

Target Product Profile (TPP) Template for APP Antiviral Therapeutics

Arenavirus 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) that can progress to hemorrhagic fever and/or neurological complications
- Geographical distribution – Old World arenaviruses are endemic in Africa (Lassa virus, Lujo virus); New World arenaviruses circulate in South America (Machupo virus, Guanarito virus, Junin virus, Chapare virus, Sabia virus) and are localized to specific areas/countries
- Lymphocytic Choriomeningitis Virus (LCMV) is an exception, both in clinical presentation and geographical distribution; it causes severe neurological disease (meningitis and encephalitis) and is seen worldwide (classified as Old-World arenavirus)
- Arenaviruses are transmitted by rodents and majority of human infections follow rodent-to-human transmission route with some human-to-human transmission that are d/t contact with contaminated body fluids and surfaces. Each virus is transmitted by a specific rodent species leading to localized geographical distribution.
- Viremia peaks ~ 15 days post-infection and remains high as secondary symptoms develop, with death mostly resulting from vascular leakage, organ failure and septic shock. Fatality rates are considerably higher in NW arenavirus outbreaks.
- OW and NW viruses differ in cell entry mechanisms and host response (i.e., OW viral infection leads to decrease in pro-inflammatory cytokines and pro-inflammatory response correlates with positive disease outcomes; while NW viral infection leads to increase in pro-inflammatory cytokines and pro-inflammatory response correlates with negative disease outcomes)
- Diagnostic – IgM serologic testing (ELISA) is the most common way to diagnose arenavirus infections. Depending on the region and clinical epidemiological picture of the patient, differential diagnoses might include other arenaviruses.
- Ribavirin has shown antiviral effect when used in early stages of Lassa and Junin virus infections. Live-attenuated vaccine against Junin virus has been approved for use in Argentina.

TPP attributes

Indication: For the treatment of arenavirus infection

Table 1. TPP attributes

Categories	Minimal Attributes	Optimal Attributes
Clinical Outcomes/Efficacy	<ul style="list-style-type: none"> • Decrease in duration of symptoms [1] [2] • Decrease in progression to severe symptoms/hospitalization [1] 	<ul style="list-style-type: none"> • Decrease in long-term symptoms and/or neurological sequelae [3] • Reduction in potential transmission of virus by survivors [4]
Target Population	<ul style="list-style-type: none"> • Adult patients with confirmed or suspected viral infection [5] 	<ul style="list-style-type: none"> • Pregnant women [1] [7] • Pediatric patients • Global population • Immunocompromised and transplant recipients

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 acute phase of febrile illness [6] [7] 	<ul style="list-style-type: none"> Single dose or once per day Treatment window after early signs of hemorrhagic and/or neurological symptomology [7] [8]
Route of Administration	<ul style="list-style-type: none"> Oral or inhaled/intranasal for self-administration 	<ul style="list-style-type: none"> Parenteral for treatment, as symptoms may prevent oral intake Pediatric formulation No adjustment for renal/hepatic impairment [9]
Safety and Tolerability	<ul style="list-style-type: none"> Safe for use in broad patient populations Acceptable safety profile for use in pregnant women [1] [7] and pediatrics 	<ul style="list-style-type: none"> AEs do not prohibit patient compliance
Drug Interactions/DDI	<ul style="list-style-type: none"> Some DDI tolerated Dose adjustment permitted with concomitant medications 	<ul style="list-style-type: none"> No dose adjustment needed with other medications
PK/PD	<ul style="list-style-type: none"> C_{min} > EC₉₀ Rapid attainment (< 24 h) of efficacious drug levels Evidence for appropriate distribution and exposure at relevant sites of infection (i.e., lymphoid system, liver, kidneys, lungs, adrenal glands, and heart) [9] 	<ul style="list-style-type: none"> Ability to rapidly cross BBB to achieve efficacious exposure in CNS
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 ≥ 2 years 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 > 5 years Ambient storage with stability
Spectrum of Activity	<ul style="list-style-type: none"> Demonstrated activity against Lassa, Junin, and Machupo virus [10] No evidence of treatment-emergent resistance 	<ul style="list-style-type: none"> Broad spectrum antiviral activity against other arenaviruses Acceptable level of resistance development with understanding of potential cross-resistance

Categories	Minimal Attributes	Optimal Attributes
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 (CC50/EC50 > 10) • Demonstration of viral load reduction in appropriate animal model with treatment dosing modality [11] 	<ul style="list-style-type: none"> • Demonstration of acceptable selectivity of antiviral activity (CC50/EC50 > 100) • Resolution of clinical endpoints in appropriate animal model with treatment dosing modality [11]

