Target Product Profile (TPP) for APP Antiviral Therapeutics

SARS-CoV-1 and MERS-CoV

**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 – febrile illness to severe respiratory illness
- Primary symptoms are high fever with cough, shortness of breath and nonspecific flu-like illness
- Geographical distribution – initial 2003 SARS outbreak in Asia was contained, not currently circulating; initial 2012 MERS outbreak occurred in Arabian Peninsula and sporadic outbreaks occurred in Middle East and Asia (most recently in Saudi Arabia in 2022)
- MERS-CoV has been identified in dromedaries in several countries in the Middle East, Africa and South Asia, and transmission mostly occurs zoonotically with limited human-to-human transmission in household and healthcare settings. Similarly, most cases of SARS-CoV-1 human-to-human transmission occurred in healthcare settings.
- PCR-based diagnostic testing for MERS-CoV is available in at risk countries through centralized hospital-based labs and in most US state medical labs

TPP attributes

Indication: For the outpatient treatment of SARS and MERS infection

Table 1. TPP attributes

Categories	Minimal Attributes	Optimal Attributes
Clinical Outcomes/Efficacy	• Decrease in progression to severe disease/hospitalization • Decrease in duration of symptoms [1]	• Decrease in long-term symptoms and/or complications [1] • Decrease in risk of ongoing transmission demonstrated by reduction in viral titers to undetectable levels [2]
Target Population	• Adults with confirmed or probable cases of viral infection [3]	• Pediatric patients • Pregnant women
Treatment Regimen, Duration, Dosage, and Treatment Window	• Up to three times per day • Administered within mild to moderate phase of symptomatic presentation • Maximum 10 days treatment course	• Once per day • Maximum 5 days treatment course
Route of Administration	• Oral or inhaled/intranasal formulation, ability to self-administer with minimal skill level [4]	• Alternate parenteral formulation for patients with symptoms prevent oral intake • Pediatric formulation • No adjustment for renal/hepatic impairment [5]
Safety and Tolerability	• Broadly acceptable risk/benefit profile in target population	• Well-established safety profile with AEs that do not require monitoring and do not compromise patient compliance • Acceptable safety profile for use in pediatrics and pregnant women

Categories	Minimal Attributes	Optimal Attributes
Drug Interactions/DDI	• Some DDIs tolerated • Dose adjustment permitted with concomitant medications	• No significant DDIs • No dose adjustment needed with concomitant medications
PK/PD	• C_{min} > EC_{50} (protein-binding adjusted) for the entire dosing interval OR rationale for alternate PK/PD profile • Evidence of appropriate distribution and exposure at primary sites of infection (upper respiratory tract, lungs)	• C_{min} > EC_{90} • Rapid attainment (< 24 h) of efficacious drug levels
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 target populations with minimal ancillary supplies
Product Stability and Storage	• Stability ≥ 2 years • Short term cold chain (at 4°C) storage with stability • Long term storage at -20°C with stability	• Stability ≥ 7 years secondary sites of infection • Ambient storage with stability
Spectrum of Activity	• Demonstrated activity against SARS-CoV-1 and/or MERS-CoV • No evidence of emergence of resistance in clinical trials	• Broad activity against betacoronaviruses • Acceptable level of resistance development with understanding of potential cross-resistance
Nonclinical Evidence of Antiviral Activity	• Demonstrated activity against clinical variants at concentrations achievable in vivo • Acceptable selectivity of antiviral activity with CC50/EC50 (SI) > 10 • Evidence of viral load reduction in appropriate animal model [6] with treatment dosing modality	• Acceptable selectivity of antiviral activity with CC50/EC50 (SI) > 100 • Resolution of clinical endpoints in appropriate animal model [6] with treatment dosing modality

Notes and References

1. Data on clinical presentation and long-term complications

- The incubation period of SARS is generally between 2 and 10 days with the mean time from onset of clinical symptoms to hospital admission between 3 and 5 days. The major clinical features include persistent fever, chills/rigor, myalgia, malaise, dry cough, headache, and dyspnea. Less common symptoms include sputum production, sore throat, coryza, dizziness, nausea, vomiting and diarrhea. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7169175/
- The median incubation period for MERS associated with limited human-to-human transmission is approximately 5 days (range 2-14 days). In MERS-CoV patients, the median time from illness onset to hospitalization is approximately 4 days. In critically ill patients, the median time from onset to intensive care unit (ICU) admission is approximately 5 days, and median time from onset to death is approximately 12 days. https://www.cdc.gov/coronavirus/mers/clinical-features.html

- A small percentage of patients had long-term effects from their illness, including depression or anxiety, cough, shortness of breath, chronic lung disease or kidney disease. However, most patients fully recover. Severe Acute Respiratory Syndrome (SARS) | American Lung Association, https://www.medicaljournals.se/jrm/content/abstract/10.2340/16501977-2694
- Clinically, diarrhea is a distinct feature of SARS, while acute kidney injury is a frequent feature of MERS. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8930171/

2. Data on transmission

- SARS-CoV transmission occurred often during the second week of illness. Virus excretion in respiratory secretions and stool followed a Gaussian distribution and peaked approximately 10 days after symptom onset when patients were often already hospitalized. Hence, most cases of SARS-CoV human-to-human transmission occurred in healthcare settings, predominantly when adequate infection control precautions were absent. Virus transmission via the air was limited to hospital procedures where mechanical aerosol formation could not be prevented. https://www.nature.com/articles/s41467-021-21918-6
- MERS-CoV, like other coronaviruses, likely spreads from an infected person's respiratory secretions, such as through coughing. MERS-CoV has spread from ill people to others through close contact, such as caring for or living with an infected person. Infected people have spread MERS-CoV to others in healthcare settings, such as hospitals. Researchers studying MERS have not seen any ongoing spreading of MERS-CoV in the community. https://www.cdc.gov/coronavirus/mers/about/transmission.html

3. Confirmed case is defined as a person with laboratory confirmation of infection with the Middle East respiratory syndrome coronavirus (MERS-CoV). Probable case is defined as a person with acute respiratory infection, no possibility of laboratory confirmation and a close contact with a laboratory confirmed case. Similar guidelines apply to SARS-CoV-1 case definition. Middle East respiratory syndrome coronavirus (MERS-CoV) (who.int), SARS | Guidance in Absence of SARS-CoV Transmission Worldwide | CDC
4. Data on conventional treatment options (there are no approved therapeutics for SARS and MERS)
   In general, the combination of antibiotics, ribavirin, and corticosteroids was considered as a standard treatment for patients with SARS. For patients with MERS, ribavirin, lopinavir/ritonavir, interferon, and convalescent plasma were continuously recommended. However, a high-dose corticosteroid was suggested for severe cases only. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7533202/
5. Studies have reported liver injury in patients with SARS and MERS. Acute kidney injury is a frequent feature of MERS. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7290752/, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8930171/
6. Data on animal models

- The development and evaluation of antiviral drugs and vaccines for SARS and MERS has been challenging, in part because of difficulties in developing animal models that provide consistent and reproducible results. The ideal animal model is one that mimics human disease in sharing the route of infection, increased severity of disease in the corresponding demographic groups and comparable levels of mortality/morbidity. The presence and distribution of viral receptors should be similar to that in humans. The virus should replicate in the selected animal species and a correlation should exist between virus titer and disease severity. Finally, animal models should be carefully assessed and selected to meet experimental goals. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4550498/