IV BRINCIDOFOVIR (BCV): PHARMACOKINETICS (PK) AND SAFETY OF MULTIPLE ASCENDING DOSES (MAD) IN HEALTHY SUBJECTS

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IV BCV Multiple-dose Study in Healthy Adults: CMX001-125

Study Design

Cohort	n	Actual Doses	IV Infusion Duration
1	3 BCV / 1 placebo	IV BCV 10 mg BIW (4 doses)	2 hours
2a	6 BCV and 2 placebo	IV BCV 20 mg QW (4 doses)	2 hours
2b	6 BCV and 2 placebo	IV BCV 20 mg QW (4 doses)	1 hours
3	6 BCV and 2 placebo	IV BCV 10 mg BIW (4 doses)	2 hours

BIW: twice weekly
QW: once weekly

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IV BCV Multiple-dose Study in Healthy Adults: CMX001-125 Demographics:

		Cohorts 1 and 3	Cohort 2a	Cohort 2b	Placebo
Demographic		Pooled 10 mg BCV IV (2h) BIW (n=9)	20 mg BCV IV (2h) QW (n=6)	20 mg BCV IV (1h) QW (n=5)	All Pooled Placebo (n=7)
Age	Years	50 (10)	55 (11)	56 (6)	55 (5)
Sex	Male	6 (66.7%)	2 (33.3%)	1 (20%)	1 (14.3%)
	Female	3 (33.3%)	4 (66.7%)	4 (80%)	6 (85.7%)
Race	White	8 (88.9%)	5 (83.3%)	5 (100%)	7 (100%)
	Native Hawaiian or Other Pacific Islander	---	1 (16.7%)	---	---
BMI	(kg/m^2)	26.3 (3.4)	25.5 (1.4)	28.9 (3.8)	24.8 (2.3)

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IV BCV PHARMACOKINETICS

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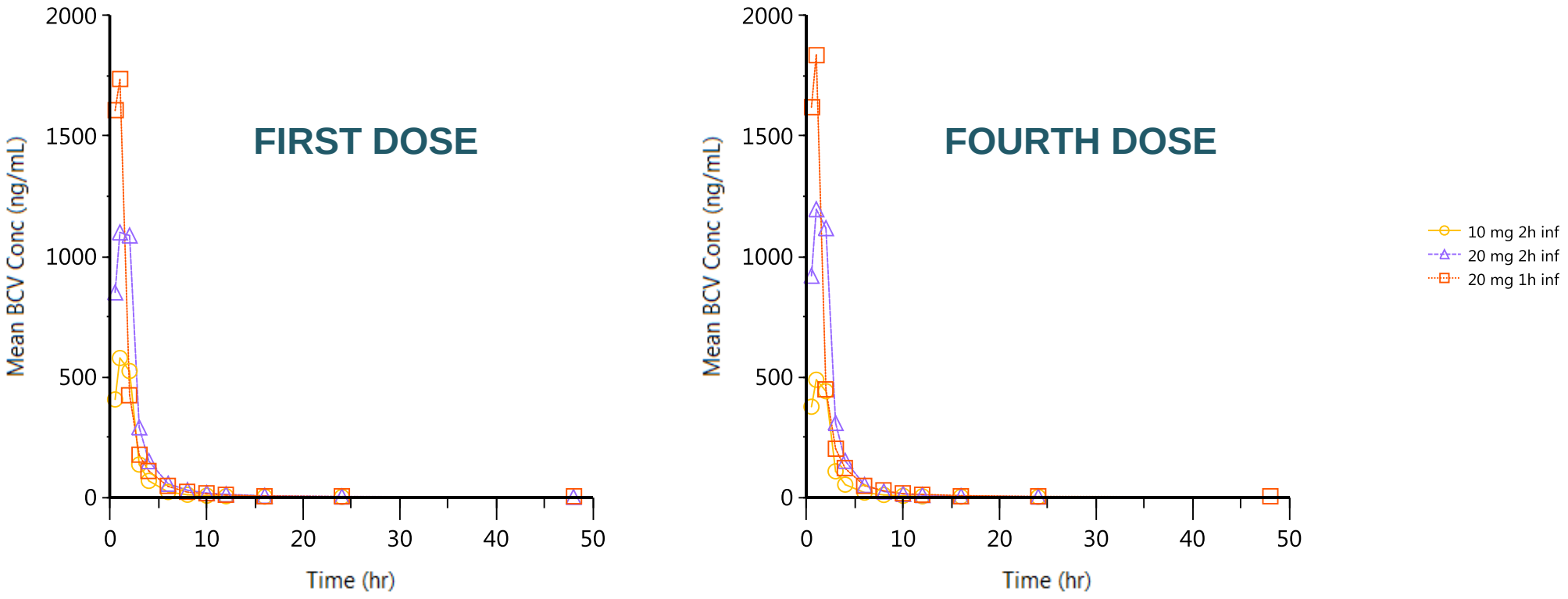
BCV exposure was dose-proportional after the first dose and no accumulation was observed



SAFETY

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Treatment Emergent AEs in >2 Subjects

