BCX7353 – APeX-1
Interim Analysis Results

February 27, 2017

BioCryst Pharmaceuticals, Inc.

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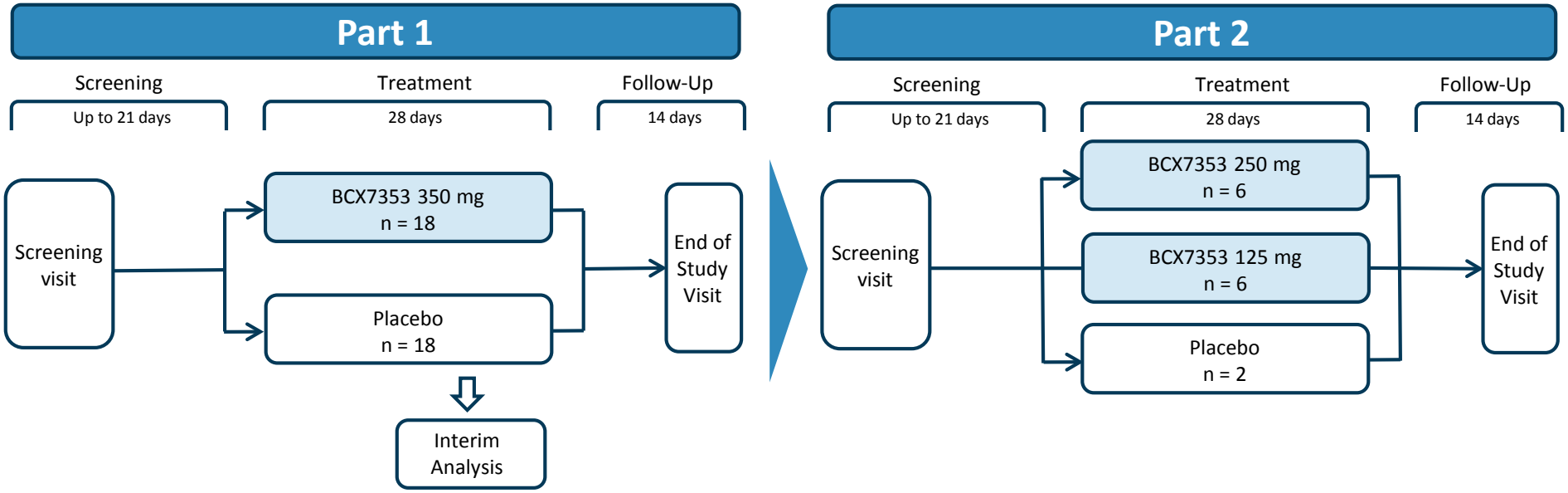
Headlines – APeX-1 study interim analysis

- BCX7353 350 mg once daily for 4 weeks achieved a statistically significant and clinically meaningful reduction in number of angioedema attacks in patients with severe hereditary angioedema
  - Robust result in a patient population with severe disease status – baseline attack rate of approximately 1 per week
  - Robust result in a short duration phase 2 study
  - Robust result with a small sample size
- Dramatic impact of BCX7353 (>80% reduction) on unequivocal angioedema attacks (peripheral and mixed peripheral + abdominal attacks)
- Oral BCX7353 350 mg once daily over 4 weeks was generally safe and well tolerated
- BCX7353 trough levels substantially exceeded the 4-8 x target EC_{50} range (11-32 x EC_{50})
- PK profile and kallikrein inhibition levels were similar to those seen in Phase 1

APeX-1: Study design



- Male/ female subjects, 18-70 years, HAE Type 1 or 2
- Qualifying attack rate ≥ 2 attacks per month (0.45 per week) for 3 consecutive months within last 6 months
- Subject- reported attacks confirmed by HAE expert adjudication panel

Objectives

- Study objectives
  - Evaluate efficacy of once daily BCX7353 over 28 days in subjects with HAE
  - Evaluate safety and tolerability
  - Describe pharmacokinetic (PK) profile in HAE subjects
  - Characterize anticipated pharmacodynamic (PD) effect in HAE subjects

- Pre-planned interim analysis objectives
  - Establish proof of concept of the highest dose evaluated
  - Estimate magnitude of treatment benefit
  - Evaluate need for any changes to remainder of APeX-1

APeX-1 Interim analysis population

		BCX7353 350mg		Placebo	
Randomized and treated		14		14	
Completed study- Intent to Treat (ITT) population		14		14	
Per Protocol (PP) population		11		13	
Excluded from PP population		3		1	
HAE Type 1 or 2 not confirmed			*1*		*1*
Did not complete 28 days of dosing with study drug			*2*		*0*
Study drug compliance	%	98		99	
Age - years	mean (SD)	46	(12)	46	(12)
Sex – female	n (%)	8	(57)	9	(64)
BMI- kg/m^2	mean (SD)	29	(5)	27	(5)
Prior androgen use	n (%)	11	(79)	6	(43)
ALT > ULN at Baseline	n (%)	5	(36)	3	(21)
Qualifying attack rate attacks/wk	mean (SD)	0.94	(0.47)	1.11	(0.60)
Baseline C1INH level	% of normal (SD)	15	(17)	19	(20)

Interim analyses conducted

Pre-Planned analyses:

- Key interim analysis end-points:
  - Efficacy: Number of HAE attacks, analyzed by: weekly attack rate; number of attacks; proportion of subjects with no attacks
  - Safety (ITT population)
  - PK/ PD (kallikrein inhibition)
- Key efficacy analyses presented run on two populations and on two dosing periods:
  - Per Protocol (PP) population: completed 28 days of dosing, no major protocol violations
  - Intent-to Treat (ITT) population: randomized and received ≥ 1 dose of study drug
  - Effective dosing period: Week 2-4 (Study Day 8-29 inclusive)
  - Entire dosing period: Week 1-4 (Study Day 1-29 inclusive)
- Analysis of peripheral vs abdominal attacks

