Target Product Profile (TPP) for APP Antiviral Therapeutics

SARS-CoV-2

**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 – respiratory illness that can progress to severe pulmonary disease
- Geographical distribution - worldwide
- COVID-19 is known to cause long-term complications (post-COVID conditions (PCC) or long COVID) that can include non-specific symptoms as well as new medical conditions (asthma, stroke, coagulation disorders).
- Diagnostic tests are widely available including RDTs for self-administration (antigen-based) and NAATs (PCR-based)
- Paxlovid can result in SARS-CoV-2 rebound in some cases, potentially due to treating too early after infection
- Pandemic demonstrated wide 'treatment gap' (time interval between symptomology and seeking medical care), contrary to expected pandemic behavior
- There is potential for recombination of SARS-CoV-2 with common cold coronaviruses
- When considering combination therapy, large difference in cost of mAbs VS direct-acting small molecule antivirals need to be considered.

TPP attributes

Indication: For the outpatient treatment of COVID-19

Table 1. TPP attributes

Categories	Minimal Attributes	Optimal Attributes
Clinical Outcomes/Efficacy	• Decrease in progression to severe disease/hospitalization OR decrease in duration of symptoms [2], similar to current COVID-19 SOCs [1]	• Decrease in long-term symptoms and/or complications [3] • Decrease in risk of ongoing transmission demonstrated by reduction in viral titers to undetectable levels [4],[5]
Target Population	• U.S. adults with diagnosis of SARS-CoV-2 infection with particular focus on those > 60 years of age and/or at high risk for complications	• Pediatric patients • Pregnant women • Global population
Treatment Regimen, Duration, Dosage, and Treatment Window	• Up to two times per day • Administered within mild to moderate phase of symptomatic presentation • Maximum 10 days treatment course	• Single dose or once per day • Maximum 5 days treatment course
Route of Administration	• Oral or inhaled/intranasal formulation, ability to self-administer with minimal skill level	• Pediatric formulation • No adjustment for renal/hepatic impairment

Categories	Minimal Attributes	Optimal Attributes
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
Drug Interactions/DDI	• No significant DDI with products licensed for COVID-19 and/or common anti-inflammatory, analgesic, and antipyretic agents • Dose adjustment permitted with concomitant medications	• 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 and secondary 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 level that allows broad use with minimal manufacturing lag time • Proof of commercial viability (low cost of goods, easily reproducible chemical formulation)
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 • Ambient storage with stability
Spectrum of Activity	• Demonstrated activity against SARS-CoV-2 • 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. CDC SOC for outpatient is to treat with Paxlovid or Remdesivir in patients who meet the following criteria: (a) test positive for SARS-CoV-2 (with PCR or antigen test, including at-home tests); (b) have symptoms consistent with mild-to-moderate COVID-19; (c) are within 5 days of symptom onset for Paxlovid or 7 days of symptom onset for Veklury/Remdesivir; (d) have one or more risk factors for severe COVID-19. NIH SOC for non-hospitalized adults with COVID-19 are symptomatic care for all patients, and Paxlovid or

Remdesivir for patients at risk of progressing to severe disease. Risk factors include age over 50 years, cancer, cardiovascular disease, chronic kidney disease, chronic lung disease, diabetes, immunocompromising conditions or use of immunosuppressive medications, obesity (i.e., body mass index ≥ 30), and pregnancy. "Interim Clinical Considerations for Covid-19 Treatment in Outpatients." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 15 June 2022, https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/outpatient-treatment-overview.html. "Nonhospitalized Adults: Therapeutic Management." *National Institutes of Health*, U.S. Department of Health and Human Services, 8 Aug. 2022, https://www.covid19treatmentguidelines.nih.gov/management/clinical-management-of-adults/nonhospitalized-adults--therapeutic-management/

2. Symptoms usually resolve in 2 weeks without intervention. Symptom Duration and Risk Factors for Delayed Return to Usual Health CDC Report, https://www.sciencedirect.com/science/article/pii/S0196655321007239
3. Data on long-term symptoms. Long COVID or Post-COVID Conditions | CDC, Long COVID | NIH COVID-19 Research
4. Data on transmissibility. Transmissibility of COVID-19 depends on the viral load around onset in adult and symptomatic patients - PubMed (nih.gov)
5. Laboratory data suggests that infected individuals appear to be most infectious just before they develop symptoms (i.e., 2 days before they develop symptoms) and early in their illness. Individuals who develop severe disease can be infectious for longer. Asymptomatic individuals can also transmit but seems less common. Additionally, therapeutics that reduce viral titers to undetectable levels or confer sterilizing immunity would be optimal. https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-covid-19-how-is-it-transmitted, Transmissibility of COVID-19 depends on the viral load around onset in adult and symptomatic patients - PubMed (nih.gov)
6. We did not find a single ideal animal model for COVID-19. Hamster models more closely mimic moderate disease in humans, while NHP models are most similar to humans in terms of physiological characteristics and immune regulation. Animal models for COVID-19: advances, gaps and perspectives.