Target Product Profile (TPP) for APP Antiviral Therapeutics

Filovirus disease

**This target product profile is intended to highlight potential product attributes that may be useful for sponsors to consider; it is not intended to be used as regulatory guidance.*

Key considerations

- Clinical presentation – hemorrhagic fever
- Initial symptoms include a non-specific febrile illness with headache, fever, myalgia and general malaise and often overlap with symptoms of other tropical diseases (malaria, typhoid fever, and other bacterial and arboviral infections)
- Geographical distribution - regions of central, eastern, and western Africa (EBOV is more prevalent in western regions, SUDV and MARV are more prevalent in eastern regions)
- Viremia peaks at ~ day 7 after onset of symptoms and decreases as specific symptoms develop, it is not uncommon for viral RNA to be undetectable by RT-PCR in the first 1–3 days after symptom onset.
- African countries at risk for filovirus outbreaks (Guinea, Liberia, Sierra Leone) have established surveillance programs. However, given the short treatment window, availability of PCR diagnostic testing in peripheral areas is still scarce. Vaccines and two monoclonal antibody treatments have been approved for EBOV, but not for MARV or other filoviruses.
- Once virus enters secondary sites of infection (CNS, eyes, testis), it may continue to reside there largely unchecked by the host immune defenses, can re-emerge in the systemic circulation of a convalescent individual several months after initial clearance, and can be involved in a new chain of transmission, including through sexual contact.

TPP attributes

Table 1. TPP attributes

Categories	Minimal Attributes	Optimal Attributes
Indication	• For the treatment of filovirus disease caused by at least one filovirus species • For the treatment of patients with mild to moderate disease	• For the treatment of filovirus disease caused by all species of filoviridae • For the treatment of severe disease
Clinical Outcomes/Efficacy	• Decrease in duration of symptoms [1] • Decrease in progression to severe disease/hospitalization	• Prevent persistent infection • Reduction in potential transmission of virus by survivors [2]
Target Population	• Adult patients with confirmed or suspected filovirus disease	• Pediatric patients • Pregnant women • Global population
Treatment Regimen, Duration, Dosage, and Treatment Window	• No more than three times per day • Treatment window within mild to moderate phase of specific symptomology • Maximum 10-day treatment course for acute disease	• Compatible with combination therapy • Single dose or once per day • Treatment window within late phase of specific symptomology

Categories	Minimal Attributes	Optimal Attributes
Route of Administration	• Any	• Multiple routes of administration based on stage of disease
Safety and Tolerability	• Safe for use in target patient populations • AEs do not prohibit patient compliance	• Acceptable safety profile for use in pediatrics and pregnant women • Safety profile appropriate for PEP and PrEP
Drug Interactions/DDI	• Some DDI tolerated • Dose adjustment permitted with concomitant medications	• No dose adjustment needed with concomitant medications • No DDIs with commonly used products
PK/PD	• $C_{min} > EC_{90}$ • Rapid attainment (< 24 h) of efficacious drug levels • Evidence of appropriate distribution and exposure at primary site(s) of infection	• Evidence of appropriate distribution and exposure at secondary site(s) of infection (i.e., immune privilege sites) [3]
Logistical Supportability and Manufacturing	• Readily available manufacturing and distribution network, appropriate to phase of project	• Capability to rapidly scale-up production at cost/dose that allows global use • Easily deliver product to populations with minimal ancillary supplies
Product Stability and Storage	• Stability ≥ 2 years • Short term cold chain (at 4°C) storage with stability • Long term at -20°C storage with stability	• Stability > 7 years • Ambient storage with stability
Spectrum of Activity	• Targeted antiviral activity • No evidence of emergence of resistance in clinical trials	• Broad spectrum antiviral activity against all filovirus species • Acceptable level of resistance development with understanding of potential cross-resistance
Nonclinical Evidence of Antiviral Activity	• Demonstrated activity against authentic, virulent clinical strains at concentrations achievable in vivo • Demonstration of acceptable selectivity of antiviral activity (CC50/EC50 > 10) • Demonstration of viral load reduction in appropriate animal model with treatment dosing modality [4]	• Demonstration of acceptable selectivity of antiviral activity (CC50/EC50 > 100) • Resolution of clinical endpoints in appropriate animal model with treatment dosing modality

Notes and References

1. Acute illness can last for 2-4 weeks. Halstead, Scott. Nelson Textbook of Pediatrics, Chapter 297, 1766-1771.e1 https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780323529501002972, CDC: Signs & Symptoms of Marburg
2. Data on transmissibility https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4845791/, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3201746/. Data suggests individuals are most infectious and can only spread Ebola to other people after they develop signs and symptoms of Ebola. Symptoms on average start 8-10 days after coming in contact with the Ebola virus. CDC: Transmission of Ebola, CDC: Signs & Symptoms of Ebola. The incubation period for Marburg virus varies from 2-21 days and like Ebola becomes infectious when an individual develops signs and symptoms. WHO: Marburg Virus Disease, CDC: Sign & Symptoms of Marburg
3. A virus, such as EVD, that enters an immune-privileged site, such as the central nervous system (CNS), eye or testis, may continue to reside there largely unchecked by the host immune defenses. For Ebola, this means that it can inflict further damage and even re-emerge in the systemic circulation of a convalescent individual months after initial clearance and can be involved in a new chain of transmission, including through sexual contact. https://www.nature.com/articles/nmicrobiol2017124, https://www.sciencedirect.com/science/article/pii/S0140673616303865?via%3Dihub, https://academic.oup.com/cid/article/63/10/1353/2452977?login=true, https://pubmed.ncbi.nlm.nih.gov/25950255/, https://www.nejm.org/doi/10.1056/NEJMoa1509773
4. NHP, especially rhesus and cynomolgus macaques, are favored for Ebola and Marburg virus disease research due to similarities with humans regarding the pathogenesis, clinical presentation, laboratory findings, and causes of fatality. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5482517/, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5869237/, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3763195/