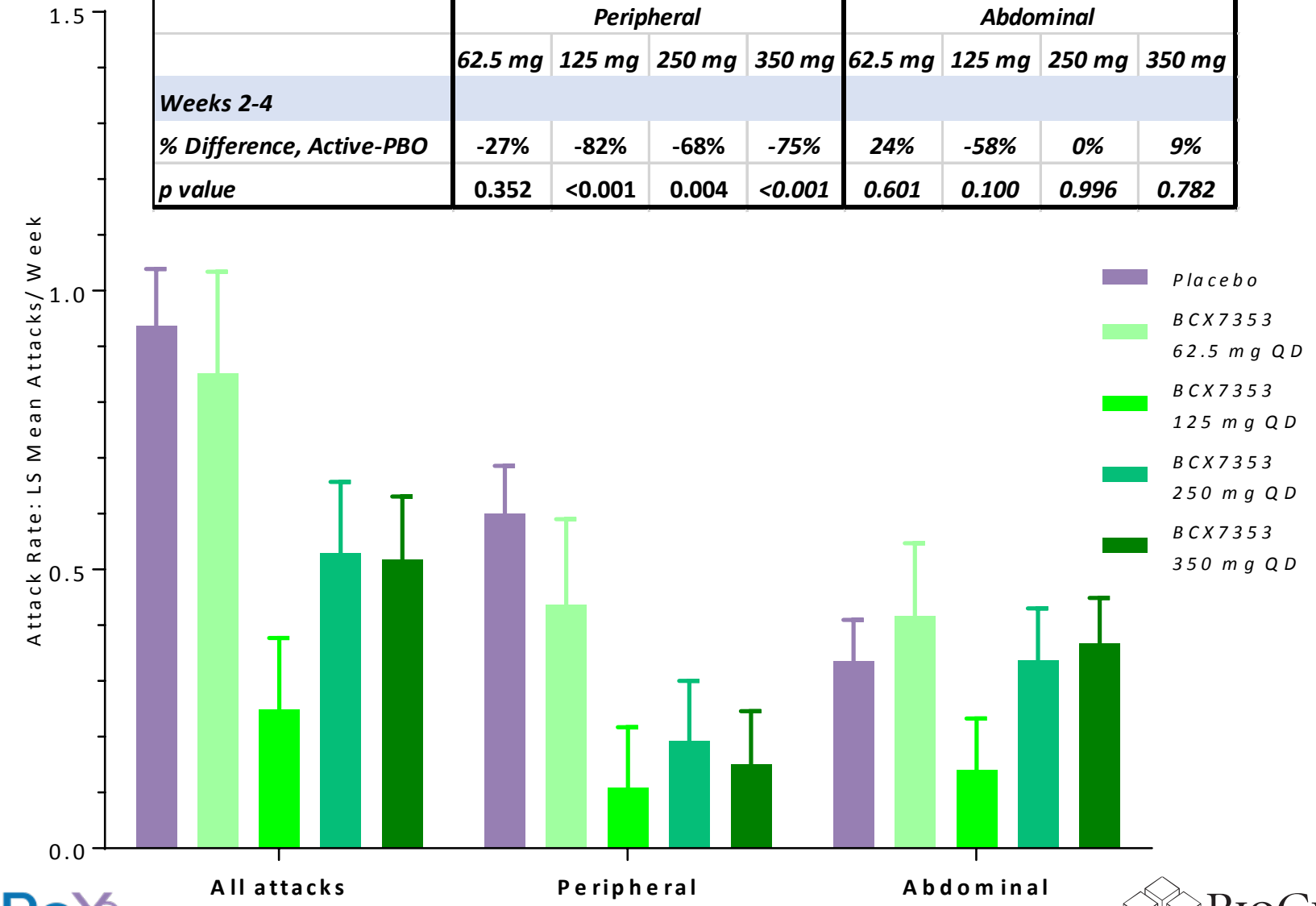
Overall angioedema attack rate per week, ITT, weeks 2-4 and 1-4

	62.5 mg	125 mg	250 mg	350 mg
Weeks 2-4				
% Difference, Active-PBO	-9%	-73%	-44%	-45%
p value	0.687	<0.001	0.014	0.007
Weeks 1-4				
% Difference, Active-PBO	-7%	-70%	-47%	-41%
p value	0.748	<0.001	0.004	0.007