Post- hoc anatomical classification of attacks:

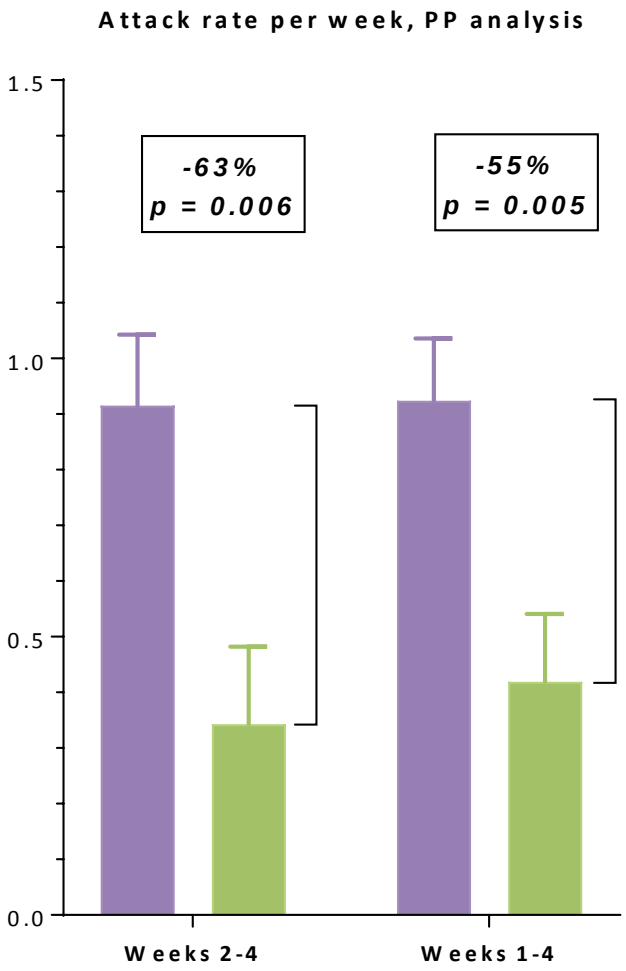
- Peripheral attacks (Non abdominal symptoms)
- Mixed attacks (Abdominal symptoms + Non-abdominal symptoms)
- Abdominal attacks (Abdominal symptoms)

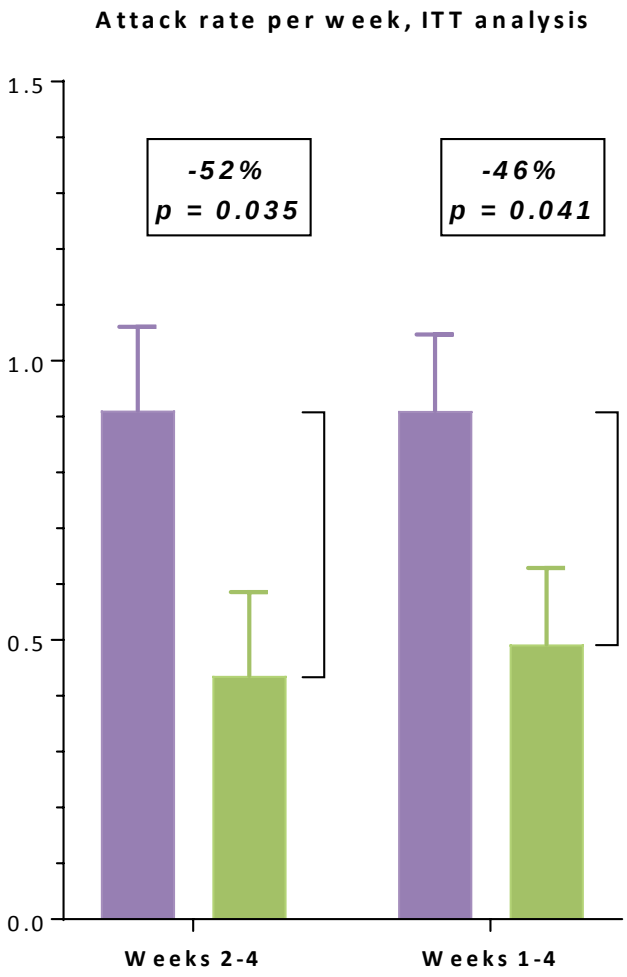
Rate of overall confirmed attacks

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 350 mg	11	0.343	-0.572	63%	0.006
Placebo	13	0.915			
Effective dosing period (Week 2-4) – ITT Population					
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