		Pooled 10mg BIW	BCV 20 mg (1h) QW	BCV 20 mg (2h) QW	Pooled PBO
SOC	**PT**	**n=9**	**n=5**	**n=6**	**n=7**
GI Disorders		**2*** **	**4** **	**5***	**1**
	Diarrhea		**1**	**3**	
	Vomiting		2	1	1
Investigations		**0**	**0**	**1**	**0**
	ALT increased			**1**	
Nervous System Disorders		**5**	4	**3**	**5**
	Headache	**5**	**4**	**3**	**5**
Vascular Disorders		**0**	**0**	**2**	**0**
	Thrombophlebitis			2	
General Disorders and Admin Site		**2**	**1**	**3**	**2**
	Fatigue			3	2

* Mouth ulcer, Defecation Urgency
** Constipation
*** Nausea, toothache

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Safety Summary

- Generally safe and well tolerated with no new BCV-related AEs identified
- No diarrhea at IV BCV 10 mg BIW
- Mild diarrhea noted after the first dose of IV BCV 20 mg QW without progression after repeated IV doses
- ALT increases were predictable, reversible upon cessation of drug and not associated with hyperbilirubinemia
- Well tolerated at the infusion site

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AE Summary by Dose

- 10 mg BIW (Cohort 1 & 3, n = 9)
  - Very well tolerated
  - All AEs were mild
  - No diarrhea
  - 5/9 subjects with headache, compared to 5/7 in pooled PBO
- 20 mg QW (Cohort 2a [2 hr; n = 6] and 2b [1 hr; n = 5])
  - Increased GI events (5 subjects in 2a, 4 subjects in 2b)
    - 3 subjects with diarrhea following 2hr infusion, 1 subject following 1 hr infusion
  - 7/11 subjects with headache, compared to 5/7 in pooled PBO

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AE Summary

- Diarrhea events
  - Overall, 4 of 20 BCV recipients with events, and all were mild
  - Occurred primarily after 1st dose, but not all subsequent doses
  - Most with onset within 1 day of dose – inconsistent with our theory that diarrhea driven by intracellular CDV-PP
  - No diarrhea seen with 10 mg BIW, but overall little correlation with AUC or Cmax
- Headache events
  - Most were mild; 4 subjects had moderate HA (all 4 received 20 mg BCV)
  - More likely after first dose, but not consistently seen after subsequent doses
  - Increased intensity/duration of headaches seen in some subjects with higher exposures, but not all

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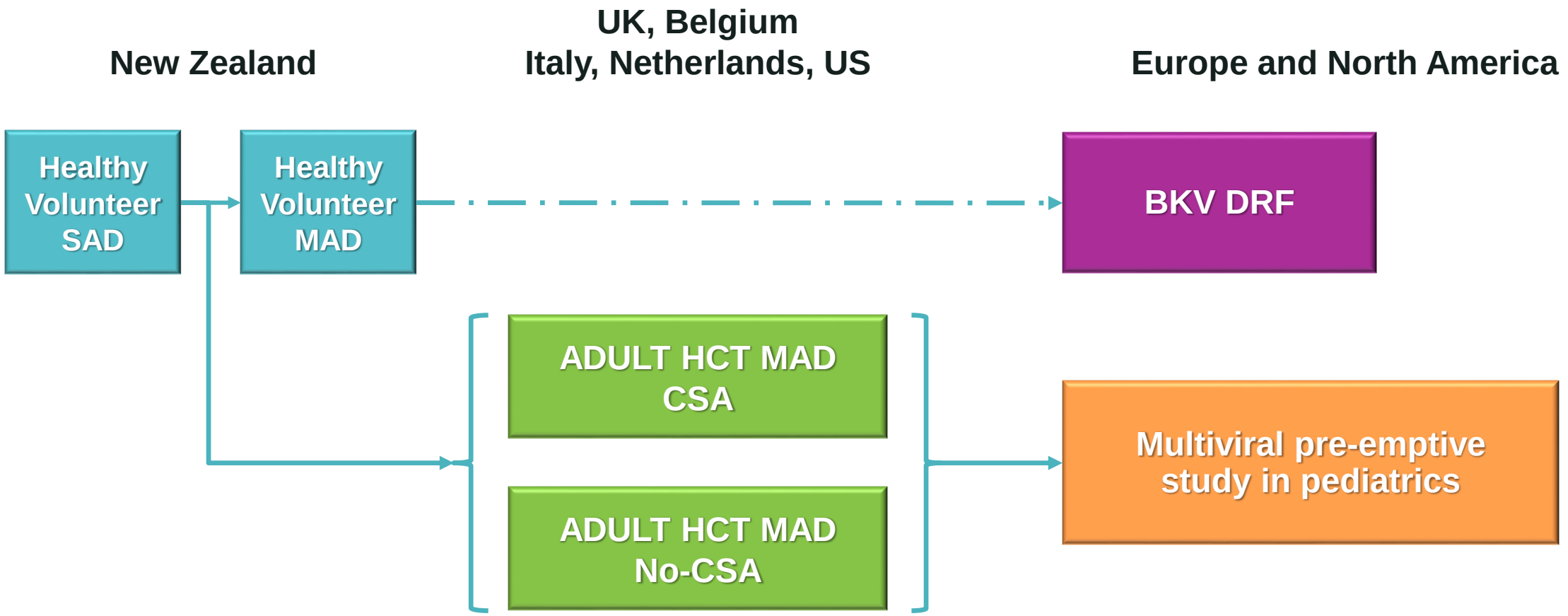
IV Development Progression Plan



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