Presentation #02819

Obeldesivir Is Efficacious as Oral Postexposure Prophylaxis for Sudan Ebolavirus and Marburg Virus Infections in Nonhuman Primates

Victor C Chu[1], Robert W Cross[2,3], Courtney Woolsey[2,3], Darius Babusis[1], Roy Bannister[1], Meghan S Vermillion[1], Romas Geleziunas[1], Kimberly T Barrett[1], Elaine Bunyan[1], Anh-Quan Nguyen[1], Tomas Cihlar[1], Danielle P Porter[1], Abhishek N Prasad[2,3], Daniel J Deer[2,3], Viktoriya Borisevich[2,3], Krystle N Agans[2,3], Jasmine Martinez[2,3], Mack B Harrison[2,3], Natalie S Dobias[2,3], Karla A Fenton[2,3], John P Bilello[1], Thomas W Geisbert[2,3]

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34th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 27-30 April 2024; Barcelona, Spain

Disclosures

- **Victor C Chu**, **Darius Babusis**, **Roy Bannister**, **Meghan S Vermillion**, **Romas Geleziunas**, **Kimberly T Barrett**, **Elaine Bunyan**, **Anh-Quan Nguyen**, **Tomas Cihlar**, **Danielle P Porter**, and **John P Bilello** are paid employees of Gilead Sciences, Inc., and may own company stock.
- All other authors declare no competing interests.

Filoviruses

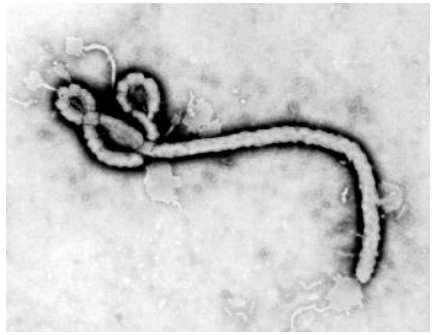
- Negative-sense single-stranded RNA viruses[1]
- *Filoviridae* family[1,2]
  - — Ebolaviruses: Zaire (EBOV), Sudan (SUDV), and others[2]
  - — Marburg virus (MARV)[1,2]

Filovirus disease outbreaks[3,4]

Filovirus	Ebola		Marburg
	Total	Sudan Only	
First report	1976	1976	1967
Outbreaks	35	8	17
Total cases	34,935	942	523
Total deaths	15,385	480	420
CFR (%)	25-90	34-65	23-90

- Outbreaks occurred mainly across sub-Saharan Africa region[3,4]
  - — Six (2 EBOV, 1 SUDV, 3 MARV) outbreaks in 2022 to 2023[3,5]

Ebolavirus micrograph[9]



CFR, case fatality rate; **EBOV**, Zaire ebolavirus; **MARV**, Marburg virus; **PEP**, postexposure prophylaxis; **SUDV**, Sudan ebolavirus; **VHF**, viral haemorrhagic fever disease.

1. Patel PR, Shah SU. Ebola virus. Last updated 17 July 2023. https://ncbi.nlm.nih.gov/books/NBK560579. **2.** Centers for Disease Control and Prevention. Filoviruses *(Filoviridae)*. Accessed 6 October 2022. https://www.cdc.gov/vhf/virus-families/filoviridae.html. **3.** Centers for Disease Control and Prevention. Ebola disease distribution map: cases of Ebola disease in Africa since 1976. Accessed 16 February 2024. https://www.cdc.gov/vhf/ebola/history/distribution-map.html. **4.** Centers for Disease Control and Prevention. Marburg virus disease distribution map. Accessed 16 February 2024. https://www.cdc.gov/vhf/marburg/outbreaks/distribution-map.html. **5.** Centers for Disease Control and Prevention. Marburg virus disease outbreaks. Accessed 16 February 2024. https://www.cdc.gov/vhf/marburg/outbreaks/chronology.html. **6.** Centers for Disease Control and Prevention. Viral hemorrhagic fevers (VHFs). Accessed 16 February 2024. https://www.cdc.gov/vhf/index.html. **7.** Cross RW, et al. *Science*. 2024;383(6688):eadk6176. **8.** US Food and Drug Administration. Ebola preparedness and response updates from the FDA. Accessed 14 March 2024. https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/ebola-preparedness-and-response-updates-fda. **9.** Murphy FA. Ebola virus. Accessed 16 February 2024. https://www.utmb.edu/virusimages/VI/ebola.

