Target Product Profile (TPP) for APP Antiviral Therapeutics

Neurological disease caused by enterovirus infection (meningitis, encephalitis, acute flaccid myelitis (AFM) [1], acute flaccid paralysis (AFP))

**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 – asymptomatic to mild illness (including HFMD) that can progress to severe neurological disease (meningitis, encephalitis, AFM, and AFP)
- Short period of viremia (2-5 days) typically corresponds with primary symptom presentation
- Geographical distribution – worldwide, in addition to polio surveillance, non-polio enteroviruses are passively surveilled across several governmental and intergovernmental agencies, primarily across the Asia–Pacific region, Europe, and the United States
- Diagnostic – Diagnosis of enterovirus infection is based on RT-PCR of clinical samples. Most hospitals can diagnose the family of enteroviruses infections, but differential diagnosis of specific enterovirus infections is usually done at CDC and some state health departments. Clinicians should consider EV-D68 infection, especially during summer and fall, as a possible cause of unexplained severe acute respiratory illness, even if patient does not have fever.
- EV-D68 is primarily a respiratory pathogen, while EV-A71 follows fecal-oral route of transmission.
- Three inactivated EV-A71 vaccines are approved in China.

TPP attributes

Indication: For the treatment of neurological disease caused by acute severe enterovirus infection [2], considering patients in the geographical area of an outbreak

Table 1. TPP attributes

Categories	Minimal Attributes	Optimal Attributes
Clinical Outcomes/Efficacy	• Decrease in duration of symptoms • Decrease in progression to severe disease/hospitalization	• Reduction in potential transmission of virus by survivors [3] • Decrease in incidence of persistent infection (i.e., cardiomyopathy)
Target Population	• Pediatric patients with symptoms suggestive of neurological disease and/or suspected or confirmed enterovirus infection [4]	• General population • Pregnant women • Global population
Treatment Regimen, Duration, Dosage, and Treatment Window	• No more than three times per day • Treatment window w/in early/acute phase of specific symptomology • Maximum 5-day treatment course	• Single dose or once per day • Effective treatment after onset of neurological symptomology
Route of Administration	• Parenteral • Pediatric formulation	• Multiple routes of administration based on stage of disease and specific symptomology

Categories	Minimal Attributes	Optimal Attributes
Safety and Tolerability	• Safe for use in broad patient populations including pediatrics	• AEs do not prohibit patient compliance • Acceptable safety profile for use in pregnant women • Safety profile appropriate for PrEP and 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 (GI tract, respiratory tract) site(s) of infection	• Evidence of appropriate distribution and exposure at primary (GI tract, respiratory tract) and secondary (brain, meninges, muscles, skin, CNS) site(s) of infection • Ability to cross BBB [5]
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 EV-D68 and EV-A71 • No evidence of treatment-emergent resistance	• Broad spectrum antiviral activity against other enteroviruses • 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 term acute flaccid myelitis (AFM) was created in fall of 2014 to describe patients with sudden onset of acute flaccid limb weakness without a known cause and with lesions in gray matter of the spinal cord. There can be some white matter involvement. Most cases are in children. AFM Clinical Presentation for Clinicians | CDC, Initial Evaluation for AFM | CDC, Diagnostic Studies for AFM | CDC In most patients, there

is a prior prodromal illness, often involving the upper respiratory tract, with a median of 5 days before onset of weakness. Acute flaccid myelitis and enterovirus D68: lessons from the past and present - PMC (nih.gov)

2. Due to generic nature of early symptoms, it is unlikely that anti-enterovirus antiviral can be efficiently used in current endemic landscape. However, such antiviral might be useful in an event of a large outbreak or a pandemic. Ideal antiviral would be safe enough and would have broad-spectrum activity to treat pediatric patients presenting with fever. To date, three vaccines against EV71 have been licensed in China, all using C4 genogroup strains. Enterovirus 71 (who.int) ~50 pediatric clinical trials for EV71 vaccine (all from China) have been registered at ClinicalTrials.gov (majority in Phase IV). There are no recent diagnostic clinical trials. Romark Laboratories has two clinical trials for use of new formulation of Nitazoxanide (NT-300) to treat colds due to Enterovirus/Rhinovirus infection for 12-year-old and above. Trial to Evaluate Efficacy and Safety of Nitazoxanide in the Treatment of Colds Due to Enterovirus/Rhinovirus Infection - Full Text View - ClinicalTrials.gov, Efficacy and Safety of Nitazoxanide in the Treatment of Colds Due to Enterovirus/Rhinovirus Infection - Full Text View - ClinicalTrials.gov
3. There is a difference between viremia (presence of virions in blood stream) and viral infection (intact virions might no longer be found, but viral proteins are still being synthesized). Some enteroviruses (i.e. coxsackievirus) do not show viremia at all. EV-D68 is sensitive to low pH and therefore does not effectively infect through the gastrointestinal tract, leaving the respiratory tract as the primary site of infection. Enterovirus D68 - an overview | ScienceDirect Topics EV-D68 likely spreads from person to person when an infected person coughs, sneezes, or touches a surface that is then touched by others. Enterovirus D68 (EV-D68) | CDC EV-A71 can be found in an infected person's respiratory secretions, such as saliva, nasal mucus, or sputum (mucus-like secretions sometimes produced in the lungs during infection), in their stool (poop), and in their blisters if they have hand, foot, and mouth disease. You can get exposed to EV-A71 through (Enterovirus A71 (EV-A71) | CDC):
    a. close personal contact, such as hugging an infected person
    b. the air, through droplets, when an infected person coughs or sneezes
    c. contact with feces (poop), such as changing diapers of an infected person, then touching your eyes, nose, or mouth before washing your hands
    d. contact with contaminated objects and surfaces, like touching a doorknob that has viruses on it, then touching your eyes, mouth, or nose before washing your hands
4. Diagnosis can be confirmed by lab testing (CSF is the best way); however, diagnosis is usually based on clinical presentation, clinical history, and geography of outbreaks. Consider EV-D68 infection, especially during summer and fall, as a possible cause of acute, unexplained severe acute respiratory illness, even if the patient does not have fever. https://www.cdc.gov/non-polio-enterovirus/about/ev-d68.html Laboratory testing is recommended for the investigation of clusters of acute, unexplained severe respiratory illness. For enterovirus/rhinovirus positive specimens, molecular typing can determine if EV-D68 is present. Without specialized patient treatment options for EV-D68, testing is unlikely to directly influence clinical management of individual patients. Enterovirus D68 (EV- D68) for Health Care Professionals | CDC Children with asthma may have a higher risk for severe symptoms from EV-D68. https://www.cdc.gov/non-polio-enterovirus/about/ev-d68.html Irrespective of viral loads, EV-D68 was associated with high morbidity in children with asthma and co-morbidities. Enterovirus D68 in Hospitalized Children: Sequence Variation, Viral Loads and Clinical Outcomes - PMC (nih.gov)
5. Primary viremia is in the blood and it would be most efficient for an antiviral to treat at primary viremia stage (2-5 days); therefore, ability to cross BBB is useful but not required.