ENOVIA

SymBio

Brincidofovir Phase 3 Study against Adenovirus: ENOVIA Launched

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TAVI FORUM
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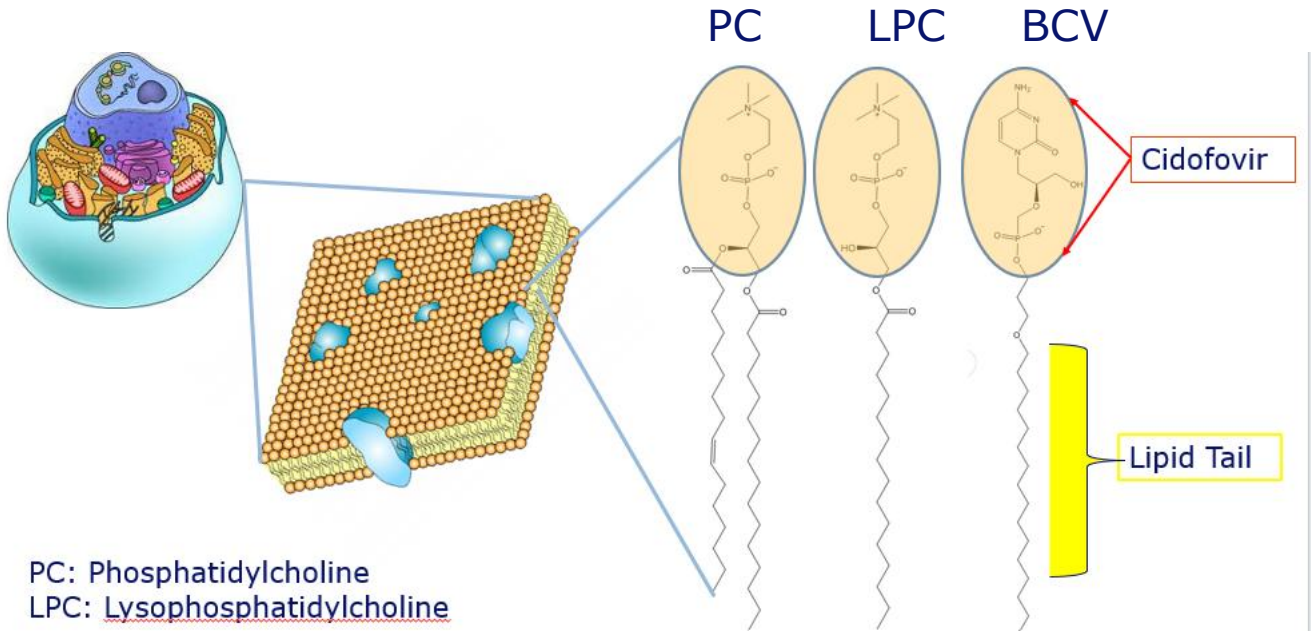
Brincidofovir: Cidofovir with lipid tail that enhances potency and Safety

Broad Spectrum
All dsDNA Viruses
ADV,BKV,CMV,HHV6,HSV
Some ssDNA like Parvo B19

IV Formulation in Phase 3
Oral approved as Tembexa

No New Safety Signals with IV
2000+ subjects in BCV Trials
>150 patients treated with IV BCV
GI tox minimal with IV



- Radio-labelled drug accumulation in rats show significantly lower GI uptake with IV
- The dose limiting GI toxicity of oral BCV may be reduced by IV administration

MOA: Cidofovir -PP selectively inhibits viral DNA synthesis by competitively inhibiting the incorporation of deoxycytidine into viral DNA