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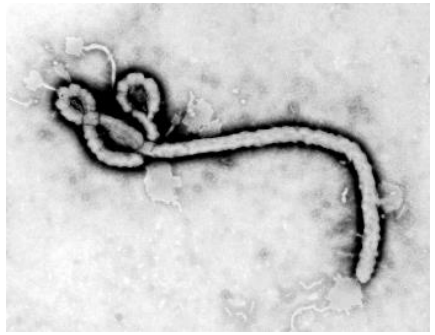

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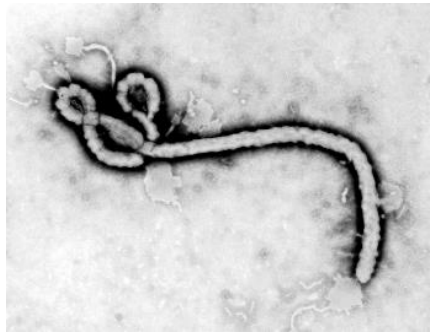
- Infections cause viral haemorrhagic fever disease (VHF): fever, fatigue, hemorrhaging/bleeding/bruising, gastrointestinal symptoms, and death[6]
- Clear unmet medical needs:
  - — No approved antiviral or vaccines for SUDV or MARV[1]
  - — No pan-filovirus countermeasures available[7]
  - — Approved EBOV therapeutics require cold-chain storage and parenteral administration[1,6,8]
  - — No approved oral therapies or postexposure prophylaxis (PEP)

Ebolavirus micrograph[9]



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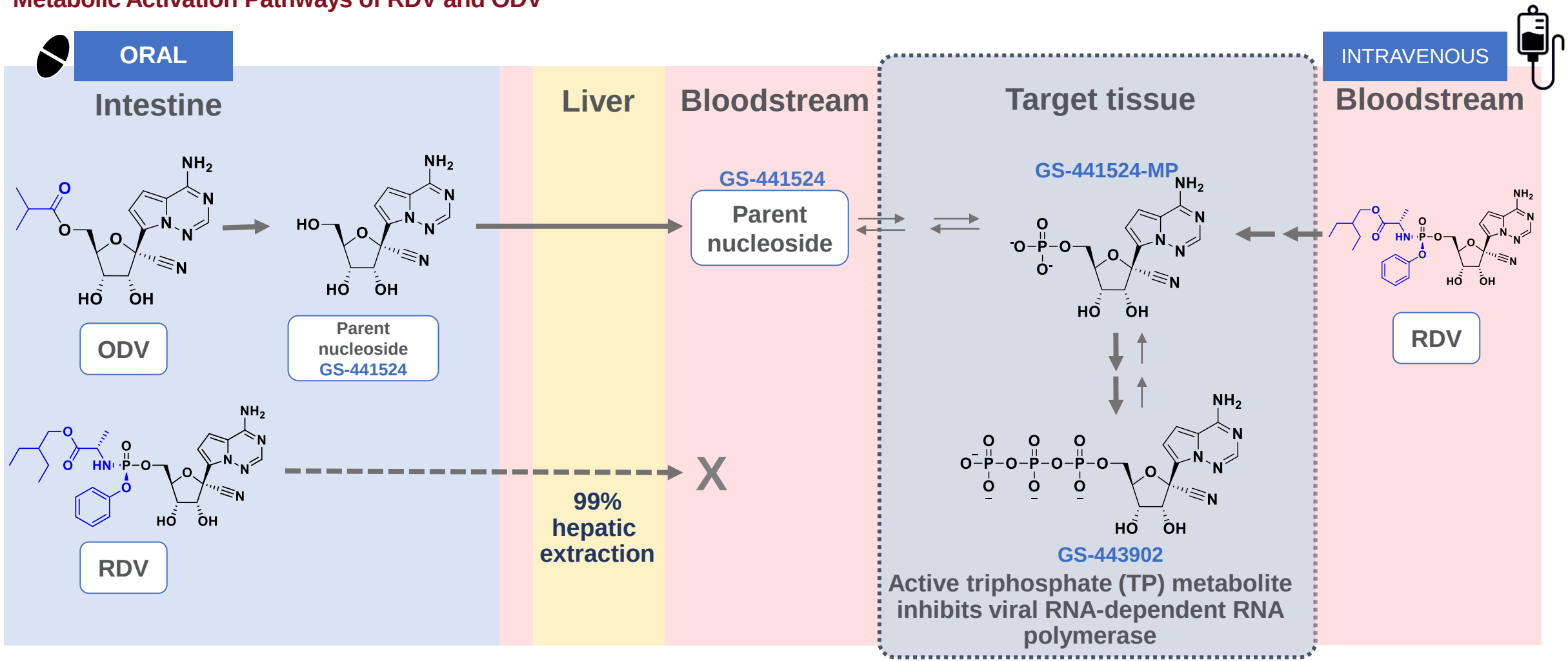
Obeldesivir (ODV): An Oral Prodrug of GS-441524, the Parent Nucleoside of Remdesivir (RDV)