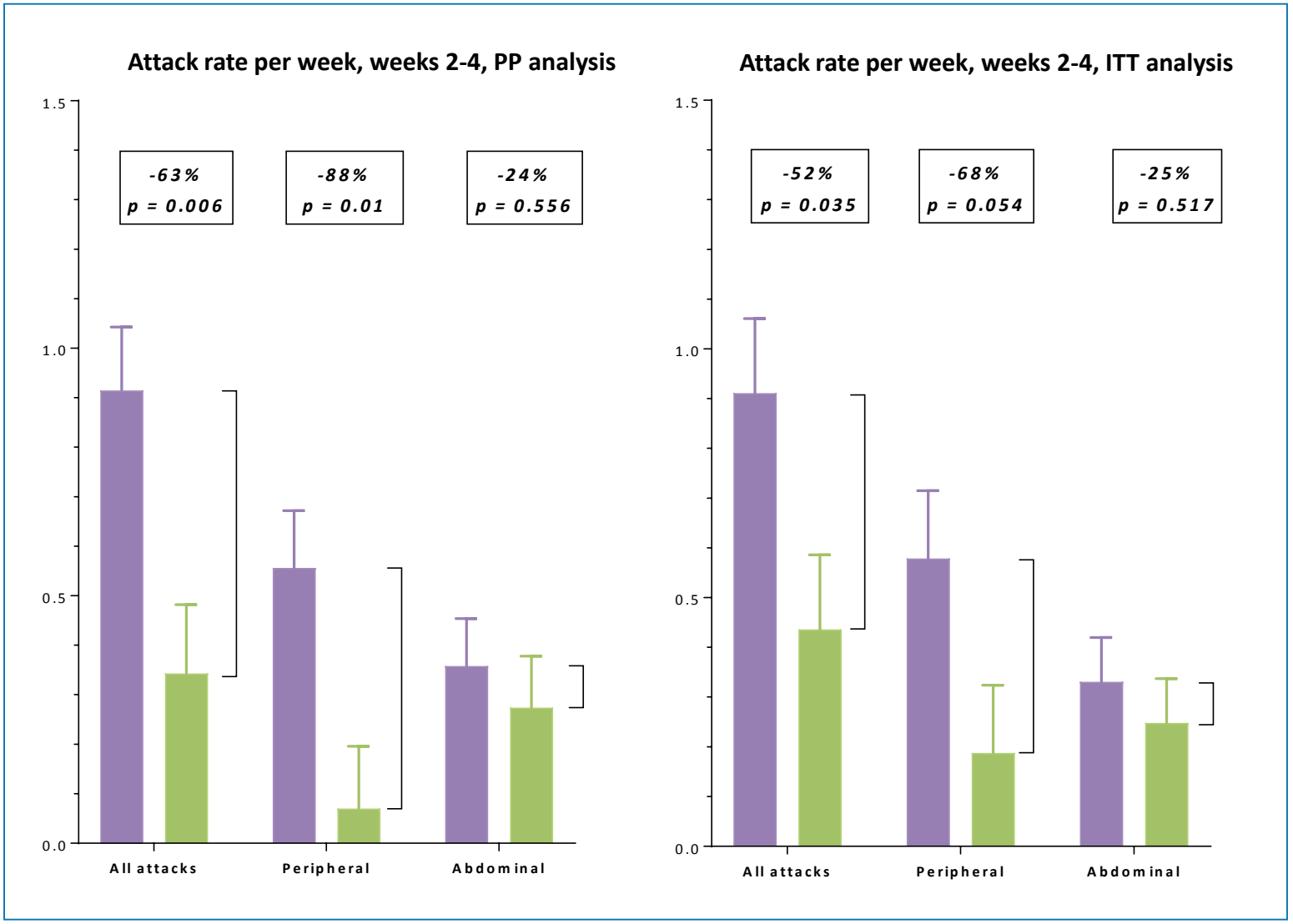
Overall angioedema attack rate



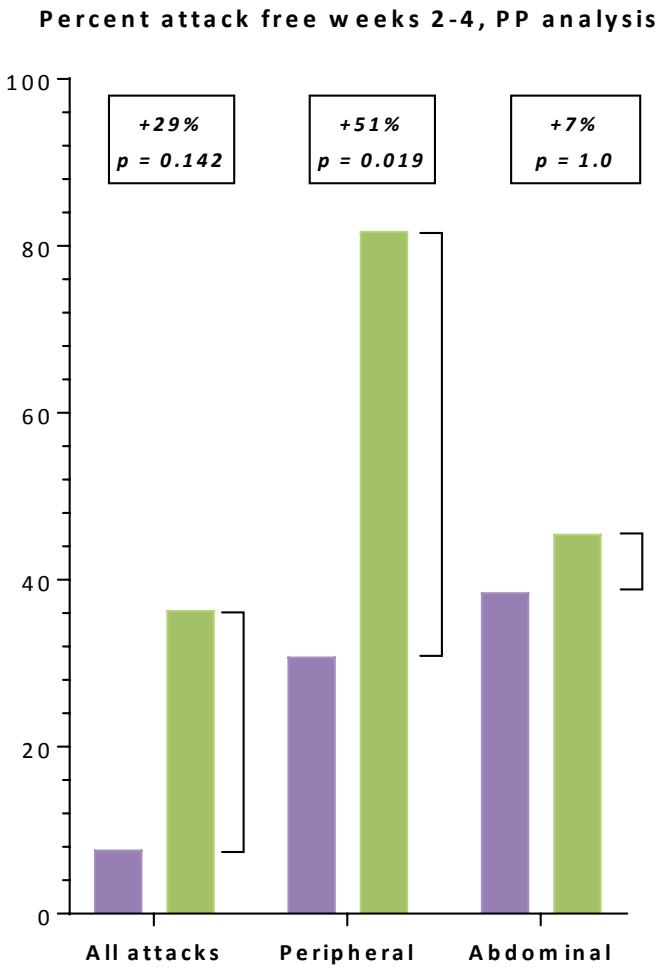


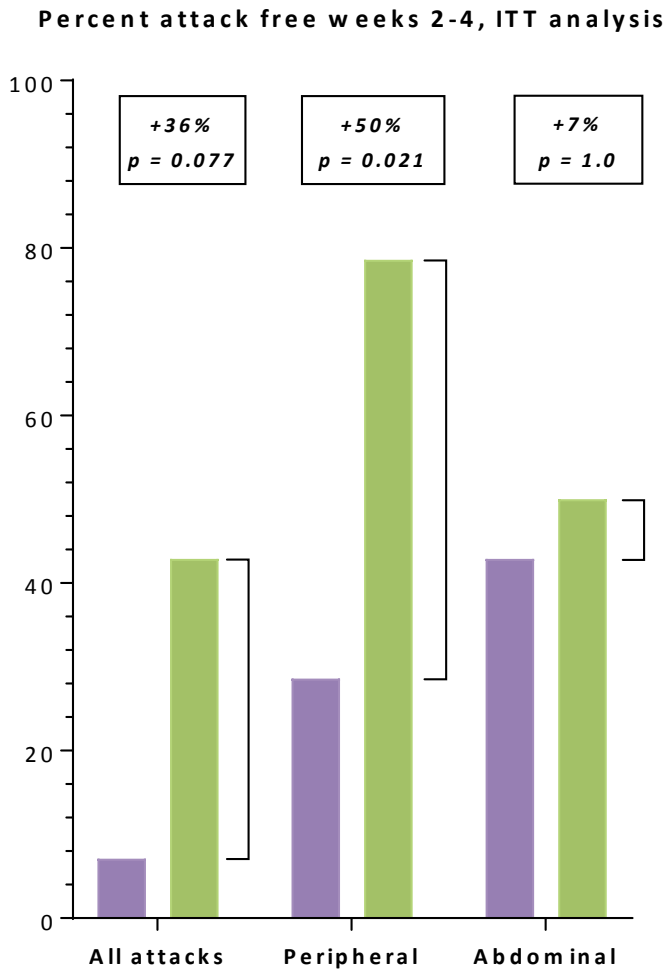
BCX7353
Placebo

Angioedema attack rates by pre-specified anatomical location



Percent of subjects who were attack free, all attacks and by pre-specified anatomical location





BCX7353
Placebo

Angioedema attacks by anatomical category

	Peripheral		Mixed		Abdominal	
Effective dosing period (Week 2-4) – Per Protocol Population						
	Attacks	**Subjects**	**Attacks**	**Subjects**	**Attacks**	**Subjects**
BCX7353	**2**	2	**2**	1	**7**	5
Placebo	**22**	9	**12**	7	**2**	1
% Change vs Placebo	**-91%**		**-83%**		**+350%**	
Effective dosing period (Week 2-4) – ITT Population						
BCX7353	**6**	3	**3**	3	**7**	5
Placebo	**25**	10	**12**	7	**2**	1
% Change vs Placebo	**-76%**		**-75%**		**+350%**	

Clear imbalance in attack reduction by location. Subjects may not have been able to distinguish between BCX7353- related GI events and early signs of an abdominal attack.

