Target Product Profile (TPP) for APP Antiviral Therapeutics

Hantavirus 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 – acute febrile illness (AFI) to severe manifestations, including hantavirus cardiopulmonary syndrome (HCPS) and hemorrhagic fever with renal syndrome (HFRS). Mortality rates vary from 10-15% for HFRS to 30-50% for HCPS.
- Geographical distribution – HFRS-causing viruses predominate in Europe and Asia (Puumala and Dobrava-Belgrade virus in Europe, Hantaan and Seoul virus in Asia), while HCPS-causing viruses are found in the Americas (Sin Nombre and Andes virus). Endemic areas in South America overlap with other hemorrhagic viruses (i.e., DENV, YFV).
- Rodents are the natural reservoir for hantaviruses and majority of human infections follow rodent-to-human transmission route. Human-to-human transmission is extremely rare. Each virus is transmitted by a specific rodent species leading to localized geographical distribution.
- Hantavirus replication cycle is rather slow, resulting in late viraemia on days 5-10 post-infection
- Diagnostic - laboratory diagnosis of acute hantavirus infections is based on serology as virtually all patients have IgM and usually also IgG antibodies present in serum at the onset of symptoms (2-4 weeks after exposure). The hantavirus infection can also be confirmed by detection of hantavirus genome in blood or serum samples by RT-PCR.
- Early symptoms of HCPS are often clinically indistinguishable from leptospirosis, bacterial pneumonia, and influenza infection. History of rodent exposure should be considered to accurately diagnose hantavirus infection.
- Seoul virus infections are often associated with hepatitis, which is generally not present in other hantavirus infections

TPP attributes

Table 1. TPP attributes

Categories	Minimal Attributes	Optimal Attributes
Indication	• For the treatment of disease caused by hantavirus infection	• For treatment or PrEP/PEP of disease caused by hantavirus infection
Clinical Outcomes/Efficacy	• Decrease in duration of symptoms • Decrease in progression to severe disease/hospitalization	• Prevention of progression to severe disease • Reduction in potential transmission of virus by survivors
Target Population	• Adult patients with confirmed or suspected hantavirus infection [1] • Patients with warning signs for severe disease [2]	• Pediatric patients • Global population • Pregnant women
Treatment Regimen, Duration, Dosage, and Treatment Window	• No more than three times per day • Treatment window w/in mild to moderate phase of acute febrile illness [3]	• Single dose or once per day • Treatment window after appearance of specific symptomology

Categories	Minimal Attributes	Optimal Attributes
Route of Administration	• Oral or inhaled/intranasal for self-administration	• Pediatric formulation • Multiple routes of administration (i.e., parenteral) based on stage of disease (i.e., HCPS or HFRS)
Safety and Tolerability	• Safe for use in broad patient populations • AEs do not prohibit patient compliance	• Acceptable safety profile for use in pediatrics and pregnant women • Safety profile appropriate for PrEP/PEP
Drug Interactions/DDI	• Some DDI tolerated • No DDIs with 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 • Evidence of appropriate distribution and exposure at primary site(s) of infection (i.e., respiratory epithelial cells)	• Evidence of appropriate distribution and exposure at secondary site(s) of infection (e.g., lung, kidneys, heart)
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 $\geq$ 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 all hantaviruses • No evidence of treatment-emergent resistance	• Broad spectrum antiviral activity against related bunyaviruses (e.g., Phenuiviridae, Arenaviridae, etc.) and other clinically related viruses (e.g., Influenza) • 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	• 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. Laboratory diagnosis of acute hantavirus infections is based on serology as virtually all patients have IgM and usually also IgG antibodies present in serum at the onset of symptoms (Avg 2-4 weeks after exposure). The hantavirus infection can also be confirmed by detection of hantavirus genome in blood or serum samples by RT-PCR.
2. Infected pregnant women and their fetuses appear to have more severe symptoms and worse clinical outcomes and mortality increases with age (30+ y.o.) similar to other infected individuals (~60+ y.o.) (Lu et al., 2021; Hjertqvist et al., 2010). Additionally, a genetic predisposition towards both severe HFRS and HCPS disease was shown to be related to SNPs in PRRs and HLA type, but different hantaviruses were associated with different HLA haplotypes and mutations.
3. The hantavirus replication cycle is rather slow, resulting in late viraemia on days 5 to 10 after infection (Terajima et al., 1999), which would suggest virus persistence rather than the acute lytic progression seen in other viral hemorrhagic fevers (Mackow et al., 2009).

- Old world viruses: Amur/Soochong, Dobrava, Hantaan, Puumala, Luxi, Saaremaa, Seoul, and Tula viruses; these are also the viruses that cause HFRS
- New world viruses: Anajatuba, Andes, Araucaria, Araraquara, Bayou, Bermejo, Black Creek Canal, Castelo dos sonhos, Choclo, Itapua, Juquitiba, Laguna Negra, Lechiguanas, Maporal, Monongahela, Neembucu, New York, Oran, Paranoa, Rio Mamore, and Sin Nombre viruses; these are also the viruses that cause HCPS