Metabolic Activation Pathways of RDV and ODV



MP, monophosphate; **ODV**, obeldesivir; **RDV**, remdesivir.

ODV Safety and Pharmacokinetics (PK)

Phase 1 Safety and PK in Healthy Volunteers[1]

- ODV was safe and well tolerated following single-dose (100-1600 mg ODV) and multiple-dose (500 mg twice daily [BID] or 900 mg once daily [QD] × 5 days) oral administration
- Oral administration of ODV resulted in high plasma exposures of the major metabolite, GS-441524, with minimal detectable levels of the parent prodrug
- GS-441524 plasma exposures were linear and dose proportional across the dose range of 100 to 900 mg and less than dose proportional across the 900 to 1600 mg doses

PK in Nonhuman Primates (NHPs)

- ODV administered at 100 mg/kg QD in cynomolgus macaques yields similar daily GS-441524 plasma exposures as those observed in recommended human dose at 350 mg BID

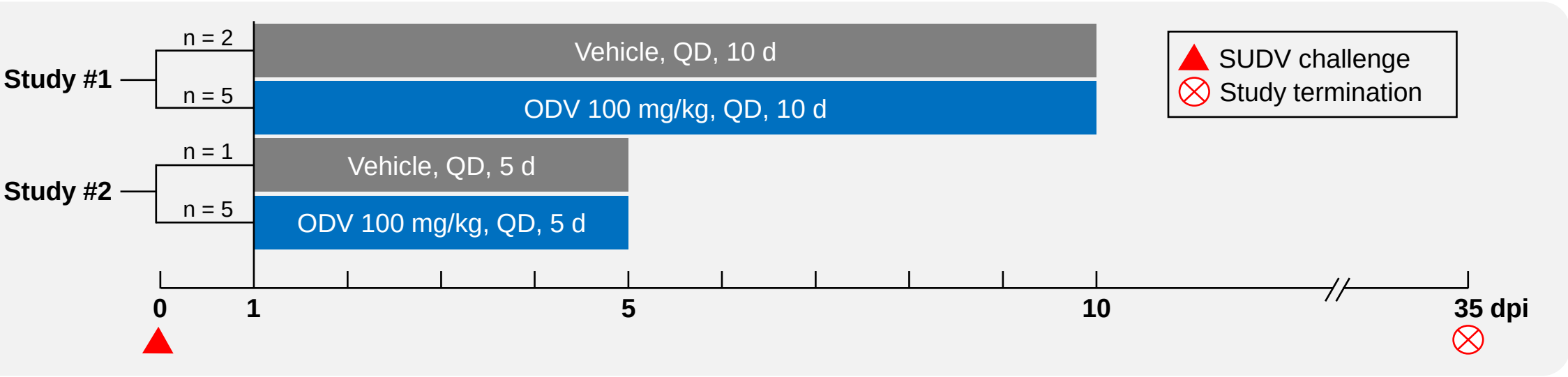
BID, twice daily; **NHP**, nonhuman primate; **ODV**, obeldesivir; **PK**, pharmacokinetic; **QD**, once daily.

1. Anoshchenko O, et al. Presented at: 33rd European Congress of Clinical Microbiology and Infectious Diseases (ECCMID); 15-18 April 2023; Copenhagen, Denmark. Poster P2620.

