Target Product Profile (TPP) for APP Antiviral Therapeutics

Neuroinvasive disease caused by West Nile Virus (WNV) and Japanese Encephalitis Virus (JEV) 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 neuroinvasive disease (meningitis, encephalitis, AFP)
- Geographical distribution - temperate (North America, Europe, South Africa, Australia) and equatorial (mostly in Asia) zones; overlaps with distribution of other mosquito-borne viruses (WNV overlaps with ZIKV and DENV in Africa and Central America, and with CHIKV in North America and Asia, JEV overlaps with CHIKV in Southeast Asia) and mosquito-borne tropical diseases (malaria)
- Diagnostic – serological testing is widely available but exhibits cross-reactivity between WNV and JEV as well as other encephalitic viruses (SLEV and MVEV). PRNTs are more reliable but only available in centralized laboratories. WNV diagnosis should be considered in all patients with AFI in endemic areas. JE diagnosis should be considered in patients with neurologic infection living or traveling in endemic areas. Diagnostic turn-around time limits treatment window.
- Neuroinvasive disease can progress quickly following defervescence as viremia decreases; therefore, prospective antivirals are most effective when administered during primary febrile phase (7-11 days) and emphasis should be on PrEP.
- Safe and effective JE vaccines are available to prevent disease, and human vaccination is recommended by WHO in endemic areas.
- Major outbreaks of JE occur every 2-15 years. JE transmission intensifies during the rainy season; however, there has not yet been evidence of increased JEV transmission following major floods or tsunamis. The spread of JEV in new areas has been correlated with agricultural development and intensive rice cultivation.

TPP attributes

Table 1. TPP attributes

Categories	Minimal Attributes	Optimal Attributes
Indication	• For the treatment of disease caused by WNV or JEV infection • For the treatment of patients with mild to moderate disease [1]	• For the treatment of patients with severe disease [1] • For PrEP
Clinical Outcomes/Efficacy	• Decrease in duration of symptoms • Decrease in progression to severe neuroinvasive disease	• Prevention of progression to severe disease and reduction of long-term morbidity
Target Population	• Otherwise healthy adult patients with confirmed or suspected WNV or JEV infection [2] • People at risk of developing severe disease [3]	• Pediatric patients • Pregnant women • Global population

Categories	Minimal Attributes	Optimal Attributes
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 (acute, febrile symptoms) • Maximum 7-day treatment course [4]	• Single dose or once per day • Treatment window after appearance of neurologic symptomology
Route of Administration	• Oral or inhaled/intranasal for self-administration	• Pediatric formulation • Multiple routes of administration (incl parenteral) based on stage of disease • No adjustment for renal impairment
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 • 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 (skin, local immune cells and local lymph nodes)	• Evidence of appropriate distribution and exposure at secondary/tertiary site(s) of infection (eyes, CNS/brain, spleen, liver and kidneys) [5] • Ability to rapidly cross BBB
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 lineages of WNV and genotypes of JEV that infect humans • No evidence of treatment-emergent resistance	• Broad spectrum antiviral activity against related flaviviruses (SLEV, MVEV, DENV, Zika, CHIKV) and other clinically related viruses (EEEV, VEEV) • Acceptable level of resistance development with understanding of potential cross-resistance