Active vs. All ADV Serotypes
No resistance Dev on Therapy

No renal or Myelo Tox
GI tox with Oral not IV

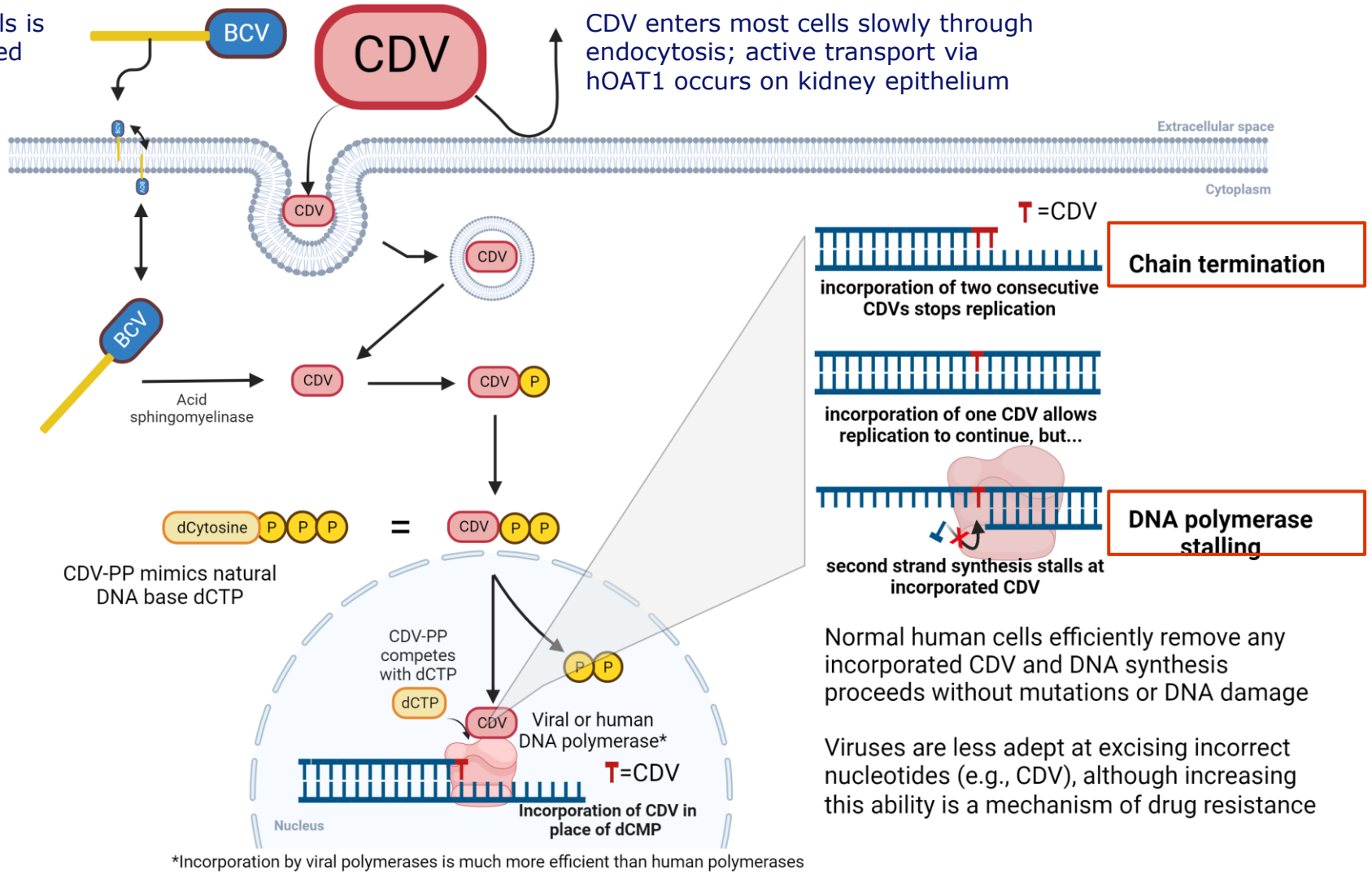
~130-hour T1/2
30% CNS Penetration
No dose adj for renal

Davis MR, et al., Medical Mycology 2019

Mechanism of action for BCV/CDV against viruses

BCV uptake in cells is efficiently mediated by the lipid tail

CDV enters most cells slowly through endocytosis; active transport via hOAT1 occurs on kidney epithelium



Normal human cells efficiently remove any incorporated CDV and DNA synthesis proceeds without mutations or DNA damage

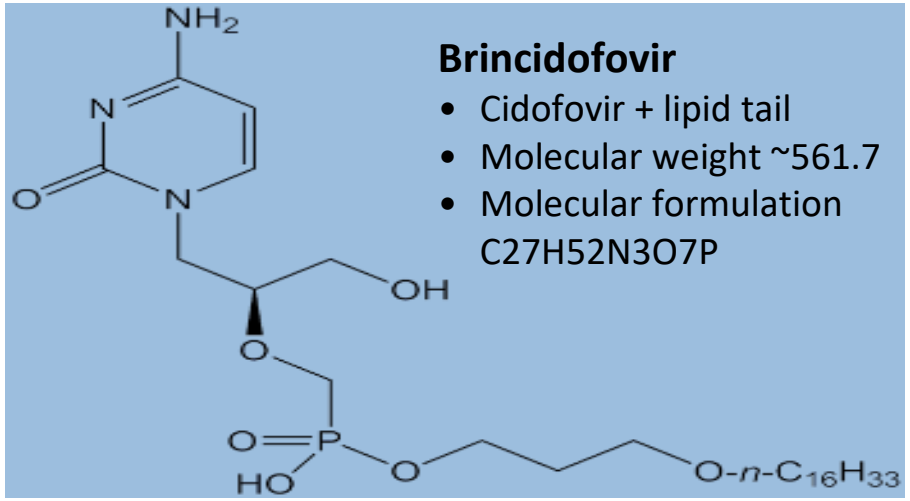
Viruses are less adept at excising incorrect nucleotides (e.g., CDV), although increasing this ability is a mechanism of drug resistance