Evaluation of ODV Efficacy as PEP for SUDV in Cynomolgus Macaques

- **Challenge:** SUDV (Gulu strain), intramuscular (IM) injection with 1000 plaque-forming units (pfu)
- **Treatment:** Oral gavage QD with 100 mg/kg ODV versus vehicle control for 10 or 5 days
- **Treatment initiation:** 1 day post infection (dpi)
- **Primary endpoint:** Survival at 35 dpi

Study Design

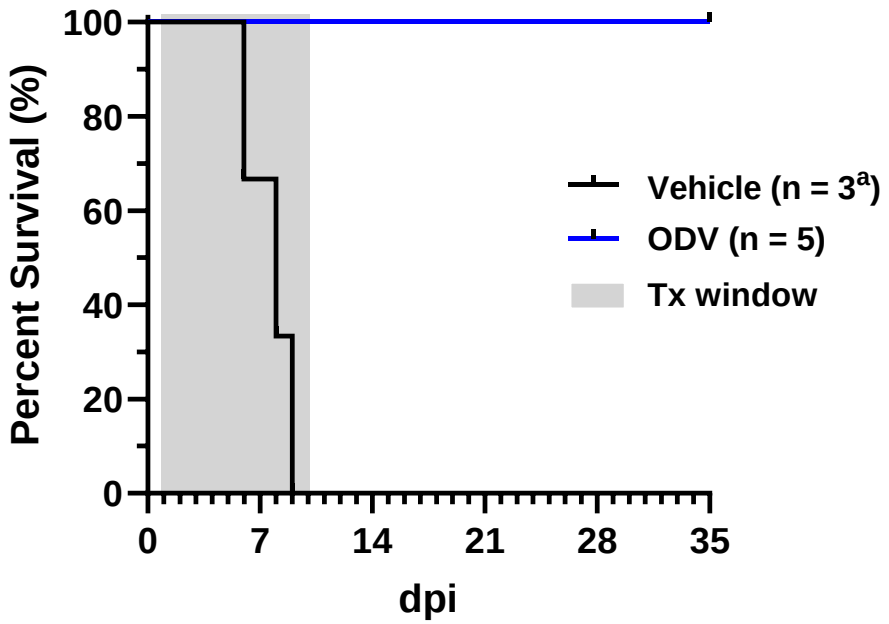


dpi, days post infection; **IM**, intramuscular; **ODV**, obeldesivir; **PEP**, postexposure prophylaxis; **pfu**, plaque-forming unit; **QD**, once daily; **SUDV**, Sudan ebolavirus.

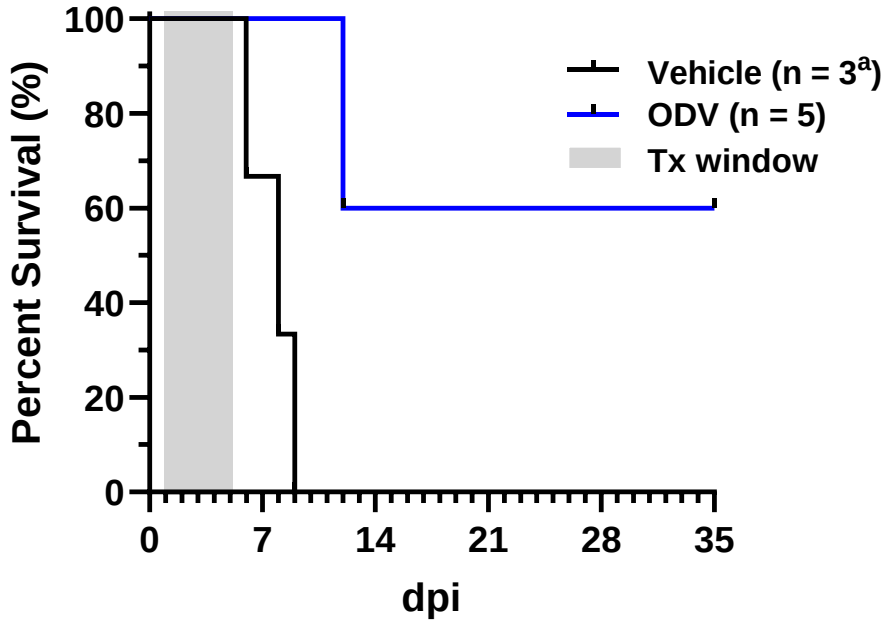
Oral ODV QD for 10 Days Results in 100% NHP Survival From SUDV Infection

