

Target Product Profile (TPP) for APP Antiviral Therapeutics

Zika (ZIKV) 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 and non-specific febrile illness (i.e., fever, rash, conjunctivitis, muscle and joint pain, malaise, or headache) in ~20% of infections, with severe presentation of neurodevelopmental injuries (microcephaly) during fetal development, and GBS in people over 50 years of age
- Geographical distribution – Central and South America, tropical regions of North America, Africa, and Asia; overlaps with geographical distribution of other flaviviruses (DENV) and CHIKV, especially in the Americas and Pacific region
- Since the Zika outbreaks of 2016, reported Zika cases in the Americas have declined by 30-70-fold and are now outnumbered by reported Dengue cases by a ratio of approximately 200:1.
- Diagnostic – preferred NAAT (PCR) but limited by viremia; serological tests exhibit cross-reactivity with related flaviviruses (most notably DENV). Diagnostic testing is widely available in at-risk areas. Testing guidelines differ by country: it is only recommended for pregnant women by CDC, but it is recommended for all symptomatic patients in Brazil (in conjunction with DENV and CHIKV testing).
- Short period of viremia (3-5 days) typically corresponds with primary symptom presentation.
- ZIKV is neurotropic but less neuroinvasive than other encephalitic flaviviruses. It rarely causes meningitis and encephalitis but is associated with Guillain Barre syndrome (ascending paralysis and polyneuropathy) and preferentially infects and injures neural progenitor cells. In both the developing fetus and adults, ZIKV exhibits tropism for components of the visual system, resulting in congenital blindness and adult uveitis.
- ZIKV can be found in bodily fluids (i.e., saliva, urine, semen, breast milk) for months after being cleared from the blood.

TPP attributes

Table 1. TPP attributes

Categories	Minimal Attributes	Optimal Attributes
Indication	<ul style="list-style-type: none"> • For the treatment of all lineages of Zika virus • For the treatment of patients with mild to moderate disease [1] 	<ul style="list-style-type: none"> • For the prevention of transmission and reducing complications in pregnant women and fetus. • For PrEP • For the prevention of severe disease
Clinical Outcomes/Efficacy	<ul style="list-style-type: none"> • Decrease in duration of symptoms • Decrease in congenital malformations (fetus) and spontaneous abortion 	<ul style="list-style-type: none"> • Prevention of CNS sequelae/Guillain-Barre Syndrome [2] • Prevention of birth defects (i.e., microcephaly and congenital Zika syndrome) • Reduction in potential transmission of virus by survivors

Categories	Minimal Attributes	Optimal Attributes
Target Population	<ul style="list-style-type: none"> • Adult patients with confirmed or suspected Zika infection • Pregnant women with confirmed Zika infection 	<ul style="list-style-type: none"> • Pediatric patients • Global population
Treatment Regimen, Duration, Dosage, and Treatment Window	<ul style="list-style-type: none"> • No more than three times per day • Maximum 7-day treatment course [3] 	<ul style="list-style-type: none"> • Once per day or optimally, slow-release single dose that remains active throughout gestational period
Route of Administration	<ul style="list-style-type: none"> • Oral or inhaled/intranasal for self-administration 	<ul style="list-style-type: none"> • Alternate, slow-release formulations for administration at routine prenatal appointments
Safety and Tolerability	<ul style="list-style-type: none"> • Safe for use in broad patient populations, including pregnancy category A/B 	<ul style="list-style-type: none"> • AEs do not prohibit patient compliance • Acceptable safety profile for use in pediatrics • Safety profile appropriate for PrEP
Drug Interactions/DDI	<ul style="list-style-type: none"> • Some DDI tolerated • Dose adjustment permitted with concomitant medications 	<ul style="list-style-type: none"> • No dose adjustment needed with concomitant medications
PK/PD	<ul style="list-style-type: none"> • $C_{min} > EC_{90}$ • Rapid attainment (< 24 h) of efficacious drug levels • Evidence for appropriate distribution and exposure at primary site(s) of infection (i.e., skin, local lymph nodes and immune cells) 	<ul style="list-style-type: none"> • Evidence of appropriate distribution and exposure at secondary site(s) of infection (i.e., eyes, CNS/brain, reproductive tract/uterus/testes, placenta) [4]
Logistical Supportability and Manufacturing	<ul style="list-style-type: none"> • Readily available manufacturing and distribution network, appropriate to phase of project 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Stability \geq 2 years • Short term cold chain (at 4°C) storage with stability • Long term at -20°C storage with stability 	<ul style="list-style-type: none"> • Stability > 7 years • Ambient storage with stability
Spectrum of Activity	<ul style="list-style-type: none"> • Demonstrated activity against all ZIKV lineages • No evidence of treatment-emergent resistance 	<ul style="list-style-type: none"> • Broad spectrum antiviral activity against related flaviviruses (i.e., YFV, DENV) and/or other clinically related viruses (CHIKV) • Acceptable level of resistance development with understanding of potential cross-resistance

Categories	Minimal Attributes	Optimal Attributes
Nonclinical Evidence of Antiviral Activity	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Demonstration of acceptable selectivity of antiviral activity (CC50/EC50 > 100) • Resolution of fetal clinical endpoints in appropriate animal model with treatment dosing modality