*Incorporation by viral polymerases is much more efficient than human polymerases

BCV High in vitro potency and broad-spectrum across dsDNA viruses

Unique BCV Pharmacology

1. Lipid tail of BCV enables efficient cell uptake
2. Sphingomyelinase cleaves CDV from lipid
3. CDV converted to active metabolite CDV-PP



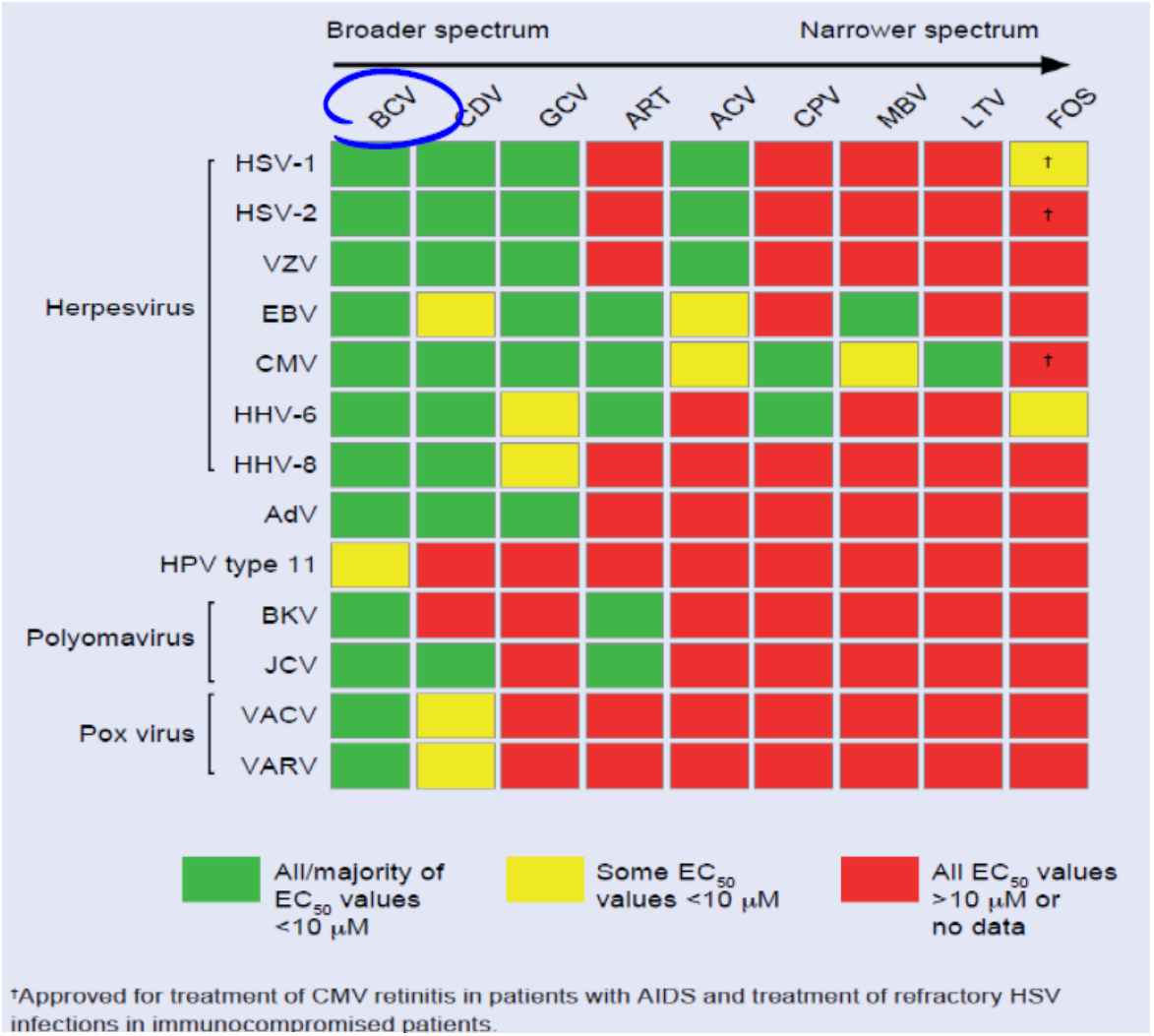
Brincidofovir

- Cidofovir + lipid tail
- Molecular weight ~561.7
- Molecular formulation C27H52N3O7P