Survival Curves of SUDV-challenged NHPs Treated With ODV Versus Vehicle[1]

ODV QD for 10 d



ODV QD for 5 d

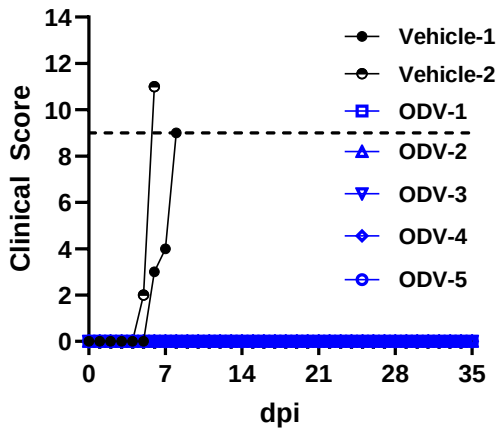


[a]Combined data.
dpi, days post infection; **NHP**, nonhuman primate; **ODV**, obeldesivir; **QD**, once daily; **SUDV**, Sudan ebolavirus; **Tx**, treatment.
1. Cross RW, et al. *Science*. 2024;383(6688):eadk6176.

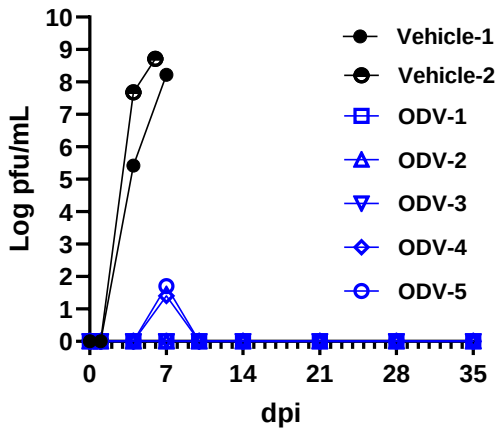
Effect of 10-day ODV Administration on Disease Manifestations and Viraemia

Clinical Scores, Viral Loads, and 6-7 dpi Haematological and Serum Chemistry Parameters in SUDV-challenged NHPs Treated With ODV vs. Vehicle Controls

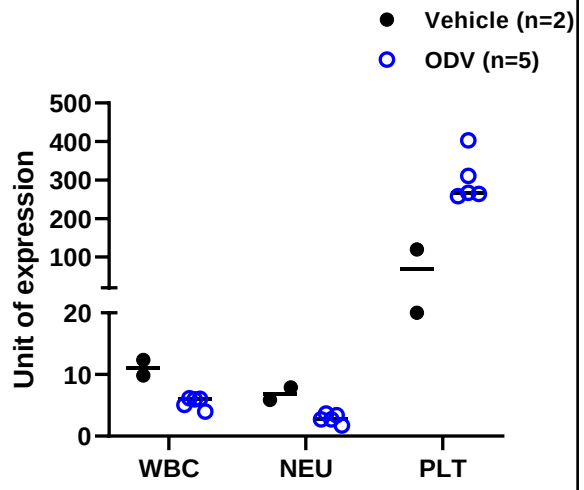
Clinical score[1]



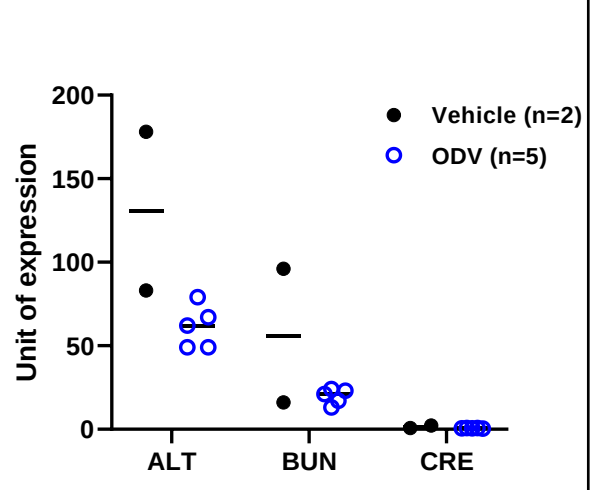
Plasma viraemia[1]