Categories	Minimal Attributes	Optimal Attributes
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. WNV and JEV infections are predominantly asymptomatic (~80% for WNV). Symptomatic illness is most often characterized by fever and flu-like illness, including symptoms such as weakness, joint pain, chills. Rare cases (~1% of infected individuals) are diagnosed with severe WNV or JEV neuroinvasive disease characterized by meningitis, encephalitis, acute flaccid paralysis, and neurological sequelae may persist in some cases (Gray and Webb, 2014; Sharma et al., 2021). Additionally, permeability of the blood brain barrier has been shown to be critical to susceptibility of neuroinvasive WNV infection (Cho et al., 2012). Persistent movement disorders, cognitive dysfunction, and long-term disability all occur after WNV neuroinvasive disease (Cho and Diamond, 2012). While rare, neuroinvasive JEV infections are fatal in ~30% of cases, and 30-50% of the survivors develop permanent neurological sequelae (Sharma et al., 2021; Solomon, 2004). Non-neuroinvasive forms of WNV infection can also be severe; in one study, 38% of patients with WNV fever were hospitalized (~5.4 days on average) (Huhn et al., 2005).
2. Diagnosis for encephalitic flaviviruses is based on serological (or CSF) testing and detection of anti-WNV antibodies or positive PCR test. CSF testing may appear negative upon initial test and require subsequent testing to confirm viral encephalitis. WNV and JEV share cross-reacting antibodies with each other and other encephalitic viruses including SLEV and MVEV (Gray and Webb, 2014; Shirato et al., 2003).
3. Risk factors associated with increased morbidity and mortality due to WNV disease are older age (65 y.o.), chronic renal disease, diabetes, alcohol abuse, hypertension, cancer and immunosuppression (Montgomery et al., 2015). Children are at additional risk (5x compared to adults) of higher rates of infection and infants at higher risk of developing severe disease (Mandalakas et al., 2005). In JEV infection, children aged 0-15 y.o. are the most affected group and more likely to have more neurological complications than adults (Bulletin of the World Health Organization (nih.gov)).
4. WNV viremia typically lasts for 7-11 days with a peak approximately 4 days prior to the detection of IgM (Busch et al., 2008). While virus can be found in animal models for more than 4 months following infection (i.e., NHP, hamster and mouse), viral persistence in the CNS has not been documented in humans. However, chronic WNV infection in the kidney has been reported in some patient cohorts (Pogodina et al., 1983; Appler et al., 2010; Nolan et al., 2012). JEV produces a short duration, low viremia but may persist at human mucosal sites for more than 28 days (Chapagain et al., 2022). Similarly, JEV can replicate and remain in porcine tonsils for up to 25 days enabling its persistence in seasons when mosquitos are inactive (García-Nicolás et al., 2018).
5. Following mosquito bite, WNV and JEV replicate within epidermal keratinocytes and Langerhans/dendritic cells (Byrne et al., 2001; Lim et al., 2011). Migratory dendritic cells travel to draining lymph nodes (Byrne et al., 2001) and can enter circulation. Viremia allows spread to secondary lymphoid and visceral organs including the spleen and kidney (Diamond et al., 2003; Eldadah et al., 1967). Secondary replication is typically restricted to the spleen, and central nervous system in humans and WT mice but ocular symptoms have been frequently reported during infections as well (Samuel et al., 2006). In JEV infection, apart from the CNS, the virus also replicates in sites like connective tissue, skeletal muscle, myocardium,

endocrine and exocrine glands and has been shown to cause renal dysfunction (Patgiri et al., 2014), dysfunction in the liver and thrombocytopenia (Kumar et al., 2006).

6. Other references:
    a. Japanese encephalitis (who.int)
    b. Flavivirus Encephalitis | NEJM
    c. Vector-Virus Interactions and Transmission Dynamics of West Nile Virus - PMC (nih.gov)
    d. Pathobiology of Japanese encephalitis virus infection - ScienceDirect
    e. West Nile Virus: Review of the Literature - PMC (nih.gov)
    f. Calgary experience with West Nile virus neurological syndrome during the late summer of 2003 - PubMed (nih.gov)
    g. Human Immunoglobulin as a Treatment for West Nile Virus Infection | The Journal of Infectious Diseases | Oxford Academic (oup.com)
    h. Humanized Monoclonal Antibody against West Nile Virus Envelope Protein Administered after Neuronal Infection Protects against Lethal Encephalitis in Hamsters | The Journal of Infectious Diseases | Oxford Academic (oup.com)
    i. Impact of rituximab-associated B-cell defects on West Nile virus meningoencephalitis in solid organ transplant recipients - PMC (nih.gov)
    j. West Nile virus encephalitis acquired via liver transplantation and clinical response to intravenous immunoglobulin: case report and review of the literature - Rhee - 2011 - Transplant Infectious Disease - Wiley Online Library
    k. Role for Intravenous Immunoglobulin in the Treatment of West Nile Virus Encephalitis | Clinical Infectious Diseases | Oxford Academic (oup.com)
    l. IVIG - West Nile Encephalitis: Safety and Efficacy - Full Text View - ClinicalTrials.gov
    m. CCR5 deficiency increases risk of symptomatic West Nile virus infection - PMC (nih.gov)