BCV Features

- Broad spectrum across dsDNA viruses
- Amelioration of cidofovir nephrotoxicity
- High blood-brain barrier (BBB) permeability

Broad spectrum



Chemaly et al. 2019

Brincidofovir (BCV) Demonstrates broad-spectrum antiviral activity

Antiviral Activity (EC50, µM)

C_{max} after IV 10 mg BCV: 0.98 µM

Viral Family	Virus	BCV	Cidofovir	Maribavir	Letermovir	Ganciclovir*	Foscarnet	Acyclovir
Herpes	Cytomegalovirus	0.001	0.4	0.31	0.005	3.8	50-800	>200
	Epstein-Barr Virus	0.03	65.6	0.63	>10	0.9	<500	6.2
	Human Herpesvirus 6	0.003	2.7	Inactive	>10	5.8	16	10
	Human Herpesvirus 8	0.02	2.6	Inactive	—	8.9	177	>100
	Herpes Simplex Virus 1	0.01	3.0	Inactive	>10	0.7	92-95	3.8
	Herpes Simplex Virus 2	0.02	6.5	Inactive	>10	2.5	91-96	4.4
	Varicella Zoster Virus	0.0004	0.5	Inactive	>10	1.3	39.8	3.6
Adenovirus	Adenovirus (AdV-B7)	0.02	1.3	—	>10	4.5-33	Inactive	>100
Polyoma	BK Virus (BKV)	0.13	115	—	—	>200	Inactive	>200
	JC Virus (JCV)	0.045	>0.1	—	—	—	Inactive	—
Papilloma	Human Papillomavirus	17	716	—	—	Inactive	—	Inactive
Pox	Variola	0.1	27	—	—	—	—	—
	Vaccinia	0.8	46	—	—	>392	Inactive	>144

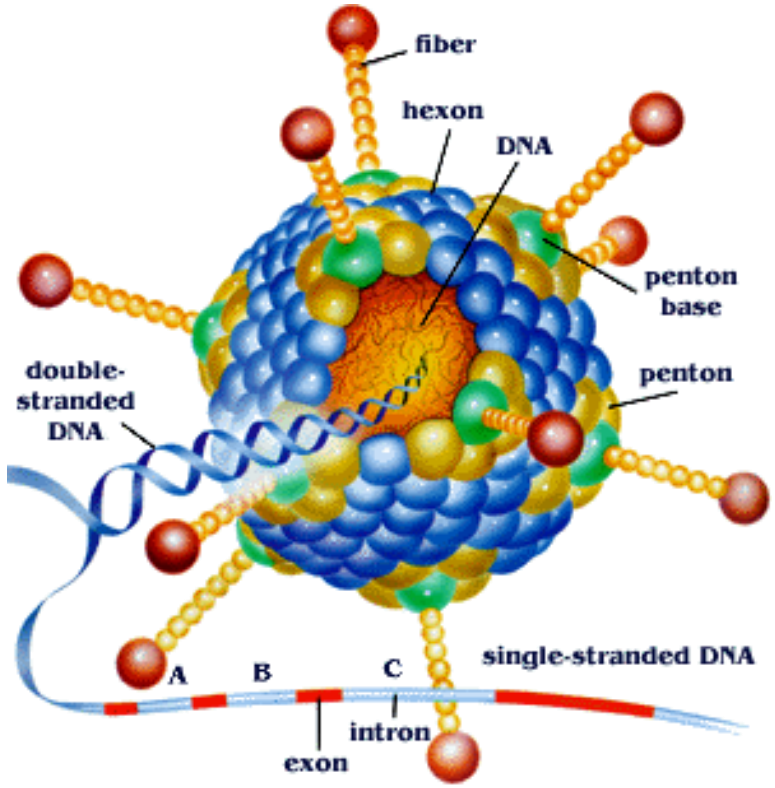
Key Takeaways

- **Broad-spectrum high potency against dsDNA viruses *in vitro***
- **65-fold increased antiviral activity against AdV vs. cidofovir *in vitro***

Potency expressed as EC50 = concentration in µM required to reduce viral replication by 50% in vitro; "—" indicates no data.
*Valganciclovir is rapidly converted to ganciclovir in vivo; ganciclovir is the relevant compound for cell activity studies.
Source: Data are compiled from multiple sources and include multiple materials and methodologies.

*HPV assay based on cytotoxicity against HPV-transformed cell lines, so values reported are cytotoxicity (CC_{50}) rather than EC_{50} values.