Notes and References

1. Arenaviruses cause diseases with two types of clinical presentations: neurological and hemorrhagic fever (however, asymptomatic arenavirus infection may occur):
 - Neurological: aseptic meningitis, encephalitis, or meningoencephalitis, caused by the LCM virus. Overall case fatality is <1%. Fetal infections can result in congenital abnormalities or death. Immunosuppressed patients, such as organ transplant recipients, can develop fatal hemorrhagic fever-like disease. Transmission of LCMV and an LCMV-like arenaviruses via organ transplantation has been documented.
 - Viral hemorrhagic fever: Lassa fever usually presents as a non-specific illness: with fever, headache, dizziness, asthenia, sore throat, pharyngitis, cough, retrosternal and abdominal pain, and vomiting. In severe forms, facial oedema is associated with hemorrhagic conjunctivitis, moderate bleedings (nose, gums, vagina...), and exanthema. Neurological signs may develop and progress to confusion, convulsion, coma, and death. Severe prognosis is associated with a high viraemia, a serum AST level >150 IU/L (aspartate aminotransferase), bleedings, encephalitis, and edema. There is a very high risk of fetal mortality in pregnant women during the third trimester of pregnancy. Case fatality rates range from 5 to 20% for hospitalized cases. Case fatality rates may be higher, up to 30% for Guanarito virus, although the available epidemiological data is very limited. See ECDC website for details.
2. Old World Arenaviruses: Pharyngitis, vomiting and diarrhea more common in Guanarito virus infections. Erythema, petechiae, facial edema and shock more common in Junin or Machupo virus infections. [Boston University New World Arenaviruses Page](#)
3. Survivors of Lassa Fever often recover without sequelae. However, long-term unilateral or bilateral sensorineural deafness can affect a significant (≈13%–30%) number of survivors. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7567487/>
4. People become infected by breathing in the virus after rodent urine, droppings, or nesting materials are stirred up, such as during cleaning. People can also get infected by touching their face after touching the virus, through the bites or scratches of infected rodents, and by eating contaminated food. In some instances, arenaviruses can spread to people when consuming infected rodents as a food source. Person-to-person transmission can occur with certain arenaviruses, such as Chapare, Lassa, Machupo, and Lujo viruses. This type of transmission usually occurs when there is direct contact with the blood or other body fluids of infected individuals. Contact with contaminated objects, such as medical equipment, is also associated with spreading these viruses. Use of protective clothing and disinfection procedures while caring for a sick person can help prevent further spread of disease. [CDC Arenavirus Page](#)
5. Due to the high risk of these pathogenic arenaviruses to the public health and national security, LASV, JUNV, and MACV are classified as category A priority pathogens in the United States. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5625494/>

6. The results described in the present study establish ribavirin as a mutagenic agent for LCMV (arenavirus, lymphocytic choriomeningitis virus) replicating in cell culture. It remains to be determined whether this mutagenic activity of ribavirin can also be observed in LCMV-infected mice and whether these findings could be extended to other arenaviruses. Ribavirin has been shown to be mutagenic for several RNA viruses. However, for some other RNA viruses tested, ribavirin did not exhibit noticeable mutagenic activity. Ribavirin is currently the only drug therapy recommended to treat arenavirus infections, but its mechanism of action has not been entirely elucidated. There is, however, evidence indicating that ribavirin likely targets different steps of the arenavirus life cycle. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3126590/>
7. Ribavirin treatment has been shown to be efficient for Lassa fever. It is more effective when started within the first 6 days of illness. It is presently contraindicated in pregnancy, although may be warranted if mother's life is at risk. [ECDC Arenavirus Information](#)
8. Treatment is aggressive supportive care and is directed at maintaining renal function and electrolyte balance, addressing coagulopathy and combating hemorrhage and shock. Ribavirin has been used to treat infection with both viruses with benefit. In Lassa, most benefit with ribavirin is in first 7 days of illness. [Boston University Old World Arenaviruses Page](#)
9. Antigen-presenting cells (APCs), DCs and macrophages, are prominent targets in the initial stages of infection, and facilitate virus access to the lymphoid system and subsequent systematic spread to other organs and tissues including liver, kidneys, lungs, adrenal glands, and heart. LASV has also been recovered from placenta, mammary glands, and aborted fetal tissues, and in cases of AHF, virion-like particles were detected in the central nervous system (CNS), ovaries, and testes. LCMV load can reach high levels in meninges, choroid plexus, and ventricular ependymal linings, where the inflammatory response produces the characteristic LCM pathology. LCMV exhibits a strong tropism for the fetal brain, where LCMV congenital infection produces its most common and severe pathologic effects, including microencephaly, periventricular calcifications, hydrocephalus, cerebellar hypoplasia, focal cerebral destruction, and gyral dysplasia. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7567487/>
10. Arenavirus distribution, host species and disease incidence in humans <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4093776/>
11. There are some arenaviruses – both New and Old World — that have been identified in host animals, but no human infection has been reported yet.
 - Various strains of guinea pigs, including Strain 13 guinea pigs (inbred) and outbred Hartley guinea pigs, have been used as a model to study Venezuelan hemorrhagic fever and Lassa fever.
 - The Syrian golden hamster is commonly used to study hemorrhagic fever in the PICV surrogate system, in addition to testing product efficacy.
 - The mouse model is not as common a model to study arenaviral hemorrhagic fever when compared to the hamster and guinea pig models. However, some investigators have developed murine models to study hemorrhagic fever pathogenesis and treatment efficacy.
 - Non-human primates have also been used to study arenavirus hemorrhagic fever. The rhesus monkey is an established model to study LASV pathogenesis.
 - The mouse model has historically been the dominant animal model to study LCMV, which is due to the ease of manipulating various aspects of the mouse including age and genetics and the ability to study various aspects of the disease including viral persistence, autoimmunity, viral clearance, and viral pathogenesis. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3499831/>