Notes and References

1. Symptomatic disease occurs in ~20% of infected individuals and presents as a mild and non-specific febrile illness (i.e., fever, rash, conjunctivitis, muscle and joint pain, malaise or headache). Severe disease most often occurs during fetal development and less frequently in people over 50 y.o., with an increased risk for Guillain Barre syndrome ([Zika Virus and Older Adults | National Institute on Aging \(nih.gov\)](#)). Preferred diagnostic is nucleic acid amplification tests (NAAT) with high specificity but a limited window of the first week following symptoms due to short duration and low amplitude of viremia ([Santiago et al., 2018](#)). Serological tests are also frequently used but exhibit cross-reactivity with related flaviviruses (most notably DENV). [Testing Guidance | Zika Virus | CDC](#)
2. ZIKV is neurotropic but less neuroinvasive than WNV and other encephalitic flaviviruses. Rarely causes meningitis and encephalitis ([Carteaux et al., 2016](#)), but is associated with Guillain Barre syndrome (ascending paralysis and polyneuropathy). Notably, ZIKV preferentially infects and injures neural progenitor cells ([Tang et al., 2016](#)), which may explain its ability to impair development of the fetal brain and cause microcephaly and other neurodevelopmental injuries. Hearing loss and blindness are frequent and most mild congenital manifestations. ZIKV also can infect the eye and cause uveitis in adults, a potentially blinding inflammatory disease ([Furtado et al., 2016](#); [Miner et al., 2016](#)). Human uterine fibroblasts are susceptible to virus and may contribute to congenital infections and abnormalities.
3. Typical viremia lasts for 3-5 days and generally coincides with symptoms (2-7 days) ([Ng et al., 2018](#)). Virus may persist in body sites (and immune privileged sites) anywhere from 11 days after the start of symptoms to 11 weeks ([Murray et al., 2017](#)), and virus can be found in bodily fluids (i.e., saliva, urine, semen, breast milk) for months after being cleared from the blood ([Osuna et al., 2016](#); [Bonaldo et al., 2016](#); [Sotelo et al., 2017](#)). Chronic persistence in sperm has been reported for up to 6 months ([Mansuy et al., 2016](#)). Additionally, there is potential for prolonged persistence of viral RNA in human blood/urine in pregnancy. ZIKV RNA has been detected in serum of pregnant women up to 10 weeks after symptom onset ([Driggers et al., 2016](#)). [Zika virus \(who.int\)](#)
4. ZIKV infection in the adult population has been linked to GBS, transverse myelitis, meningoencephalitis, peripheral neuropathy, and various ophthalmological complications ([Acosta-Ampudia et al., 2018](#)). In both the developing fetus and adults, ZIKV exhibits tropism for components of the visual system ([de Paula Freitas et al., 2017](#)). Additionally, a recent imaging study reported neurological symptoms revealed reduced gray matter volume in specific motor-associated cortical regions, indicating potential long-term impact on the adult CNS ([Bido-Medina et al., 2018](#)). Another study found retinopathy and the presence of viral RNA in retinal cells following in utero or early postnatal exposure to ZIKV but minimal effects following adult exposure, which suggests a selective vulnerability before the retina-blood barrier is fully established ([Zhao et al., 2017](#)). Apoptosis was observed in both infected and noninfected cortical cells taken from a 20-week-old fetus and likely contributes to congenital defects ([Ho et al., 2017](#)).
5. Additional References:
 - a. [WHO Map of ZIKV distribution \(Feb 2022\)](#)

- b. [Rapid development of a DNA vaccine for Zika virus | Science](#)
- c. [Vaccine protection against Zika virus from Brazil | Nature](#)
- d. [SciELO - Brazil - Zika virus damages the human placental barrier and presents marked fetal neurotropism Zika virus damages the human placental barrier and presents marked fetal neurotropism](#)
- e. [Biology of Zika Virus Infection in Human Skin Cells \(asm.org\)](#)
- f. [Zika virus infection of Hofbauer cells \(wiley.com\)](#)
- g. [Zika Virus Infects Human Placental Macrophages - ScienceDirect](#)
- h. [Zika Virus Infects Human Cortical Neural Progenitors and Attenuates Their Growth - ScienceDirect](#)
- i. [Type III Interferons Produced by Human Placental Trophoblasts Confer Protection against Zika Virus Infection - ScienceDirect](#)
- j. [Zika Virus Targets Human STAT2 to Inhibit Type I Interferon Signaling - ScienceDirect](#)
- k. [Identification of small-molecule inhibitors of Zika virus infection and induced neural cell death via a drug repurposing screen | Nature Medicine](#)
- l. [Drug Repurposing: New Treatments for Zika Virus Infection? - ScienceDirect](#)
- m. [Predicting Zika virus structural biology: Challenges and opportunities for intervention \(sagepub.com\)](#)
- n. [A sensitive virus yield assay for evaluation of Antivirals against Zika Virus - ScienceDirect](#)
- o. [A second look: Efforts to repurpose old drugs against Zika cast a wide net | Nature Medicine](#)
- p. [The Viral Polymerase Inhibitor 7-Deaza-2'-C-Methyladenosine Is a Potent Inhibitor of In Vitro Zika Virus Replication and Delays Disease Progression in a Robust Mouse Infection Model | PLOS Neglected Tropical Diseases](#)
- q. [A Screen of FDA-Approved Drugs for Inhibitors of Zika Virus Infection - ScienceDirect](#)
- r. [ZIKA virus elicits P53 activation and genotoxic stress in human neural progenitors similar to mutations involved in severe forms of genetic microcephaly and p53 - PMC \(nih.gov\)](#)
- s. [Differential Responses of Human Fetal Brain Neural Stem Cells to Zika Virus Infection - PMC \(nih.gov\)](#)