BCV Inhibits All Adenovirus Species/Types In Vitro



- Nonenveloped, double-stranded DNA viruses with 7 major species (A-G)
- >100 distinct types defined by serology or hexon gene sequence

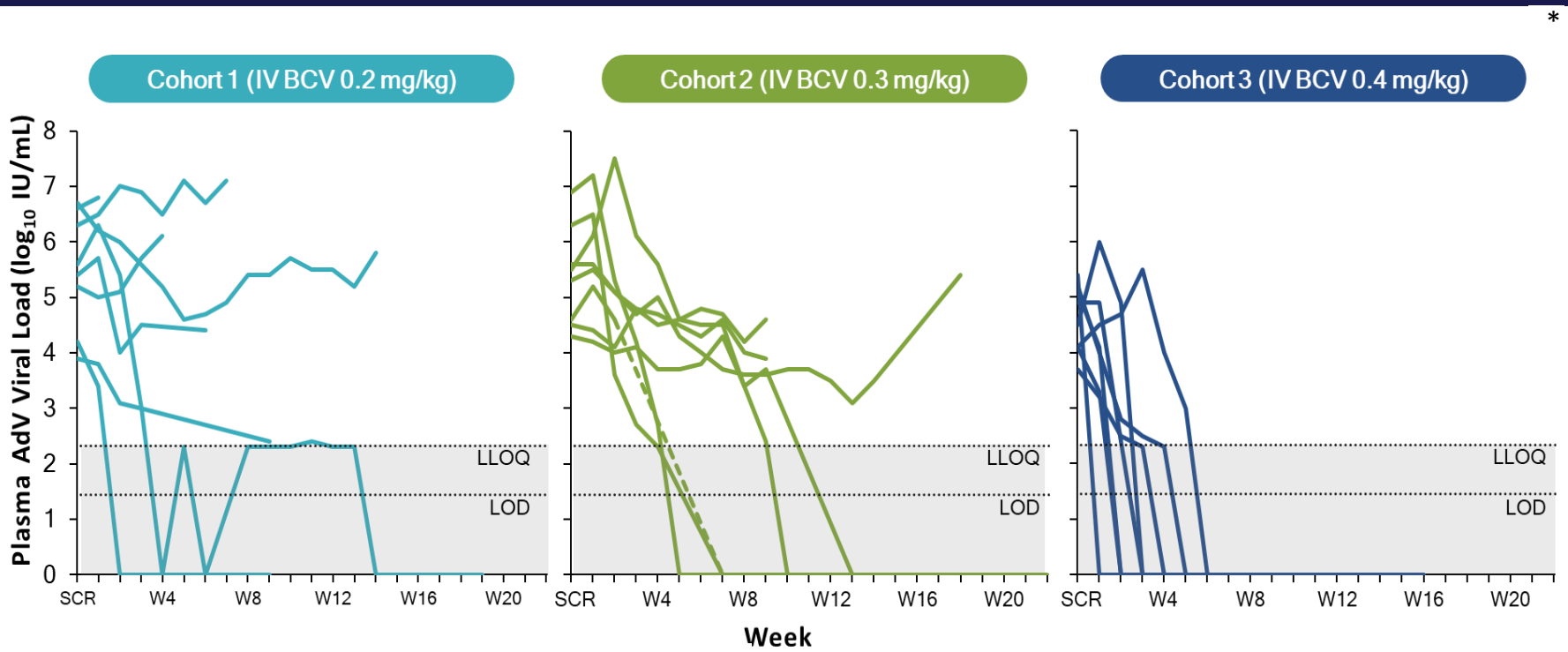
Adenovirus Serotype	BCV EC_{50} (µM)	CDV EC_{50} (µM)
AdV**A**31	0.020	1.4
AdV**B**7	0.020	1.3
AdV**C**1	0.006	N.D.
AdV**D**8	0.027	1.0
AdV**E**4	0.007	N.D.
AdV**F**40	0.006	N.D.

- BCV is active *in vitro* against all AdV species tested and 37 to 70-fold more active than CDV *in vitro*

- Nonenveloped, double-stranded DNA viruses
- 7 major species (A–G)
- >70 distinct types defined by serology or hexon gene sequence

Phase 2 study in AdV infection in Immunocompromised

Completed in 10 USA sites



Antiviral Activity Data

Viral clearance achieved in 100% of patients (0.4 mg/kg BIW BCV)

~90% of patients achieved viral clearance within 4 weeks

Safety Data

Appears safe and well-tolerated in immunocompromised patients with AdV infection post-HCT

Gut and liver safety appear acceptable for this population

BCV-PA02- ENOVIA

A Phase 3, Multicenter, Prospective, Randomized, Open-label Efficacy and Safety Study of Intravenous Brincidofovir versus Intravenous Cidofovir for Treatment of Adenovirus Infection in Pediatric and Adult Subjects After Allogeneic Hematopoietic Cell Transplantation (allo-HCT)

