Target Product Profile (TPP) for APP Antiviral Therapeutics

Arthropathic disease caused by Chikungunya 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 – mild febrile illness with characteristic joint pain (polyarthralgia) that can progress to chronic arthritis; ~40% of patients develop long-term disabilities with chronic phase lasting few months to several years
- Neonates exposed intrapartum, older adults (> 65 years), and persons with underlying medical conditions (hypertension, diabetes, or cardiovascular disease) are at higher risk for developing severe disease. Mortality is rare and occurs mostly in older adults.
- Geographical distribution – tropical, subtropical, and temperate areas of Africa, Americas, and Southeast Asia; overlaps with distribution of other mosquito-borne viruses (ZIKV, DENV) and mosquito-borne tropical diseases (malaria)
- Short period of viremia (3-7 days) typically corresponds with primary symptom presentation.
- Diagnostic – NAAT (PCR) testing is limited by viremia and not widely available, serological testing is most efficient by the end of the first week of symptomatic presentation. The differential diagnosis of chikungunya virus infection varies based on place of residence, travel history, and exposures. Dengue, Zika, and chikungunya viruses are transmitted by the same mosquitoes and have similar clinical features. Diagnostic turn-around time limits treatment window.

TPP attributes

Indication: For the treatment of patients with CHIKV disease

Table 1. TPP attributes

Categories	Minimal Attributes	Optimal Attributes
Clinical Outcomes/Efficacy	• Decrease in duration of symptoms • Ability to limit short-term disabilities and disease morbidity	• Decrease in incidence of chronic infection and associated long-term disabilities [1] • Reduction in potential transmission of virus during acute phase of disease
Target Population	• Adult patients with confirmed diagnosis [2] or suspicion of Chikungunya viral infection	• Pediatric patients, including neonates [3] • Patients 65 years of age and older • Pregnant women • Global population
Treatment Regimen, Duration, Dosage, and Treatment Window	• No more than three times per day • Treatment window w/in early phase of specific symptomology • Maximum 7-day treatment course [4]	• Single dose or once per day • Treatment window w/in mild to moderate phase of specific symptomology
Route of Administration	• Oral or inhaled/intranasal for self-administration	• Pediatric formulation

Categories	Minimal Attributes	Optimal Attributes
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 • 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 for appropriate distribution and exposure at primary site(s) of infection (i.e., skin fibroblasts and local lymph nodes)	• Evidence for appropriate distribution and exposure at secondary site(s) of infection (i.e., brain, spleen, liver, muscles, and joints) [5] • Evidence for appropriate PKPD in pediatric patients
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 • 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 CHIKV • No evidence of treatment-emergent resistance	• Broad spectrum antiviral activity against related alphaviruses (e.g., SFV) or geographically and clinically similar viruses (i.e., DENV, ZIKV) • 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 [6]	• Demonstration of acceptable selectivity of antiviral activity (CC50/EC50 > 100) • Resolution of clinical endpoints in appropriate animal model with treatment dosing modality [6]

Notes and References

1. Chronic morbidity/disabilities are most commonly joint inflammation or joint pain followed by arthritis and chronic inflammation, depression, and alopecia. Approximately 40% of patients developed long-term

disabilities after 6 months of CHIKV disease and 28% patients still suffer from this disease after 18 months of acute infection. Prevalence of and risk factors for long-term disabilities following chikungunya virus disease: A meta-analysis - ScienceDirect, Long-term sequelae of chikungunya virus disease: A systematic review - ScienceDirect

2. Diagnosis is based on clinical symptoms including fever and arthralgia confirmed via serological tests or RT-PCR. IgM levels are typically detectable by the end of the first week of infection while the virus can be detected within the first 2-3 days of infection. CHIKV infection causes high levels of viremia, which usually last for 4 to 6 days after the onset of symptoms but up to 12 days has been reported. During the acute phase of illness, the intensity of the clinical symptoms correlates with the viremia during the acute infection, usually lasting 1 week when anti-CHIKV IgM antibodies appear. Disabling polyarthralgia is a key symptom for differential diagnosis with a positive predictive value greater than 80%. Chikungunya fever: Epidemiology, clinical syndrome, pathogenesis and therapy - ScienceDirect, Chikungunya fact sheet (who.int), Arthritogenic alphaviruses--an overview - PubMed (nih.gov)
3. Severe disease occurs in neonates exposed during pregnancy, the elderly (65 years or older), and those with comorbid diabetes, renal, liver, and heart disease. Neonates are more likely to experience encephalitis during infection. Serious complications include myocarditis, uveitis, retinitis, hepatitis, acute renal disease, severe bullous lesions, meningoencephalitis, Guillain-Barré syndrome, myelitis, and cranial nerve palsies. Chikungunya: Epidemiology, Pathogenesis, Clinical Features, Management, and Prevention - ScienceDirect
4. Acute infection typically lasts for 1 week but up to 4 weeks is possible, CHIKV infection is symptomatic in most children and adults who are infected, with less than 15% having asymptomatic seroconversion. Acute disease is manifests in mild, febrile illness with characteristic joint pain (similar to Dengue and Zika). The chronic phase can last a few months to several years (more than 6 years for a small group of patients in Reunion Island) with ongoing disabilities. Estimated risk of Chikungunya viremic blood donation during an epidemic on Reunion Island in the Indian Ocean, 2005 to 2007 - Brouard - 2008 - Transfusion - Wiley Online Library, Chikungunya: Epidemiology, Pathogenesis, Clinical Features, Management, and Prevention - ScienceDirect
5. Immuno-biology of Chikungunya and implications for disease intervention - ScienceDirect
6. The most commonly used animal models are mice and NHPs (non-human primates). Mice represent a popular model for early therapeutics testing however they fail to recapitulate increased severity in older age and chronic symptomology seen in human infections. There are several macaque models of infection (rhesus, bonnet and cynomolgus macaques) that are extremely useful model systems that closely mirror human infections, including tissue persistence but are exceptionally expensive and resource limited. Animal Models of Chikungunya Virus Infection and Disease - PMC (nih.gov)