

Target Product Profile (TPP) for APP Antiviral Therapeutics

Disease caused by Rift Valley Fever Virus (RVFV), Crimean-Congo Hemorrhagic Fever Virus (CCHFV), and Severe Fever with Thrombocytopenia Syndrome Virus (SFTSV)

**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 of RVFV - self-limiting, acute febrile illness (AFI) to severe manifestations including neurological disease, ocular disease or hemorrhagic fever
- Geographical distribution of RVFV – Africa and Arabian Peninsula; transmitted by several mosquito genera including *Aedes*
- Short period of RVFV viremia (3-4 days) coincides with the febrile period of illness; CCHFV and SFTSV period of viremia is longer (10-11 days).
- Clinical presentation of CCHFV – acute febrile illness (AFI) that quickly progresses to severe disease with vascular leak, multi-organ failure, shock and hemorrhage; fatality rates in case reports has ranged from 5-50%. Severely ill patients often develop a striking pattern of large ecchymoses (bruising), not seen in other types of viral hemorrhagic fever.
- Geographical distribution of CCHFV – eastern and southern Europe, sub-Saharan Africa, Middle East and central Asia; transmitted by ticks
- Clinical presentation of SFTSV – abrupt onset of high fever accompanied by thrombocytopenia and gastrointestinal symptoms that can progress to hemorrhage and liver damage
- Geographical distribution of SFTSV – South-East Asia; transmitted by ticks
- Patients with close contact with infected animals, including animal herders, livestock workers, veterinarians, and slaughterhouse workers, are at highest risk of RVFV/CCHFV infection and associated severe disease. Both farming and outdoor recreational activities are risk factors for infection with CCHFV and SFTSV which are tick-borne diseases. Healthcare workers are also at risk as person-to-person transmission (e.g., bodily fluids) is possible for all three viruses.
- Diagnosis - RT-PCR and ELISA are the best diagnostic option where available, virus isolation produces the most definitive diagnosis but requires BSL-3 and BSL-4 facilities. The insufficient laboratory capacity in endemic areas is a significant barrier for early diagnosis. Outbreaks in domestic animals that lead to mass animal death/abortions usually precede human outbreaks and can help with diagnosis.

TPP attributes

Table 1. TPP attributes

Categories	Minimal Attributes	Optimal Attributes
Indication	<ul style="list-style-type: none"> • For the treatment of disease caused by RVFV, CCHFV or SFTSV 	<ul style="list-style-type: none"> • For the treatment of disease caused by RFFV, CCHFV and SFTSV • For PrEP/PEP
Clinical Outcomes/Efficacy	<ul style="list-style-type: none"> • Decrease in duration of symptoms • Decrease in progression to severe disease/hospitalization 	<ul style="list-style-type: none"> • Prevention of progression to severe disease
Target Population	<ul style="list-style-type: none"> • Adult patients with confirmed or suspected viral infection and those at risk of severe disease [1][2] 	<ul style="list-style-type: none"> • Pediatric patients • Pregnant women • Global population

Categories	Minimal Attributes	Optimal Attributes
Treatment Regimen, Duration, Dosage, and Treatment Window	<ul style="list-style-type: none"> No more than three times per day Treatment window w/in mild to moderate phase of specific symptomology Maximum 4-day (RVF) or 10-day (CCHF, SFTSV) treatment course [3] 	<ul style="list-style-type: none"> Single dose or once per day Treatment window w/in early phase of specific symptomology
Route of Administration	<ul style="list-style-type: none"> Oral for self-administration 	<ul style="list-style-type: none"> Pediatric formulation Multiple routes of administration (incl parenteral) based on stage of disease
Safety and Tolerability	<ul style="list-style-type: none"> Safe for use in broad patient populations 	<ul style="list-style-type: none"> AEs do not prohibit patient compliance Acceptable safety profile for use in pediatrics and pregnant women Safety profile appropriate for PrEP
Drug Interactions/DDI	<ul style="list-style-type: none"> Some DDI tolerated No DDIs with antimalarials Dose adjustment permitted with concomitant medications 	<ul style="list-style-type: none"> No dose adjustment needed with concomitant medications No DDIs with HIV antiretrovirals
PK/PD	<ul style="list-style-type: none"> $C_{min} > EC_{90}$ Rapid attainment (< 24 h) of efficacious drug levels Evidence of appropriate distribution and exposure at primary site(s) of infection 	<ul style="list-style-type: none"> Evidence of appropriate distribution and exposure at secondary site(s) of infection (i.e., liver, spleen, lymph nodes, adrenal glands, lungs, and kidneys; brain/CNS with neurological disease)
Logistical Supportability and Manufacturing	<ul style="list-style-type: none"> Readily available manufacturing and distribution network, appropriate to phase of project 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Stability \geq 3 years [4] Short term cold chain (at 4°C) storage with stability Long term at -20°C storage with stability 	<ul style="list-style-type: none"> Stability > 10 years Ambient storage with stability
Spectrum of Activity	<ul style="list-style-type: none"> Demonstrated activity against individual target viruses (RVFV, CCHFV, SFTSV) No evidence of treatment-emergent resistance 	<ul style="list-style-type: none"> Broad spectrum antiviral activity against CCHFV, SFTSV, related Phleboviruses/Phenuiviruses and other clinically related viruses (e.g., YFV, DENV, viruses that cause hepatitis) Acceptable level of resistance development with understanding of potential cross-resistance
Nonclinical Evidence of Antiviral Activity	<ul style="list-style-type: none"> Demonstrated activity against authentic, virulent clinical strains at concentrations achievable in vivo Demonstration of acceptable selectivity of antiviral activity ($CC_{50}/EC_{50} > 10$) Demonstration of viral load reduction in appropriate animal model with treatment dosing modality 	<ul style="list-style-type: none"> Demonstration of acceptable selectivity of antiviral activity ($CC_{50}/EC_{50} > 100$) Resolution of clinical endpoints in appropriate animal model with treatment dosing modality