Haematology (at 6-7 dpi)



Clinical chemistry (at 6-7 dpi)

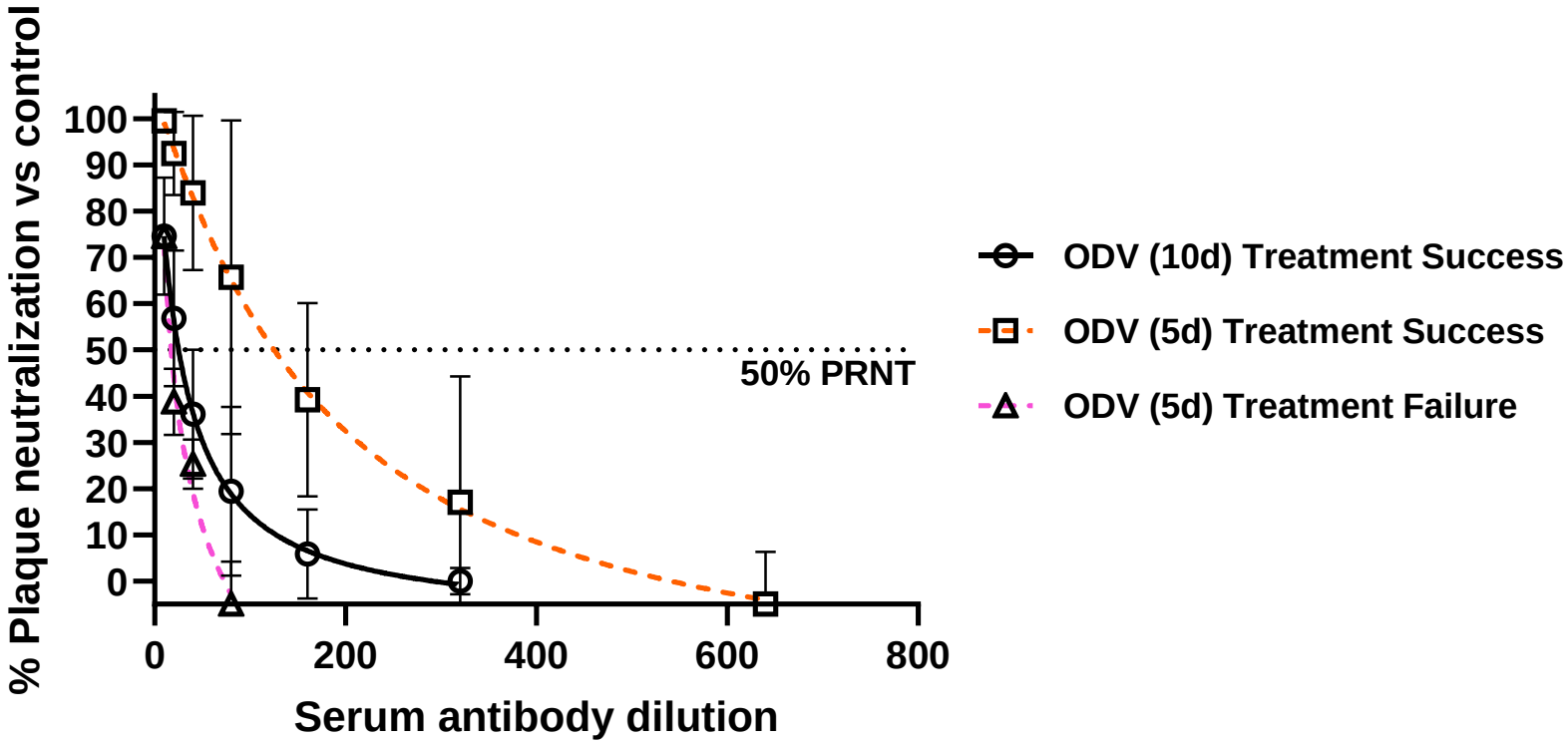


ALT, alanine aminotransferase; **BUN**, blood urea nitrogen; **CRE**, creatinine; **dpi**, days post infection; **NEU**, neutrophil; **NHP**, nonhuman primate; **ODV**, obeldesivir; **pfu**, plaque-forming unit; **PLT**, platelet; **SUDV**, Sudan ebolavirus; **WBC**, white blood cell.