Design Considerations for Phase 3 Trial

Target disease:

- Treatment for adenovirus viremia with or without symptoms or end organ disease

Design considerations:

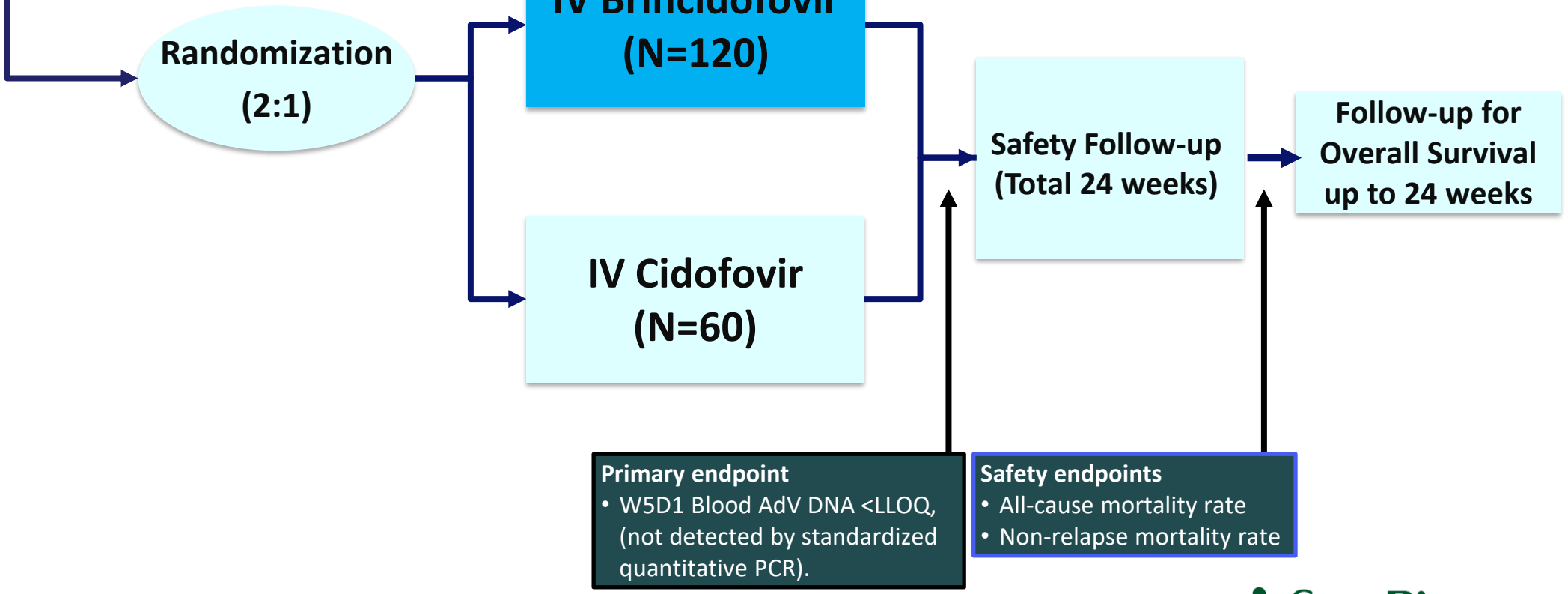
- No therapies approved for treatment of adenovirus infections
  - Thus, no precedented benchmark for regulatory approval of an ADV antiviral drug
- Treatment guidelines recommend antiviral treatment and immune modulation
  - In patients intolerant to CDV, only immune modulation is to be used
- Intravenous Cidofovir (CDV) is standard of care (SOC) for initiation of therapy for Adenovirus viremia
  - Blinding trial with CDV control arm challenging due to need for concurrent fluids and probenecid

Phase 3 Trial Design
Adenovirus Infection after allogeneic-HCT

Patient population, N=180
≥ 2 months with AdV infection after allo-HCT.
Region
Approximately **80** sites in EU/UK/US/Japan

Treatment
（4–12 weeks*）

* **Treatment duration** 4 – 12 weeks, until 2 consecutive undetectable blood AdV DNA readings (<LLOQ)



Endpoints

Primary Endpoint - Proportion of subjects with AdV virological success by Week (W) 5 Day (D) 1

- AdV virological success is defined as 2 AdV consecutive qPCR viral samples determined to be <LLOQ, Not Detected (central lab), collected 7 days apart (1 week).