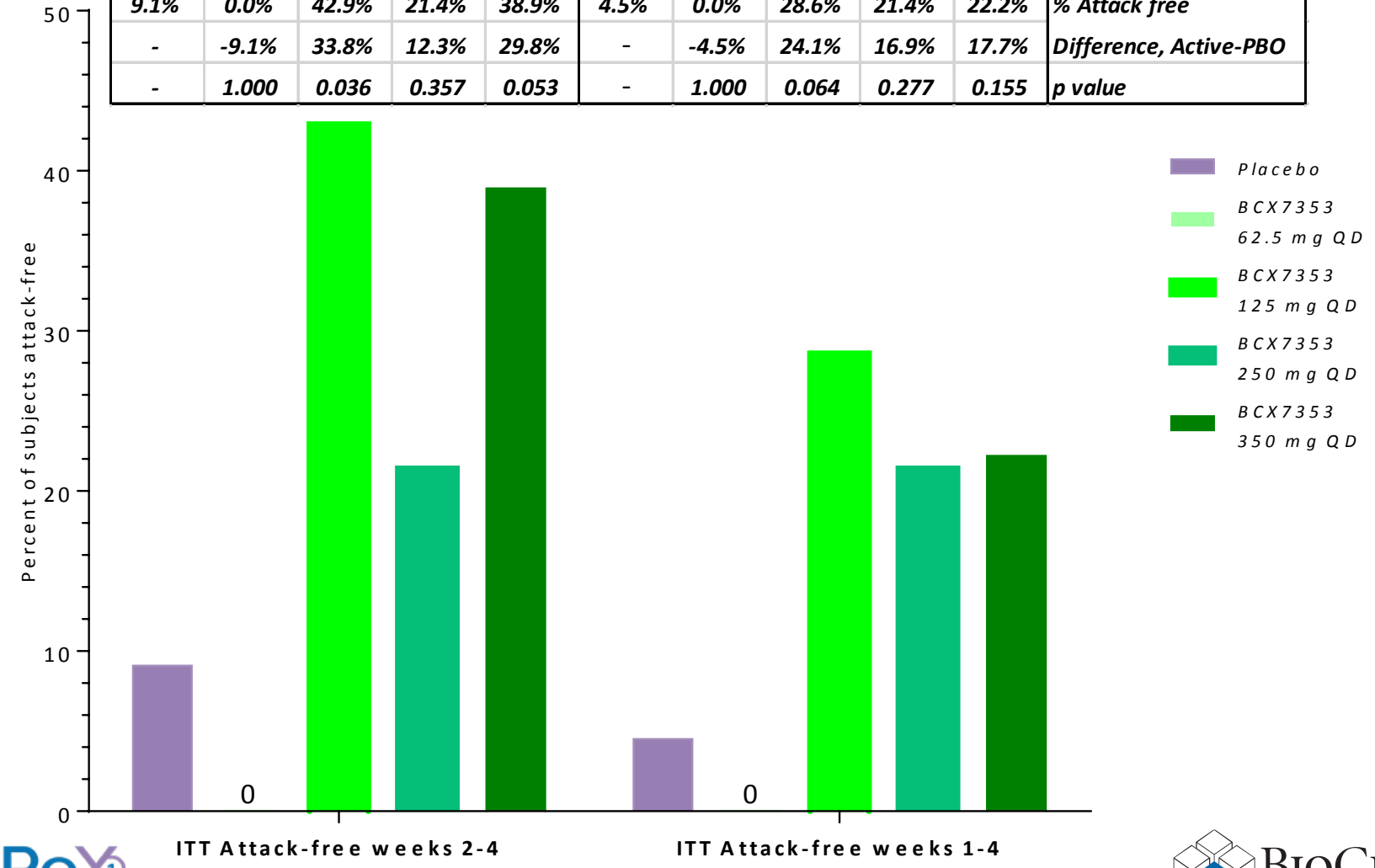
Angioedema attack rates by prespecified anatomical location, ITT

	Peripheral				Abdominal			
	62.5 mg	125 mg	250 mg	350 mg	62.5 mg	125 mg	250 mg	350 mg
Weeks 2-4								
% Difference, Active-PBO	-27%	-82%	-68%	-75%	24%	-58%	0%	9%
p value	0.352	<0.001	0.004	<0.001	0.601	0.100	0.996	0.782