1. Cross RW, et al. *Science*. 2024;383(6688):eadk6176. Reprinted with permission from AAAS.

Strong Neutralising Antibody Titres From Surviving Animals Post ODV Administration[1]

Endpoint 50% Plaque Reduction Neutralisation Test (PRNT50) From SUDV-challenged NHPs



- Highest endpoint neutralising antibody titre was observed from 3 surviving animals treated with 5-day ODV treatment regimen
- Despite successful ODV treatment and profound reduction of viraemia, animals still mount neutralising antibody response

Sera were collected prior to euthanasia due to terminal disease or at the study endpoint (35 dpi). Data shown are the percent reduction in SUDV plaque counts following incubation with the indicated dilution of sera compared to a control plate (no sera). Horizontal dashed line indicates serum dilution to achieve 50% plaque neutralisation from Vero cells infected with SUDV.

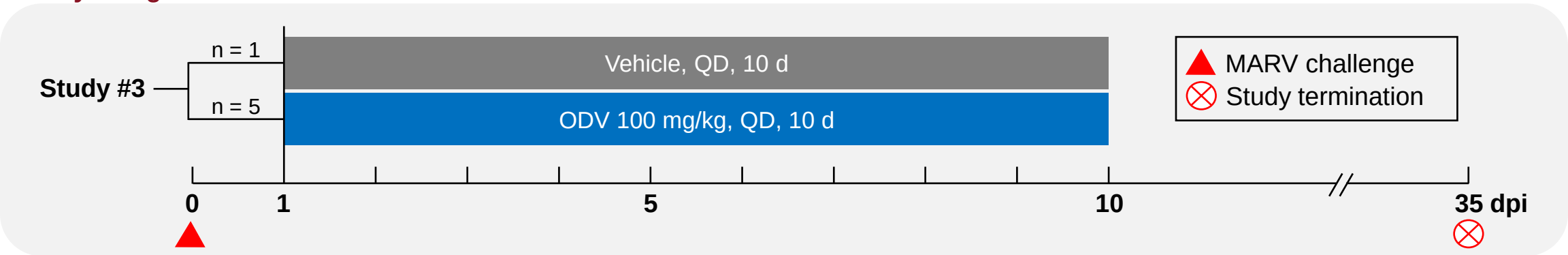
NHP, nonhuman primate; **ODV**, obeldesivir; **PRNT**, plaque reduction neutralisation test; **SUDV**, Sudan ebolavirus.

1. Cross RW, et al. *Science*. 2024;383(6688):eadk6176.

ODV Efficacy Evaluation as PEP for MARV Infection in Cynomolgus Macaques

- **Challenge:** MARV (Angola strain), IM injection with 1000 pfu
- **Treatment:** Oral gavage QD with 100 mg/kg ODV versus vehicle control for 10 days
- **Treatment initiation:** 1 dpi
- **Primary endpoint:** Survival at 35 dpi

Study Design

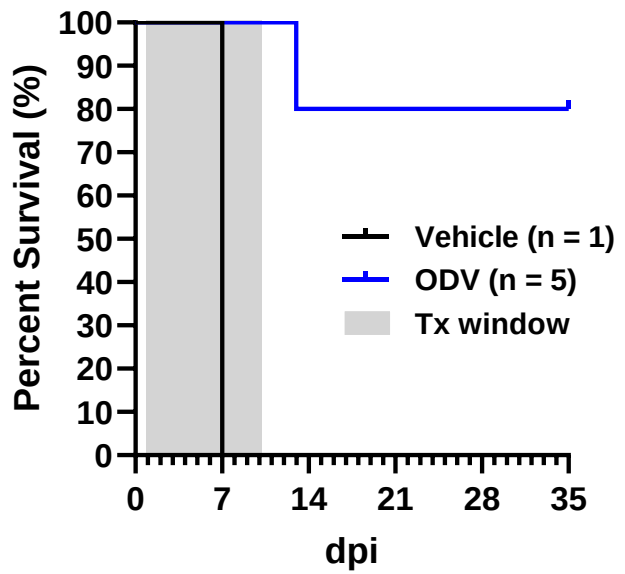


dpi, days post infection; **IM**, intramuscular; **MARV**, Marburg virus; **ODV**, obeldesivir; **PEP**, postexposure prophylaxis; **pfu**, plaque-forming unit; **QD**, once daily.

