Target Product Profile (TPP) for APP Antiviral Therapeutics

Encephalitic disease caused by Venezuelan equine encephalitis virus, Western equine encephalitis virus, and Eastern equine encephalitis 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 – acute febrile illness (AFI) that can progress to neurological disease (meningitis and encephalitis)
- Encephalitis from EEEV infection has substantial mortality (~30%) and survivors develop neurological sequelae in 75% of cases. WEEV has similar progression, but the incidence rate is very low. VEEV shows the smallest percentage of neurological sequelae (~14%), but hypothetical large North American outbreak of VEEV would likely cause severe cases in at-risk populations (children/elderly/immunocompromised), because the entire US/Canada population is naive.
- Geographical distribution – Western hemisphere; overlaps with distribution of other encephalitic enteroviruses and arboviruses (WNV)
- EEEV infection confers life-long immunity against re-infection; however, there is no cross-immunity against WEEV and VEEV.
- Diagnostic – serologic testing is the primary method for diagnosing equine encephalitis virus infection. In US, EEEV virus IgM testing is available at CDC and some state health departments.
- Humans are considered dead-end hosts since viremia does not reach high enough levels to allow the transmission to the feeding mosquitoes.

TPP attributes

Indication: For the treatment of mild/moderate infection with encephalitic Togaviruses

Table 1. TPP attributes

Categories	Minimal Attributes	Optimal Attributes
Clinical Outcomes/Efficacy	• Decrease in duration of symptoms • Decrease in progression to severe neurological disease [1]	• Ability to prevent sequelae and reduce mortality [2]
Target Population	• Adult patients with confirmed or suspected viral infection	• Pediatric patients • Pregnant women • Global population
Treatment Regimen, Duration, Dosage, and Treatment Window	• No more than three times per day • Treatment window w/in mild to moderate phase of specific symptomology	• Single dose or once per day • Effective treatment after onset of encephalitic symptoms
Route of Administration	• Oral route for self-administration (required for PEP) • Parenteral for treatment, as symptoms prevent oral intake	• Pediatric formulation • No adjustment for hepatic impairment
Safety and Tolerability	• Safe for use in broad patient populations [3] • AEs do not prohibit patient compliance	• Acceptable safety profile for use in pediatrics and pregnant women

Categories	Minimal Attributes	Optimal Attributes
Drug Interactions/DDI	• Some DDI tolerated • Dose adjustment permitted with concomitant medications	• No dose adjustment needed with concomitant medications
PK/PD	• $C_{min} > EC_{90}$ • Evidence for appropriate distribution and exposure at relevant sites (CNS, lymphoid tissue, and liver) [4] • Rapid attainment (< 24 h) of efficacious drug levels	• $C_{min} > EC_{90}$ • Evidence for appropriate distribution and exposure at relevant sites (CNS, lymphoid tissue, and liver) [4] • Rapid attainment (< 24 h) of efficacious drug levels
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 • 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 for EEEV and VEEV • No evidence of emergence of resistance in clinical trials	• Broad spectrum antiviral activity against related viruses (WEEV) • 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 [5]	• Demonstration of acceptable selectivity of antiviral activity (CC50/EC50 > 100) • Resolution of clinical endpoints in appropriate animal model with treatment dosing modality [5]

Notes and References

1. There are no approved therapeutics. Clinical management is supportive. Patients with severe meningeal symptoms often require pain control for headaches and antiemetic therapy and rehydration for associated nausea and vomiting. Patients with encephalitis require close monitoring for the development of elevated intracranial pressure, seizures, and inability to protect their airway. https://www.cdc.gov/easternequineencephalitis/healthcare-providers/treatment-prevention.html
2. Neurological sequelae have been documented in up to 75%, 14%, and 90% of EEEV, VEEV, and WEEV survivors, respectively. Sequelae observed following VEEV infection includes convulsions, somnolence, confusion, photophobia, and coma in 4–14% of survivors. EEEV infections can result in convulsions, seizures, and paralysis in 50–90% of survivors, whereas 15–30% of WEEV survivors have confusion, visual disturbances, photophobia, seizures, somnolence, coma, and spastic paresis. In addition, intellectual

disability and behavioral changes are sequalae common amongst VEEV, EEEV, and WEEV infection survivors. https://www.tandfonline.com/doi/full/10.1080/14787210.2022.2141224

3. Point-of-care differential diagnostics for the many arboviral and non-arboviral causes of encephalitis are currently lacking and would be of limited value without effective treatments. Although antiviral drug screening efforts have been undertaken in vitro and in vivo, no antiviral drug has thus far been demonstrated to have efficacy against EEEV. An important requirement of such a drug, were it available, would be the ability to cross the blood–brain barrier. EEE-specific monoclonal antibodies have been effective in an experimental animal model only when given before infection, and data from experiments with VEEV suggest that immunopathogenic mechanisms could be involved. Supportive care, often including admission to an intensive care unit with ventilatory support, is the mainstay of treatment. Patients need not be isolated, since they are not infectious. Given the seriousness of the disease, social support and counseling of the patient and family are critically important. https://www.nejm.org/doi/full/10.1056/NEJMp1914328
4. PK/PD: Primary/secondary sites of infection: CNS, lymphoid tissue, liver, and uterus. https://ann-clinmicrob.biomedcentral.com/articles/10.1186/s12941-020-00360-4
5. The encephalitis caused by VEEV, EEEV, and WEEV is important natural disease of horses and humans and viruses are potential agents of biowarfare or bioterrorism. No licensed vaccines or specific therapies exist to prevent or treat human infections with VEEV, EEEV, or WEEV. Well-characterized animal models are needed to support the development of such medical countermeasures under the United States Food and Drug Administration's "Animal Rule". https://pubmed.ncbi.nlm.nih.gov/20551475/