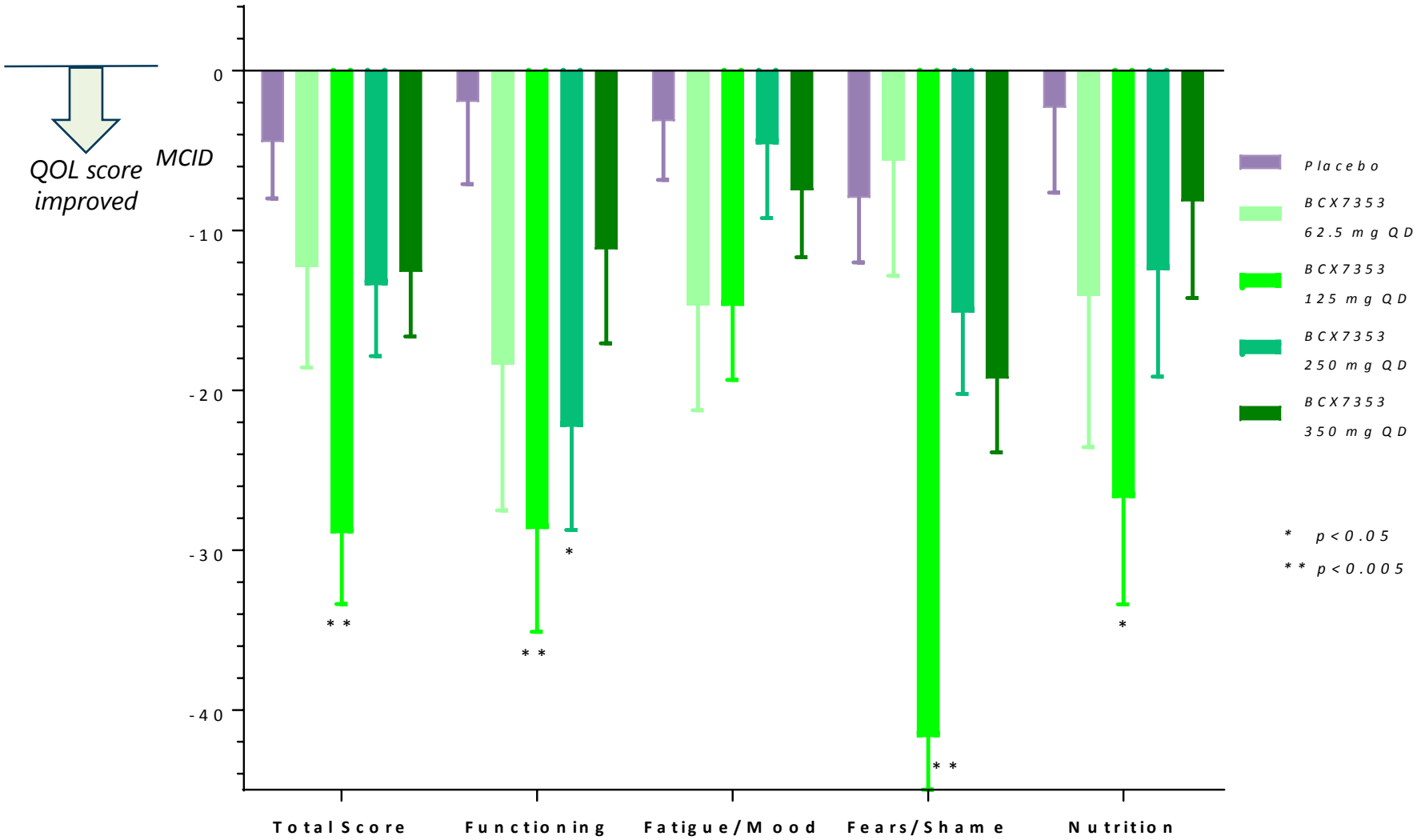


Percent of subjects attack-free, ITT

PBO	62.5 mg	125 mg	250 mg	350 mg	PBO	62.5 mg	125 mg	250 mg	350 mg	
Weeks 2-4					Weeks 1-4					
9.1%	0.0%	42.9%	21.4%	38.9%	4.5%	0.0%	28.6%	21.4%	22.2%	% Attack free
-	-9.1%	33.8%	12.3%	29.8%	-	-4.5%	24.1%	16.9%	17.7%	Difference, Active-PBO
-	1.000	0.036	0.357	0.053	-	1.000	0.064	0.277	0.155	p value



Angioedema quality of life (AE-QoL): LS mean change from BL at day 29, ITT



Difference in adjusted least square means are shown (Active treatment minus Placebo).
ANCOVA Model includes terms of treatment and adjusted qualifying attack rate.
Reductions (negative changes from BL) represent improvement in quality of life scores.
MCID, minimum clinically important difference, -6 points (*Weller, K. 2016. Allergy 71(8): 1203-1209.)*
BCX7353 dose level compared with placebo