Key Secondary Endpoint - Proportion of subjects with overall success, as adjudicated by the Endpoint Adjudication Committee (EAC) at Test of Cure (TOC which is 30 days post last dose), defined as:

- Virologic success, AND
- Clinical improvement/resolution of any baseline adenovirus disease, AND
- No new attributable signs or symptoms of adenovirus end-organ disease, AND
- No use of exogenous T-cell therapy, such as viral-specific T-cells (VST) AND
- Alive

Key Inclusion criteria

- In the investigator's judgement, the subject's clinical condition justifies treatment with IV BCV or IV CDV for AdV infection.
- Has adenoviremia, based on any of:
  - AdV viremia DNA ≥10,000 IU/mL, OR
  - Two consecutive and rising AdV viremia DNA results of ≥1,000 IU/mL at screening, OR
  - AdV viremia DNA of ≥1,000 IU/mL, AND
    1. Lymphocyte count <180/mm^3, OR
    2. Received T-cell depletion, cord blood, or haploidentical transplant, OR
    3. prior alemtuzumab, OR
    4. anti-thymocyte globulin (ATG)

Key Exclusion criteria

1. Subject received an allo-HCT with a matched sibling donor
2. Subject received more than 5 mg/kg of CDV for any reason in the 21 days prior to first dose of study drug.
3. Subject is allergic or hypersensitive to IV BCV or IV CDV or any of their components.
4. Subject received anti-AdV-specific cell-based therapy within 3 weeks prior to W1D1 or an anti-AdV vaccine at any time.
5. Subject has participated in any other investigational study within 30 days (or within 5.5 half-lives of the investigational product, whichever is longer) before signing the informed consent form (ICF), is currently participating in another interventional treatment trial with an investigational agent or is using an investigational device at the time of Screening.

Regulatory Status – BCV-PA02

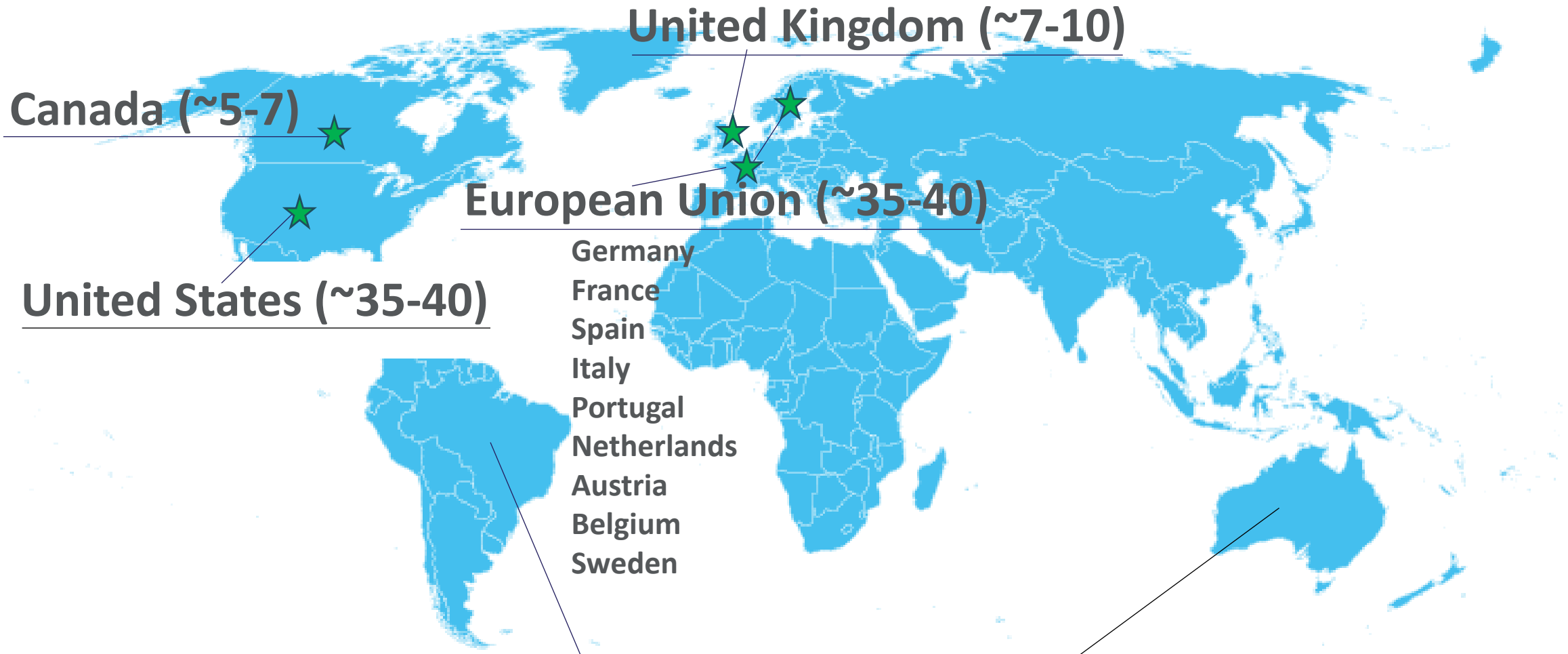
Global Protocol - Approved for Patient Enrollment

