Target Product Profile (TPP) for APP Antiviral Therapeutics

Dengue 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) to hemorrhagic fever
- Mild symptoms of dengue can be confused with other illnesses that cause AFI with or without a rash
- Geographical distribution of dengue virus (DENV) - equatorial belt (Central and South America, Africa, South-East Asia, and Pacific Islands)
- Geographical distribution of DENV overlaps with other mosquito-borne viruses (ZIKV, YFV, CHIKV) and mosquito-borne tropical diseases (malaria)
- Almost half of the world's population, ~4 billion people, live in areas with a risk of dengue. It is often a leading cause of illness in the endemic areas. It is common in many popular tourist destinations. In the United States, limited transmission of DENV resulting in autochthonous cases of dengue occurs periodically in states with hot, humid climates and Aedes aegypti and Aedes albopictus mosquitoes.
- Dengue can quickly progress from febrile phase (onset of symptoms, peak viremia ~ day 1) to critical phase (within 3-6 days) and warning signs of severe disease appear with defervescence as viremia decreases; therefore, prospective antivirals are most effective when administered during febrile phase and emphasis should be on PrEP.
- The risk of severe disease increases with secondary DENV infection and decreases with subsequent infections.
- Diagnostic – preferred NAAT (PCR) but limited by viremia; serological tests exhibit cross-reactivity with related flaviviruses (most notably ZIKV). Diagnostic testing is wildly available in at-risk areas, but results might take several days, limiting treatment window.

TPP attributes

Table 1. TPP attributes

Categories	Minimal Attributes	Optimal Attributes
Indication	• For the treatment of disease caused by all four serotypes of Dengue virus • For the treatment of patients with mild to moderate disease	• For the treatment of patients with severe disease • For PrEP (e.g., short-term travel risk)
Clinical Outcomes/Efficacy	• Decrease in duration of symptoms • Decrease in progression to severe disease/hospitalization	• Prevention of progression to severe disease
Target Population	• Adult dengue fever [1] • Patients with warning signs for severe disease [2]	• 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 • Maximum 5-day treatment course	• Single dose or once per day • Treatment window w/in early phase of specific symptomology

Categories	Minimal Attributes	Optimal Attributes
Route of Administration	• Oral or inhaled/intranasal for self-administration	• Pediatric formulation • Multiple routes of administration based on stage of disease
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
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	• Evidence of appropriate distribution and exposure at secondary site(s) of infection
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 $\geq$ 5 years [3] • Short term cold chain (at 4°C) storage with stability • Long term at -20°C storage with stability	• Stability > 10 years • Ambient storage with stability
Spectrum of Activity	• Demonstrated activity against all 4 Dengue virus serotypes • Acceptable frequency of resistance with understanding of potential cross-resistance	• Broad spectrum antiviral activity against related flaviviruses (i.e., YFV, ZIKV) and other clinically related viruses (CHIKV) • 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. The virus may be isolated from the blood during the first few days of infection by RT-PCR and NS1 antigen assay. Serological methods (ELISA) detect anti-dengue antibodies. IgM antibodies are detectable ~1 week after infection and up to 3 months. IgG antibody levels take longer to develop and remains in the body for years.
2. Warning signs usually appear around the time of defervescence and include: Belly pain, tenderness; Liver enlargement; Vomiting (at least 3 times in 24 hours); Bleeding from the nose or gums; Vomiting blood, or blood in the stool; Feeling tired, restless, or irritable; Symptoms and Treatment | Dengue | CDC, Dengue and severe dengue (who.int)
3. Dengue cases are detected year-round with increase in incidence in rainy season in endemic countries, but typically epidemics occur on 3–5-year cycles. For this reason, it is good if drug is stable for the course of an outbreak (a rainy season) but would be better if supply lasted until next outbreak. (*from comments by Kay Tomashek*)