Notes and References

1. RVF infections can only be diagnosed definitively by RT-PCR, IgM/IgG ELISA or virus isolation from serum ([Mansfield et al., 2015](#)). ELISAs can be employed to confirm the presence of either specific IgM antibodies, which appear transiently from 4 days after infection or specific IgG antibodies, which appear from 8 days after infection and may persist for several years ([Paweska et al., 2005](#)). CCHF infections include recovery of infectious virus as the “gold standard” for diagnosis, but it requires Biosafety Level 4 containment, which is not available in any CCHF-endemic country except for South Africa. RT-PCR is also viable and can be considered the standard diagnostic method.
2. People at most risk of severe RVF disease are those in close contact with animals (i.e., herding occupation), caring for animals during birthing or touching aborted fetuses, and consuming or handling products from sick animals ([Anyangu et al., 2010](#)). Coinfection with other pathogens may increase susceptibility. For example, HIV-1 coinfection was found to increase the likelihood of severe disease and death due to RVF, with case fatality estimated at 75 % ([Mohamed et al., 2010](#)). There is also a role for host genetic factors on susceptibility, identifying an association between single nucleotide polymorphisms in genes involved in immunological pathways and severe disease ([Hise et al., 2015](#)). Those at risk of severe SFSTV are those with pre-existing conditions including neuropsychiatric disorders, bleeding disorders, hyponatremia or advanced age ([Liu et al., 2014](#)).
3. RVF exhibits a short duration of viraemia (3–4 days) which coincides with the febrile period of illness ([Ikegami and Makino, 2011](#); [Sabin et al., 1947](#); [Smithburn et al., 1949](#); [Mansfield et al., 2015](#)). Alternatively, CCHF patients are typically viremic during the first 7–10 days of illness ([Bente et al., 2013](#)). Virus-specific IgM becomes detectable by the end of the first week, with IgG appearing shortly afterwards. A high viremia coincides with SFTSV’s acute febrile illness for approximately 5-11 days and can be used for diagnosis ([Liu et al., 2014](#)).
4. Outbreaks of RVFV are associated with unusually heavy rainfall, especially cyclical El Niño-Southern Oscillation (ENSO) weather patterns. Epizootic outbreaks persist for 1-3 years and occur at 2-4-year intervals in moderate-to-heavy rainfall areas or 5-15-year intervals in low rainfall areas (i.e., East and South Africa) ([Davies et al., 1985](#)).
5. The failure of CCHFV to cause illness in common laboratory animals has seriously impaired efforts to develop new antiviral drugs and vaccines against the disease.
6. Other references:
 - [Rift valley fever surveillance in the lower Senegal river basin: update 10 years after the epidemic - PubMed \(nih.gov\)](#)
 - [First isolation of the Rift Valley fever virus from Culex poicilipes \(Diptera: Culicidae\) in nature. in: The American Journal of Tropical Medicine and Hygiene Volume 62 Issue 6 \(2000\) \(ajtmh.org\)](#)
 - [Factors Associated with Severe Human Rift Valley Fever in Sangailu, Garissa County, Kenya - PMC \(nih.gov\)](#)
 - [Risk Factors for Severe Rift Valley Fever Infection in Kenya, 2007 - PMC \(nih.gov\)](#)
 - [Rift Valley Fever Epidemic in Saudi Arabia: Epidemiological, Clinical, and Laboratory Characteristics | Clinical Infectious Diseases | Oxford Academic \(oup.com\)](#)
 - [Rift Valley fever knowledge, mitigation strategies and communication preferences among male and female livestock farmers in Eastern Province, Rwanda | PLOS Neglected Tropical Diseases](#)
 - [Crimean-Congo hemorrhagic fever: History, epidemiology, pathogenesis, clinical syndrome and genetic diversity - ScienceDirect](#)
 - [Clinical and laboratory characteristics of severe fever with thrombocytopenia syndrome in Chinese patients - ScienceDirect](#)
 - [Clinical and Epidemiological Study on Severe Fever with Thrombocytopenia Syndrome in Yiyuan County, Shandong Province, China in: The American Journal of Tropical Medicine and Hygiene Volume 88 Issue 3 \(2013\) \(ajtmh.org\)](#)
 - [Severe Fever with Thrombocytopenia Syndrome Virus, Shandong Province, China - PMC \(nih.gov\)](#)
 - [Preparation and Evaluation of Recombinant Severe Fever with Thrombocytopenia Syndrome Virus Nucleocapsid Protein for Detection of Total Antibodies in Human and Animal Sera by Double-Antigen Sandwich Enzyme-Linked Immunosorbent Assay - PMC \(nih.gov\)](#)
 - [A Cross-Sectional Survey of Severe Fever with Thrombocytopenia Syndrome Virus Infection of Domestic Animals in Laizhou City, Shandong Province, China \(jst.go.jp\)](#)
 - [Seroprevalence of severe fever with thrombocytopenia syndrome virus in China: A systematic review and meta-analysis - PMC \(nih.gov\)](#)