Target Product Profile (TPP) for APP Antiviral Therapeutics

Nipah virus infection

**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 – Non-specific flu-like symptoms (fever, headaches, myalgia, vomiting and sore throat) that can rapidly (within 5-7 days) progress to acute encephalitis or severe respiratory problems. Encephalitis and seizures occur in severe cases, progressing to coma within 24 to 48 hours.
- Virus can persist in CNS of survivors for months/years following primary infection, leading to late-onset or relapsed encephalitis and/or death
- Geographical distribution – Indian subcontinent, Southeast Asia, Australia, overlaps with JEV, DENV, malaria
- Henipaviruses are spread by Pteropus bats and all areas within their habitat range are considered at risk.
- Bangladesh and Eastern India are the only areas reporting recent outbreaks. Bangladesh has robust hospital-based surveillance system with ELISA IgM testing primarily used for diagnostic in peripheral settings and centralized PCR confirmation. Reliable RDTs need to be developed to decrease diagnosis time and increase window of treatment.
- NiV infection occurs in relatively small, focal outbreaks and low disease incidence poses a major challenge for conducting clinical trials with adequate statistical power. Alternative regulatory pathways may need to be considered (FDA animal rule).
- Hendra virus is localized to Australia and mainly infects horses with occasional horse-to-human transmission; human symptomatic presentation is similar to Nipah virus infection.

TPP attributes

Indication: For the treatment of Nipah virus infection [1], to improve survival and decrease associated morbidity and long-term disability

Table 1. TPP attributes

Categories	Minimal Attributes	Optimal Attributes
Clinical Outcomes/Efficacy	• Decrease in duration of symptoms [2], reduction in viral burden and decrease in progression to severe disease	• Decrease in incidence of latent infection and/or late-onset encephalitic disease [3] • Decrease in incidence of ongoing transmission
Target Population	• Patients with laboratory-confirmed diagnosis [4] or suspected Nipah virus infection [5]	• Pediatric patients • Pregnant women • Global population
Treatment Regimen, Duration, Dosage, and Treatment Window	• No more than three times per day [7] • Maximum 5-day treatment course	• Single dose or once per day • Extended treatment course to clear latent infections
Route of Administration	• Oral or inhaled/intranasal for PEP • Parenteral for treatment, as symptoms prevent oral intake	• Pediatric formulation