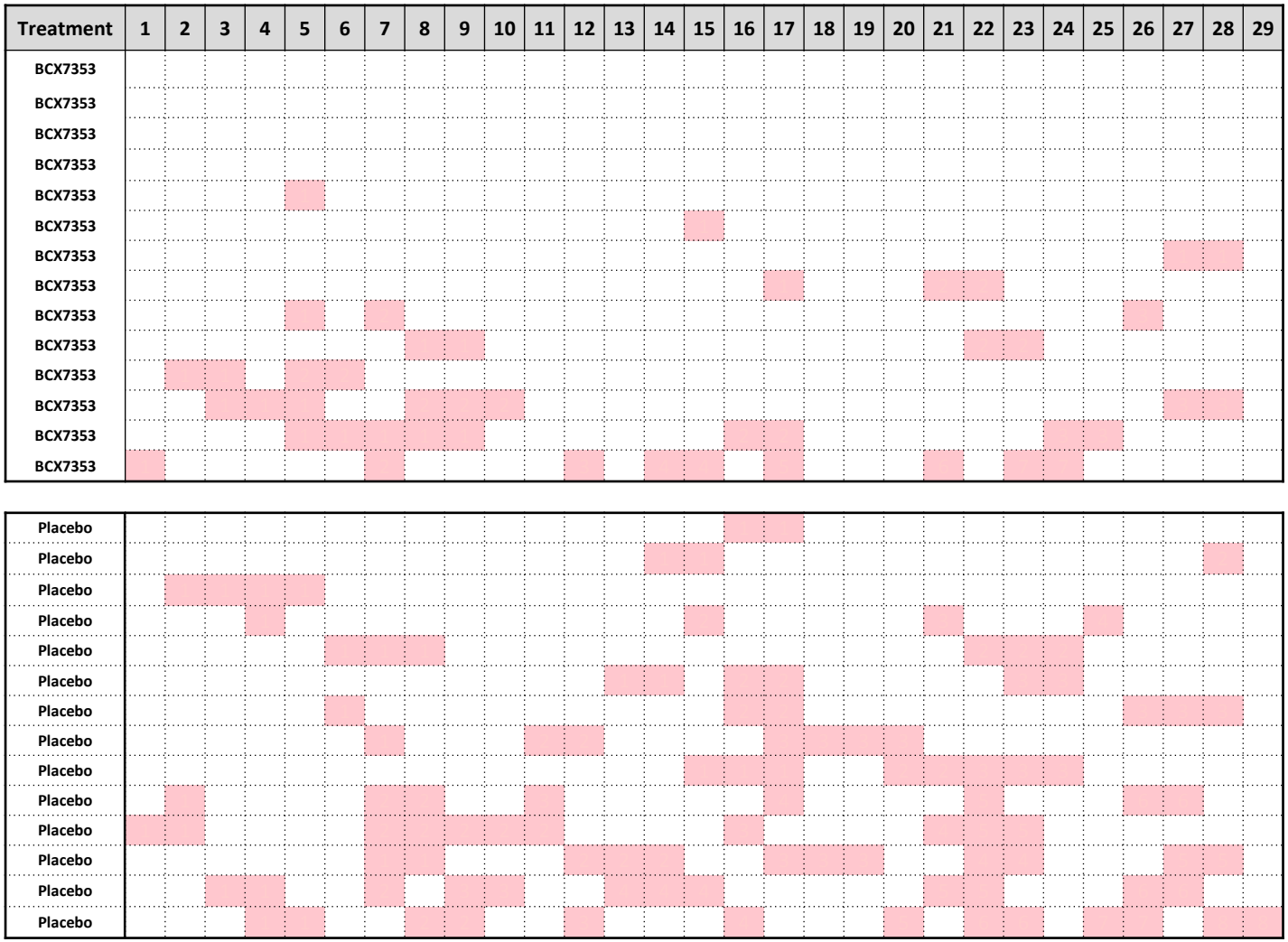
Post- hoc analysis

Analysis of gastrointestinal symptoms in the subject diary

AE or symptom	Reported as AE		Reported as attack-related symptoms			
			Mixed peripheral + abdominal attack category [1]		Abdominal-only attack category [1]	
	BCX7353 (n=14)	Placebo (n=14)	BCX7353 (n=14)	Placebo (n=14)	BCX7353 (n=14)	Placebo (n=14)
Abdominal pain	1 (7.1%)	0	1 (7.1)	6 (42.9)	7 (50.0)	3 (21.4)
Nausea	1 (7.1%)	0	1 (7.1)	6 (42.9)	4 (28.6)	2 (14.3)
Vomiting	1 (7.1%)	0	0	0	1 (7.1)	1 (7.1)

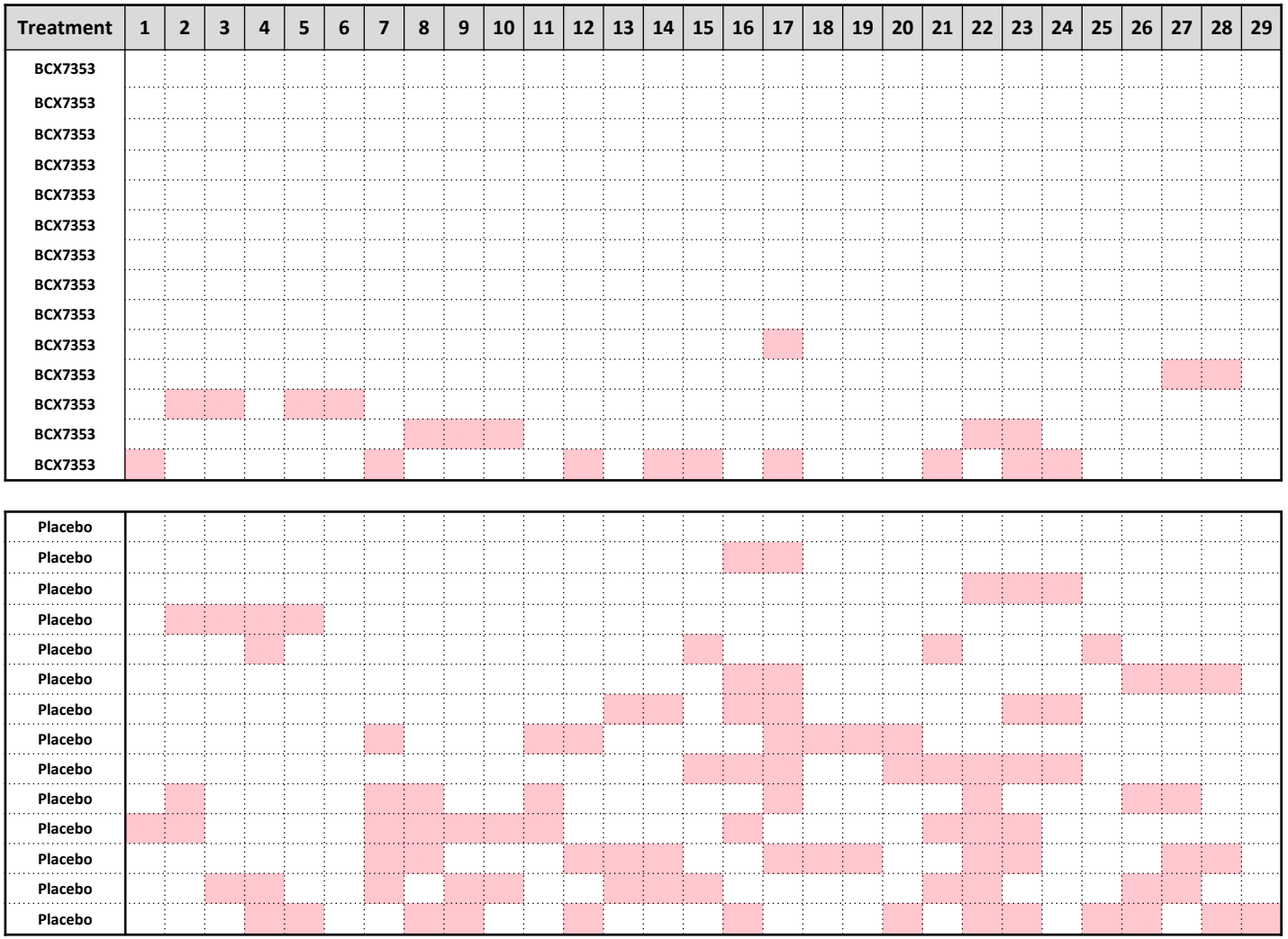
[1] Includes all subject-reported attacks, including those rejected by expert adjudication committee. Multiple reports of the same event in the same subject are only tabulated once

