Target Product Profile (TPP) for APP Antiviral Therapeutics

Visceral / liver-tropic disease caused by Yellow Fever virus

**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 severe liver disease
- Geographical distribution – tropical and subtropical areas of Africa and South America; overlaps with distribution of other mosquito-borne viruses (ZIKV, DENV, CHIKV) and mosquito-borne tropical diseases (malaria)
- Short period of viremia (3-4 days) typically corresponds with non-specific symptom presentation and most patients make full recovery; however, in approximately 15% of cases, the illness recurs in more severe form within 48 hours with viremia mostly absent (toxic stage)
- Diagnostic – preferred NAAT (PCR) but limited by viremia; serological tests exhibit cross-reactivity with related flaviviruses (most notably DENV). Preliminary diagnosis is based on clinical presentation, vaccination status, and travel history. Diagnostic turn-around time limits treatment window.
- YFV vaccine is available and vaccination is recommended in endemic areas. Rare but serious reactions to YFV vaccine include yellow fever vaccine-associated viscerotropic disease (YEL-AVD), and yellow fever vaccine-associated neurologic disease (YEL-AND).

TPP attributes

Indication: For the treatment of viral infection caused by Yellow Fever virus and vaccine-induced illness [1]

Table 1. TPP attributes

Categories	Minimal Attributes	Optimal Attributes
Clinical Outcomes/Efficacy	• Decrease in duration of symptoms • Decrease in progression to severe disease/hospitalization	• Decrease in duration of symptoms • Decrease in progression to severe disease/hospitalization
Target Population	• Adult patients with confirmed [2] or suspected YFV infection	• Pediatric patients, including infants younger than 5 months • Pregnant women • Elderly patients of 70 years of age and above • Immunocompromised population • 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 7-day treatment course [3]	• Single dose or once per day • Treatment window w/in early phase of specific symptomology • Maximum 5-day treatment course

Categories	Minimal Attributes	Optimal Attributes
Route of Administration	• Oral [4] for self-administration • Parenteral if symptoms prevent oral intake	• Pediatric formulation • Multiple routes of administration based on stage of disease • No adjustment for renal/hepatic impairment
Safety and Tolerability	• AEs do not prohibit patient compliance	• Acceptable safety profile for use in pediatrics and pregnant women • Acceptable safety profile for use in elderly and patients with comorbidities • Safety profile appropriate for PrEP [5]
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 relevant primary and/or secondary site(s) of infection (e.g., liver, heart, spleen, and kidneys)	• $C_{min} > EC_{90}$ • Rapid attainment (< 24 h) of efficacious drug levels • Evidence for appropriate distribution and exposure at relevant primary and/or secondary site(s) of infection (e.g., liver, heart, spleen, and kidneys)
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 • Acceptable frequency of resistance with understanding of potential cross-resistance	• Broad spectrum antiviral activity against related flaviviruses (i.e., DENV, ZIKV) and other clinically related viruses (CHIKV) • Acceptable level of resistance development with understanding of potential cross-resistance
Nonclinical Evidence of Antiviral Activity	• Demonstrate 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. Vaccine associated disease has a clinical presentation similar to wild-type YF disease with nonspecific initial symptoms, including fever, headache, malaise, myalgia, arthralgia, nausea, vomiting, and diarrhea, starting 2–8 days after vaccination. Jaundice can appear, along with thrombocytopenia and the elevation of hepatic transaminases, total bilirubin, and creatinine. Severe disease is characterized by hypotension, hemorrhage, and acute renal and respiratory failure, leading to multiorgan system failure. Yellow fever vaccine — how does it work and why do rare cases of serious adverse events take place? - ScienceDirect
2. Confirmed cases can be defined by positive detection of YFV IgM, viral antigen or viral culture in the absence of vaccination (within 30 days) and negative diagnosis for other flaviviruses or similar illness (e.g., malaria, leptospirosis, other VHF, etc). Flaviviruses often had cross-reactivity in serology assays and YF vaccine strain can be difficult to differentiate from WT. PCR diagnostic can confirm early cases and cases for up to 20 days after exposure and onset of illness. Suspected cases include persons presenting with an acute febrile illness (e.g., with fever, muscle pain with prominent backache, headache, loss of appetite, and nausea or vomiting) who develops jaundice within 14 days of symptom onset in endemic areas or having traveled to tropical/subtropical regions of Africa and Central/South America. Yellow fever in the diagnostics laboratory (tandfonline.com), Yellow fever (who.int), Yellow Fever Virus: Diagnostics for a Persistent Arboviral Threat (asm.org)
3. Viremia typically corresponds to the "period of infection" with an average duration of 3-6 days but may continue for up to 8 days into the "period of intoxication," with severe disease and fatalities occurring within 7-10 days. Viral load peaks with abrupt symptom onset but may be detectable 1-2 days after infection and prior to symptoms. Yellow fever: an update - ScienceDirect, Yellow fever (who.int), Yellow Fever Virus: Diagnostics for a Persistent Arboviral Threat (asm.org)
4. YFV replicates at site of inoculation (dendritic cells in epidermis), and spreads via lymphatics to regional lymph nodes. Monocyte-macrophages and large histiocytes preferred cells for replication. YFV goes via lymph and then the blood to tissues (liver, lymph nodes, and spleen) (from comment by Kay Tomashek)
5. The vaccine is safe and effective as a pre-exposure prophylaxis. In endemic or high-risk areas where vaccination coverage is low, prompt recognition and control of outbreaks using mass immunization is critical. It is important to vaccinate most (80% or more) of the population at risk to prevent transmission in a region with a yellow fever outbreak. Vaccines are contraindicated for immunocompromised individuals (especially those with severe immunodeficiency or thymus dysfunction), children less than 9 mos., pregnant women, and people with severe allergies to egg protein. Assess risk for individuals 60+ years as they have increased risk of serious adverse events. Yellow fever (who.int)
6. Mouse, hamster and NHP (rhesus macaque) models are commonly used for YFV. Mouse models exhibit very severe, neurotropic disease while hamsters exhibit viscerotropic illness more similar to human disease. Macaques generally experience more severe and rapid disease progression than humans but are vital in testing safety of new therapeutics prior to clinical trials. Animal models of yellow fever and their application in clinical research - ScienceDirect
7. Other references:

- Remdesivir shows no hepatotoxicity/contraindications during YFD Remdesivir efficacy against yellow fever in a hamster model - ScienceDirect
- NIAID sponsored a Galidesivir phase 1 clinical trial in Brazil, trial was terminated d/t COVID-19 disruptions A Study to Evaluate the Safety, Pharmacokinetics and Antiviral Effects of Galidesivir in Yellow Fever or COVID-19 - Full Text View - ClinicalTrials.gov
- Sofosbuvir is a promising treatment option Sofosbuvir use for yellow fever: a new perspective treatment - PMC (nih.gov)
- Ribavirin is active against YFV but only at very high concentrations Efficacy of post-exposure treatment of yellow fever with ribavirin in a hamster model of the disease - PubMed (nih.gov)