- **EMA** — EUROPEAN MEDICINES AGENCY
  SCIENCE MEDICINES HEALTH
- **MHRA** — GOV·UK
  Medicines & Healthcare products Regulatory Agency
- **FDA** — FDA U.S. FOOD & DRUG ADMINISTRATION
- **HC** — Government of Canada / Gouvernement du Canada

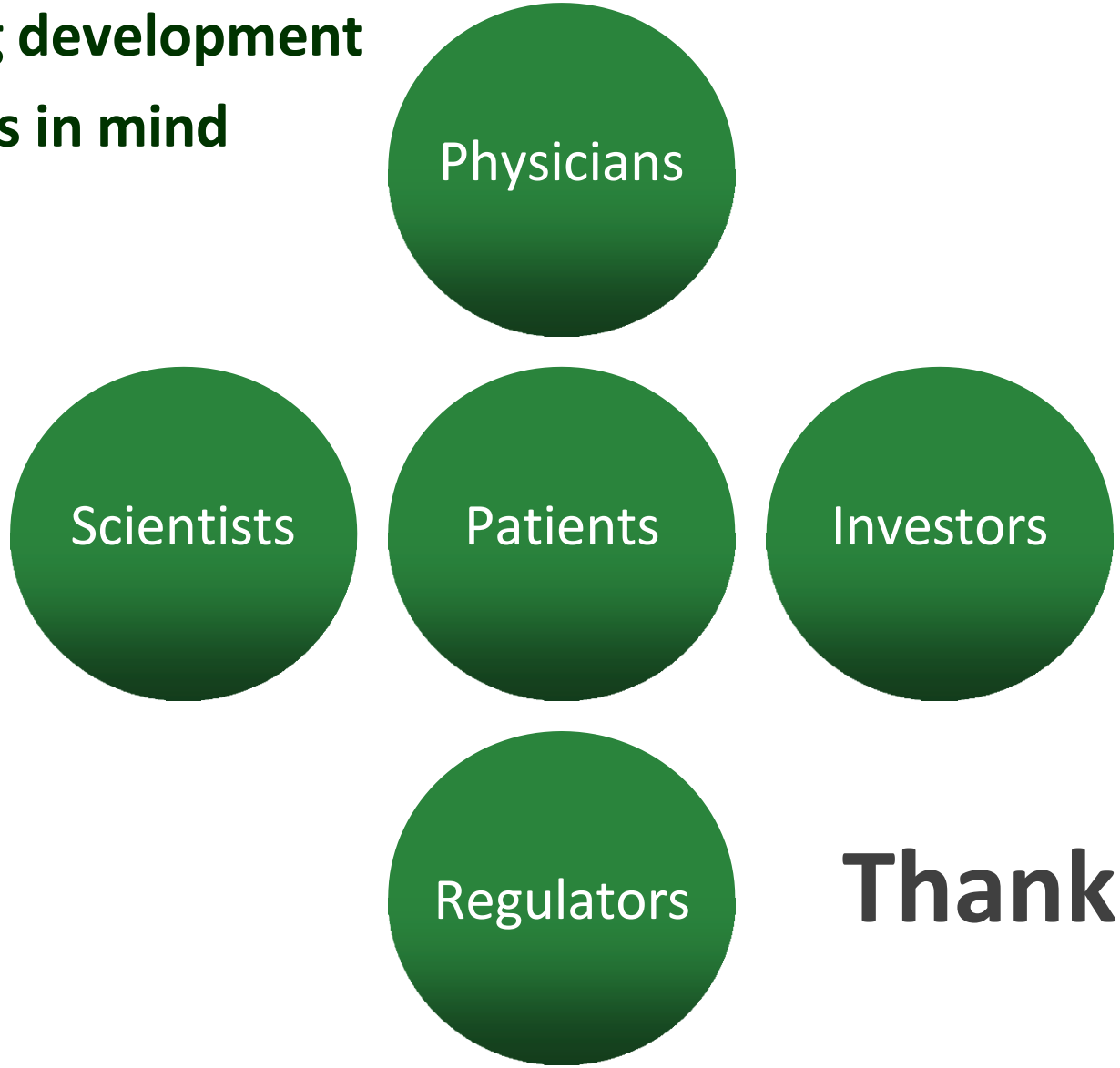
ClinicalTrials.gov

NCT: 07387367

Participating Countries / 85+ Sites



Approaching drug development with patients in mind



Thank You!