Days with any angioedema symptoms recorded in the subject diary



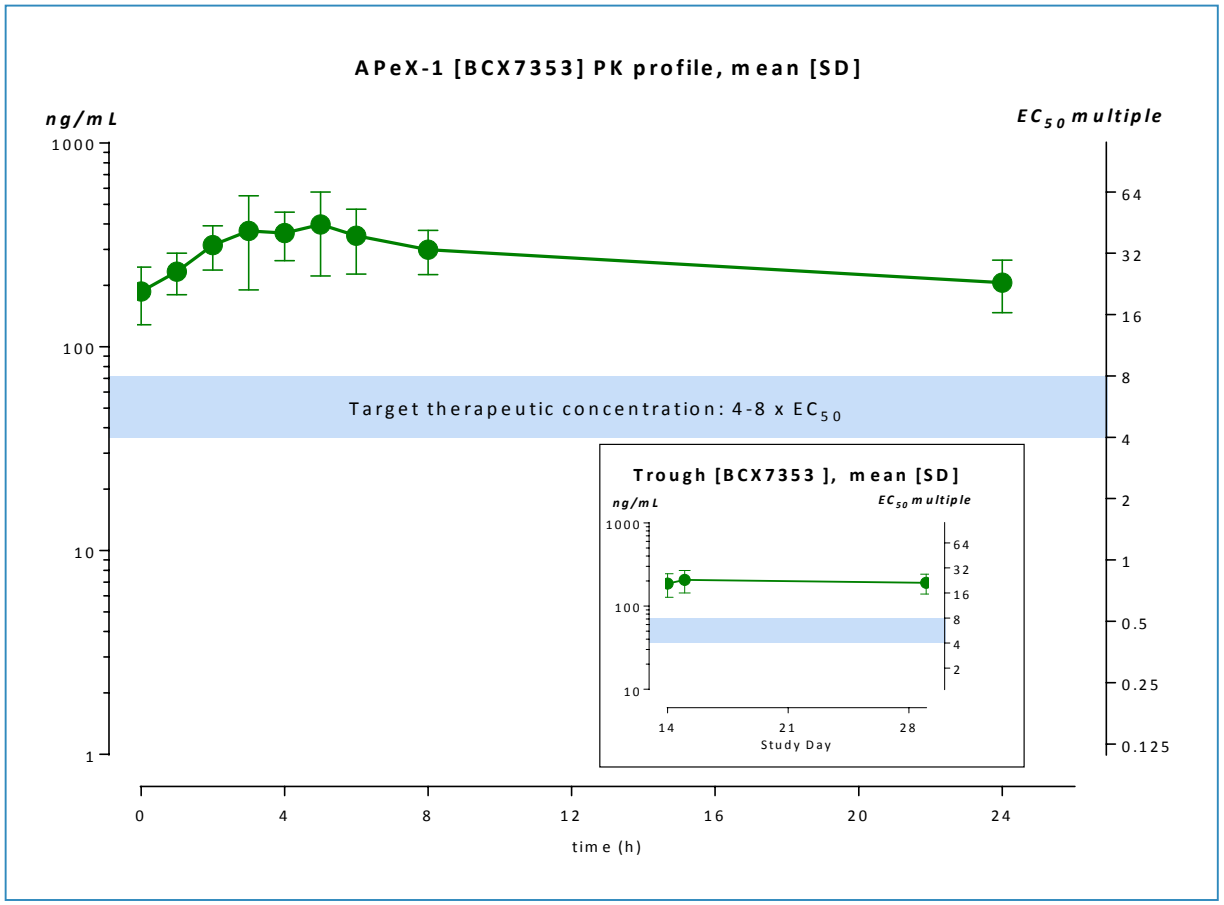
Post-hoc analysis including all days with any symptoms recorded by subjects as attack of HAE.
Study subjects (rows) in each treatment group ordered by increasing number of days with symptoms

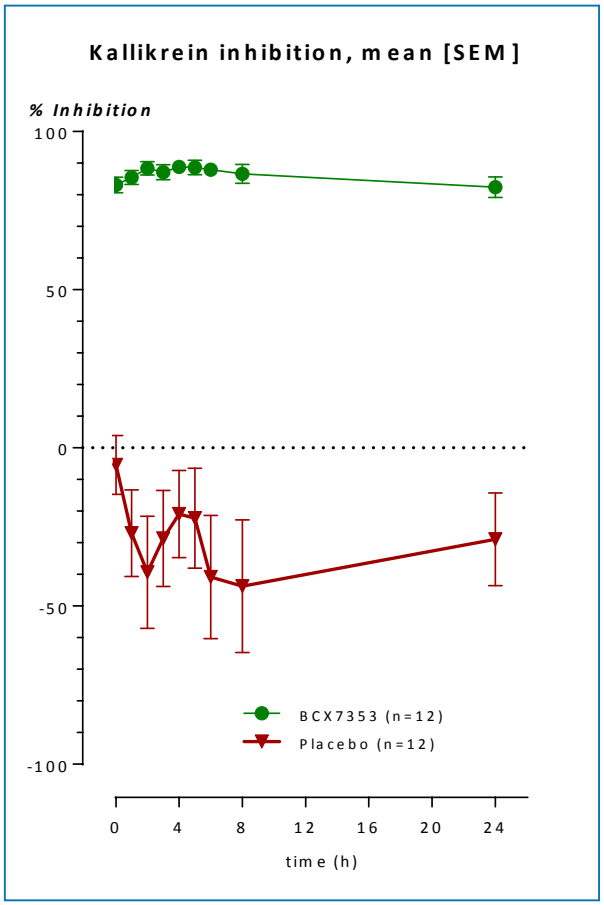
Days with unequivocal angioedema symptoms recorded in the subject diary



Post- hoc analysis excluding any attacks with only abdominal symptoms.
Study subjects (rows) in each treatment group ordered by increasing number of of days with symptoms

Blood drug levels of BCX7353 with once daily oral dosing of 350mg were well above target range





- Trough plasma levels between 11-32 fold of the EC_{50} of BCX7353
- Kallikrein inhibition sustained throughout the dosing interval