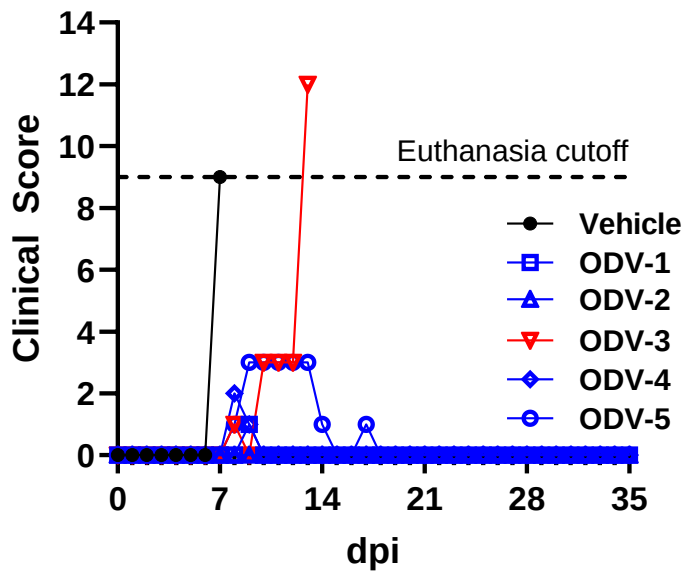
10-day ODV QD Administration Confers 80% NHP Survival From MARV Infection

Survival Analysis, Clinical Scores, and Viral Loads in SUDV-challenged NHPs Treated With ODV Versus Vehicle

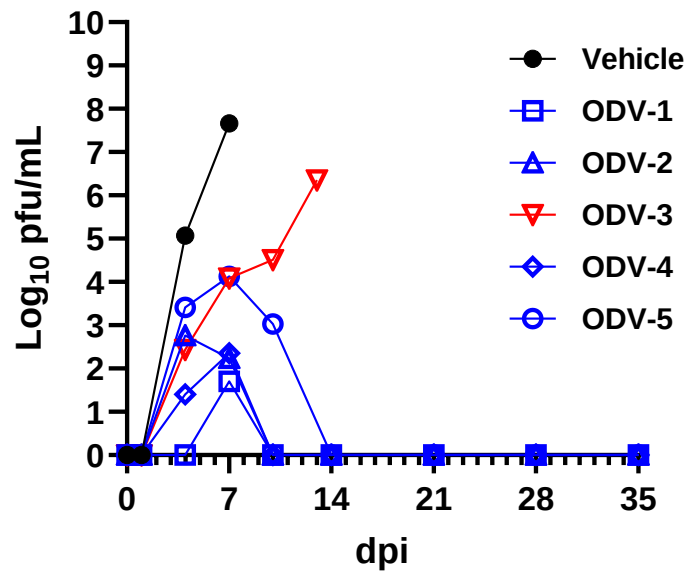
Survival



Clinical score



Plasma viraemia



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Conclusions

- Currently, there are no oral treatments for filovirus infections
- ODV is efficacious as PEP for both SUDV- and MARV-infected cynomolgus macaques at doses providing exposures similar to those provided by doses tested and found safe in humans
  - 10-day course of ODV 100 mg/kg (starting 1 day after inoculation) showed 100% and 80% survival, compared to 0% in vehicle controls in animals infected with SUDV and MARV, respectively
  - 10-day course of ODV suppressed viral replication
    - All surviving animals became aviraemic by 14 dpi and remained aviraemic until the end of the study at 35 dpi
  - ODV delayed or prevented the onset of disease
  - Surviving animals treated with ODV showed high titres of neutralising antibodies
- These findings warrant further evaluation of ODV as an easily administered oral PEP and treatment for filoviruses

dpi, days post infection; **MARV**, Marburg virus; **ODV**, obeldesivir; **PEP**, postexposure prophylaxis; **SUDV**, Sudan ebolavirus.

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