Categories	Minimal Attributes	Optimal Attributes
Safety and Tolerability	• Broadly acceptable risk/benefit profile in target population	• Well-established safety profile with AEs that do not require monitoring and do not compromise patient compliance • Acceptable safety profile for use in pediatrics and pregnant women • Appropriate safety profile for PrEP and PEP [8]
Drug Interactions/DDI	• No significant DDI with therapeutics against endemic diseases in targeted geographical locations (including antimalarials) • Dose adjustment permitted with concomitant medications	• No dose adjustment needed with concomitant medications
PK/PD	• $C_{min} > EC_{90}$ • Rapid attainment (< 24 h) of efficacious drug levels • Distribution to CNS and evidence of post-treatment viral clearance [9]	• $C_{min} > EC_{90}$ • Rapid attainment (< 24 h) of efficacious drug levels • Distribution to CNS and evidence of post-treatment viral clearance [9]
Logistical Supportability and Manufacturing	• Readily available manufacturing and distribution network, appropriate to phase of project [10]	• Capability to rapidly scale-up production at cost/dose that allows global use [11] • Easily deliver product to target populations with minimal ancillary supplies
Product Stability and Storage	• Stability $\geq$ 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	• Demonstrated activity against two NiV strains (NiV-M and NiV-B) [6] • No evidence of emergence of resistance in clinical trials	• Broad spectrum antiviral activity against other henipaviruses • Acceptable level of resistance development with understanding of potential cross-resistance
Nonclinical Evidence of Antiviral Activity	• Demonstrated activity demonstrated 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 [12] with treatment dosing modality	• 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. At least phase 3 clinical efficacy trials will need to be conducted in endemic areas. Because NiV infection occurs in relatively small, focal outbreaks, the low disease incidence poses a major challenge for conducting such trials with adequate statistical power. While it is critical to focus on approaches that make ethical and scientifically valid clinical trials feasible whenever possible, alternative regulatory pathways may need to be considered (FDA animal rule). Nipah Research and Development (R&D) Roadmap (who.int)
2. Human infections range from asymptomatic infection to acute respiratory infection, seizures and fatal encephalitis. Infected people initially develop symptoms that include fever, headaches, myalgia, vomiting and sore throat. This can be followed by dizziness, drowsiness, altered consciousness, and neurological signs that indicate acute encephalitis. Some people can also experience atypical pneumonia and severe respiratory problems, including acute respiratory distress. Encephalitis and seizures occur in severe cases, progressing to coma within 24 to 48 hours. Nipah virus infection (who.int), Signs and Symptoms | Nipah Virus (NiV) | CDC.
3. Nipah virus persists in the brains of nonhuman primate survivors - PMC (nih.gov), Rapid Nipah virus entry into the central nervous system of hamsters via the olfactory route - PMC (nih.gov), Relapsed and late-onset Nipah encephalitis - Tan - 2002 - Annals of Neurology - Wiley Online Library
4. Active NiV infection is generally screened by detection of NiV-specific IgM, NiV antigen (Ag), or NiV RNA. For peripheral settings, diagnostic options for screening can include ELISAs, lateral flow assays (LFAs), latex agglutination assays (LATs), and NPT/POC NAT platforms. WHO R&D Blueprint: Priority Diagnostics for Nipah
5. Suspected Nipah infection, defined as: person from an area/locality affected by NiV outbreak who has: acute fever with new onset of altered mental status or seizure and/or acute fever with severe headache and/or acute fever with cough or shortness of breath. NIPAH Virus Guidelines:: National Centre for Disease Control (NCDC)
6. Functionally, the two strains are largely indistinguishable, but recent animal infection studies suggest that the two viruses may be different in certain aspects. Infection studies in the African green monkey indicated that NiV-BD is more pathogenic than NiV-MY, and the window of passive antibody therapy is narrower for NiV-BD. In ferret infection studies, it was shown that NiV-BD infection resulted in increased oral shedding in comparison to NiV-MY and a more rapid onset of productive infection and higher levels of virus replication in the respiratory tract. These differences may explain why more cases in Bangladesh and India have shorter incubation periods, more respiratory symptoms, greater human-to-human transmission, and higher case fatality rates. Nipah Virus Infection - PMC (nih.gov), Pathogenic Differences between Nipah Virus Bangladesh and Malaysia Strains in Primates: Implications for Antibody Therapy - PMC (nih.gov), Transmission Routes for Nipah Virus from Malaysia and Bangladesh - PMC (nih.gov), The Nature of Exposure Drives Transmission of Nipah Viruses from Malaysia and Bangladesh in Ferrets - PMC (nih.gov)
7. 2001 Ribavirin Clinical Trial (results not confirmed in more recent experiments in NHP). Treatment of acute Nipah encephalitis with ribavirin - PubMed (nih.gov)
8. The clearest illustration of person-to-person transmission occurred during the Faridpur outbreak in 2004, where the chain of transmission eventually involved 5 generations and affected 34 people. Person-to-Person Transmission of Nipah Virus in a Bangladeshi Community - PMC (nih.gov)
9. NiV can infect CNS, proposed therapeutic agents should be able to cross BBB to inhibit viral replication and prevent severe neurologic disease. Nipah Research and Development (R&D) Roadmap (who.int)
10. High-level biocontainment requirements may pose an impediment as certain materials must be generated under the highest biosafety level (biosafety level 4 [BSL-4]) conditions, which can increase the cost of drug development. Nipah Research and Development (R&D) Roadmap (who.int)
11. Detailed review covering projected costs of henipavirus medical countermeasures and regulatory considerations Medical countermeasures against henipaviruses: a review and public health perspective - The Lancet Infectious Diseases
12. While ferrets, Syrian hamsters and interferon alpha/beta receptor knockout (IFNAR-KO) mice are well-established animal models for NiV research, the African green monkey (AGM) is regarded as the most relevant animal model for evaluation of candidate therapeutics and vaccines intended for use in humans.

Additionally, studies involving the AGM model may be required for licensure via alternative regulatory pathways (FDA animal rule). Studies in animals often evaluate the usefulness of therapeutics when delivered prior to disease onset or early during the disease course. Patients with NiV infection are often detected later in the clinical course, which creates challenges for predicting how well a therapeutic agent will work in the field. Nipah Research and Development (R&D) Roadmap (who.int)