BCX7353 APeX-1 interim analysis safety summary

Category	BCX7353 (n=14)	Placebo (n=14)
Number of Subjects with any Serious AE, n (%)	0	0
Number of Subjects with Drug-Related AE of Grade 3 or Grade 4, n (%)	0	0
Number of Subjects with AE Leading to Discontinuation from Study Drug, n (%)	2 (14.3)	0
Non- drug-related, n (%) Pre-existing liver disorder (improved from baseline, but persisting)	1 (7.1)	0
Drug-related, n (%) 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)	1 (7.1)	0
Treatment-Emergent Adverse Events occurring in ≥2 subjects overall		
Nasopharyngitis (common cold) Diarrhea Flatulence Fatigue	3 (21.4) 4 (28.6) 2 (14.3) 2 (14.3)	4 (28.6) 2 (14.3) 0 0
Clinically significant changes in clinical chemistry, hematology or urinalysis		
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*	1 (7.1)	0

Interim analysis conclusions

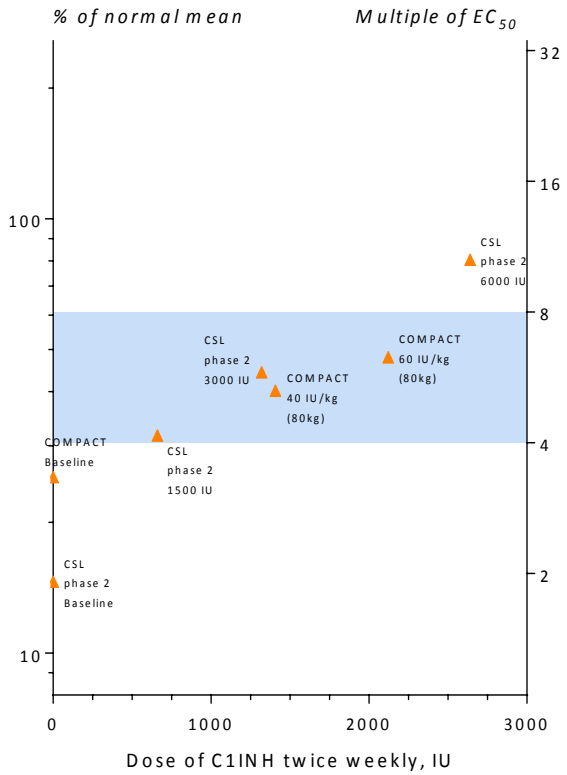
- In 28 HAE patients with frequent attacks (~ 1/ week), BCX7353 350 mg QD for 28 days showed statistically significant and clinically meaningful reductions in angioedema attacks
- Treatment effect was statistically robust

Endpoint	Analysis Population	Reduction compared to placebo - attacks/week (%)	p value
Weekly attack rate (weeks 2-4)	PP	0.572 (63%)	0.006
	ITT	0.474 (52%)	0.035

- > 80% reduction in unequivocal angioedema attacks, characterized by either peripheral symptoms only or a combination of peripheral and abdominal symptoms ("mixed")
- Some abdominal symptoms reported as angioedema attacks may in fact have been GI-related AEs
- BCX7353 was generally safe and well tolerated: common cold and diarrhea were the most common AEs
- Blood levels of BCX7353 exceeded the proposed target range for efficacy
- Interim analysis results support evaluation of lower doses of BCX7353

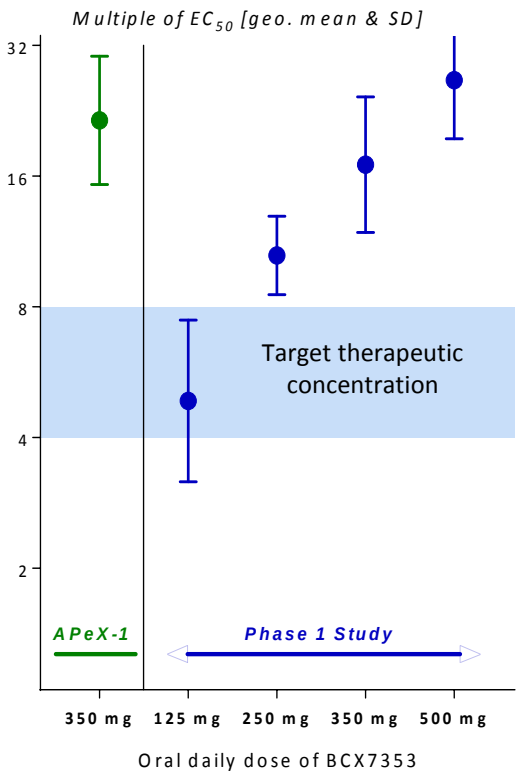
Exposure comparisons and population PK modeling support evaluation of lower doses of BCX7353

CSL-830 Ph2/ Ph3



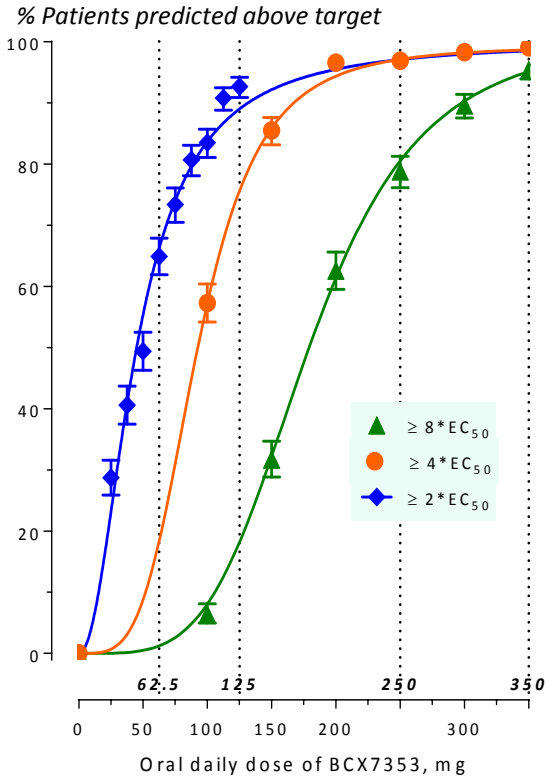
Dose Exposure analysis of CSL-830 SC C1INH [1]

BCX7353 Ph1/ APeX



BCX7353 concentrations at 24 hours post-dose

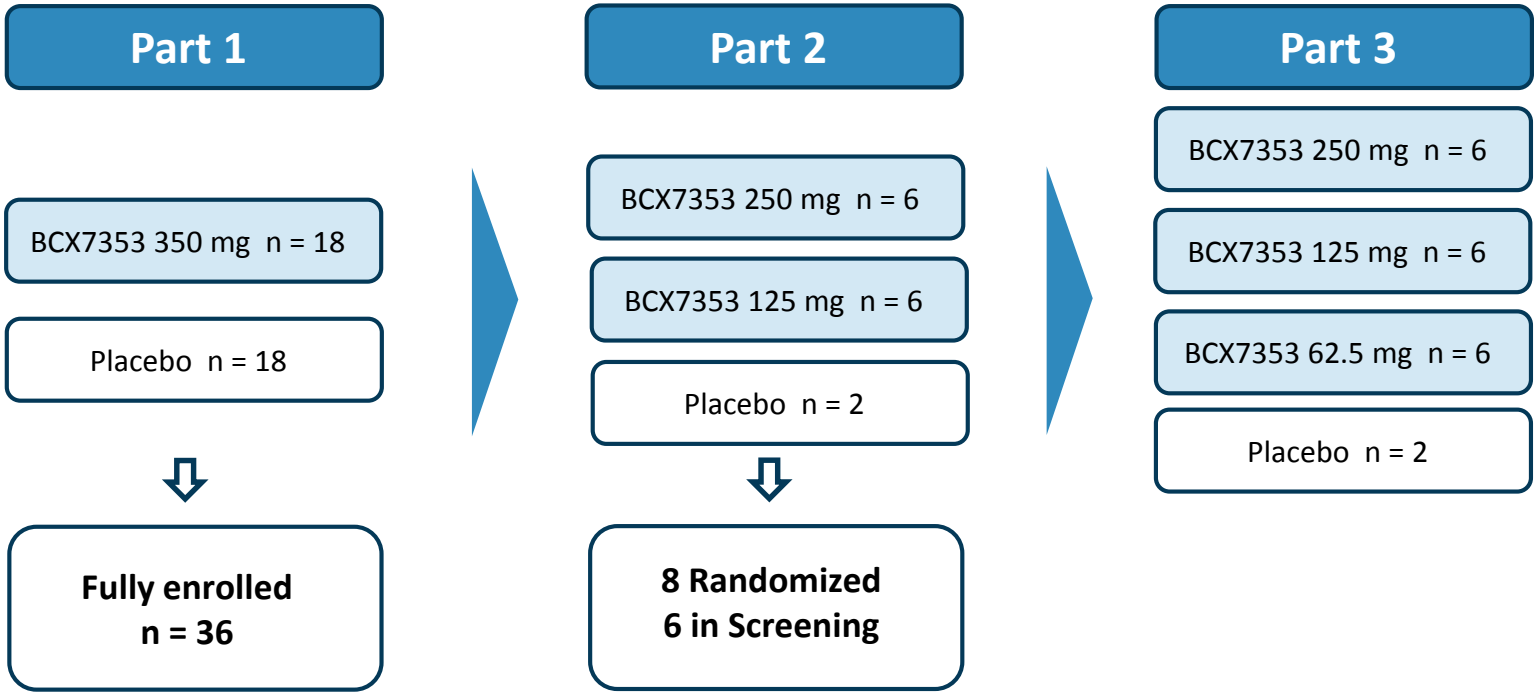
PK Modeling



Monte Carlo simulation: 1000 subjects per data point

[1] Zuraw, B. L. *et al. Allergy* ***70, 1319-1328,*** Presentation at ACAAI 2016

APeX-1: Update



Part 2 data expected 2Q2017

Adding Part 3 with lower dose cohort (62.5 mg) to ensure full evaluation of dose response

Q&A

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BCX7353 Phase 1 Daily dosing: Adverse events occurring in >1 subject

	Placebo	BCX7353			Placebo	BCX7353
Dosing regimen	***Once daily for 7 days***				***Once daily for 14 days***	
Dose	**--**	**125mg**	**250mg**	**500 mg**	**--**	**350mg**
N	6	10	10	10	2	10
Subjects (%) reporting an AE	2 (33.3)	2 (20.0)	2 (20.0)	7 (70.0)	2 (100.0)	8 (80.0)
Total number of AEs	2	5	6	22	2	21
Nature of AE						
Diarrhea	0	1 (10.0)	0	5 (50.0)	0	0
Flatulence	0	0	0	2 (20.0)	0	0
Abdominal pain	0	0	1 (10.0)	1 (10.0)	0	3 (30.0)
Abdominal distension	0	0	0	1 (10.0)	0	1 (10.0)
Dyspepsia	0	0	0	0	0	2 (20.0)
Epigastric discomfort	0	0	0	0	0	2 (20.0)
Nausea	0	0	0	1 (10.0)	0	1 (10.0)
Dizziness	0	1 (10.0)	0	1 (10.0)	0	1 (10.0)
Headache	0	1 (10.0)	0	1 (10.0)	0	1 (10.0)
Upper Resp Tract Infection	0	0	0	0	0	2 (20.0)

Presented October 8, 2015

BioCryst Pharmaceuticals, Inc.