ACT Accelerator
Therapeutics Partnership

INVESTMENT CASE SUMMARY FOR MONOCLONAL ANTIBODIES AND SMALL MOLECULES

CONTEXT AND SUMMARY

ACT-A is coordinating a global effort to combat Covid-19, of which Therapeutics is a central pillar. Within Therapeutics, **monoclonal antibodies and antivirals, currently in clinical trials, represent some of the most promising options to treat patients** across treatment settings and stages of disease severity. Both treatment modalities, however, carry steep challenges for global deployment: manufacturing capacity is scarce and competition to lock in capacity from commercial players is fierce.

To ensure equitable access to these potentially life-saving therapeutics, ACT-A must secure a share of the severely limited manufacturing capacity, and ACT-A must act now. If the Tx Partnership doesn't act decisively, ACT-A risks forfeiting the opportunity to realize global availability for these therapeutics, and access in low- and middle-income countries will be severely delayed, or worst case, foregone altogether.

In order to carry out this intervention, the Therapeutics Partnership needs ~$485mm, with funds set to be allocated to the best placed organizations within the partnership. While this intervention will only meet a proportion of unmet need for outpatient and mild cases in LMICs, it will contribute to saving lives as well as reduce morbidity and hospitalizations. The proposed investment is a first step in the broader ACT-A portfolio investment strategy; ACT-A will continue investing in effective therapeutics to ensure equitable access for millions of individuals in order to save lives, protect health systems and restore societal and economic activity.

RATIONALE

In response to the COVID-19 pandemic, the Access to COVID-19 Tools Accelerator (ACT-A) is coordinating a global effort to advance the development and delivery of Vaccines, Diagnostics and Therapeutics.

Therapeutics (Tx) represent a central pillar of this portfolio; both 'repurposed' and 'novel' pharmacological therapies are expected to provide long-term solutions. Emerging evidence demonstrates the potential impact of therapeutics. Dexamethasone, for example, has been proven to reduce mortality while Remdesivir has demonstrated a reduction in length of hospital stay. Tx uniquely have the potential to address the full spectrum of Covid-19 disease progression, from prophylaxis to severely unwell patients. As such, they are essential to save lives by preventing progression across all disease stages, enabling test & treat approaches, and complementing vaccines to provide widespread protection. Tx also provide critical coverage before vaccines are fully scaled and while safety/efficacy questions remain unanswered.

Within the Tx portfolio, the ACT-A Partnership is advancing both novel therapeutics as well as simple repurposed therapies (e.g., Dexamethasone). If repurposed therapies prove effective, the global community can move swiftly in order to scale up and deploy effectively against COVID-19. In order to do so, the ACT-A Partnership will need continued investment as clinical evidence from trial read-outs emerges starting Q3 2020 through Q1 2021.

For novel therapies, two highly promising treatment modalities have been prioritized based on an extensive R&D landscaping exercise – monoclonal antibodies (mAbs) and novel antivirals:

- Monoclonal antibodies (mAbs) are manufactured, immunological products that can help neutralize the SARS-CoV-2 virus and are expected to be highly effective.
- Novel antivirals are designed specifically to treat SARS-CoV-2 virus and are expected to exceed the efficacy of repurposed antivirals (such as Remdesivir) with a more favorable cost profile and oral administration route.

Compared to repurposed therapies, novel therapies present scalability and deliverability challenges. Manufacturing capacity will be scarce, and competitors will race to lock in such capacity. Therefore, action is needed even before definitive evidence from clinical readouts is available in order to secure access to these promising treatment modalities.

KEY CHALLENGE

While the ACT-A Tx Partnership has great optimism that these novel therapies will prove safe and efficacious, definitive evidence from trial read-outs will only be available in Q4 2020/ Q1 2021. To accelerate global availability and secure limited manufacturing capacity in the face of fierce competition from developers, the global health community must act quickly and decisively.

mAbs and novel antivirals present unique challenges for global deployment. First, the immediate need will far exceed available manufacturing capacity. Global antibody manufacturing capacity is limited and fixed: the majority (70%) is owned by companies marketing their own products and the remainder is owned by contract manufacturing organizations (CMOs), largely tied to long term contracts with developers. For novel antivirals, small molecule contract manufacturers must meet stringent quality criteria, similarly limiting available supply.

Second, there is intense competition to lock-up existing capacity. The US Research Authority (BARDA), for example, secured a deal with Regeneron (developing one of the leading antibody cocktails) to reserve up to 1.2M doses exclusively for the US market. Similarly, another leading antibody developer, VIR Biotechnology, entered into contracts with Wuxi Biologics and Samsung Biologics respectively to reserve their antibody manufacturing capacity for 2021 and 2022.

Third, the relative cost and complex in-country delivery of these products may lead to a slower dissemination to low- and middle-income countries (LMIC), with the majority of capacity dedicated to high-income countries (HIC). Approximately 80% of mAbs produced globally are deployed in HIC, with only 1.3% in Africa. The magnitude and infectiousness of COVID-19 necessitates a global response to the pandemic, mandating equitable access to effective therapies across the world.

OUR PROPOSAL

ACT-A is seeking an investment of ~$485mm to reserve LMIC-dedicated manufacturing capacity and volume guarantees for mAbs and antiviral therapies at cost. The investment approach is modular, minimizing up-front financial risk and preserving the flexibility to pursue yet-to-be identified candidates. The recipients of the investments have been identified based on the type of investment and comparative advantage of each partner organization – i.e., Unitaid for capacity reservations, UNICEF for volume guarantees (see addendum 1).

For mAbs, ACT-A will invest ~$365mm to reserve product-agnostic manufacturing capacity and secure a volume guarantee for 9 million treatment courses at cost (see table 1 in addendum). The COVID-19 Therapeutics Accelerator has negotiated the option to reserve product-agnostic capacity with a rigorously vetted, high-quality contract manufacturing organization (CMO) for 4M treatment courses in 2021 and 5M in 2022. Based on this negotiation, investment by the ACT-A Tx Partnership is needed to exercise the option and secure the volume guarantee. In parallel, the COVID-19 Therapeutics Accelerator commenced Global Access Agreement negotiations with multiple mAb developers to secure LMIC-appropriate pricing. Given that capacity reservations are product-agnostic and separate from developer agreements, ACT-A maintains the flexibility to choose between multiple mAbs based on emerging clinical evidence.

For novel antivirals, ACT-A will invest ~$120mm in three high-quality contract manufacturing organizations (CMOs) for product-agnostic manufacturing capacity reservation, procurement and distribution. The investments are staggered from Q4 2020 – Q1 2022 (see table 2 in addendum). The CMOs were down-selected by the COVID-19 Therapeutics Accelerator following a rigorous vetting procedure and can accommodate almost any small molecule candidate, pending positive clinical trial read-outs. Each CMO can produce ~10 metric tons per year, translating to as much as 10M+ treatment courses dependent on the small molecule selected. In parallel, the COVID-19 Therapeutics Accelerator commenced Global Access Agreement negotiations with multiple developers. Given that capacity reservations are product-agnostic and separate from developer agreements, ACT-A maintains the flexibility to choose between multiple small molecules based on emerging clinical evidence.

While this intervention will only meet a proportion of the total unmet need, this coordinated set of investments will nonetheless grant LMIC immediate access (i.e., in 2021) to the first wave of novel COVID-19 treatments at-cost and lay the groundwork for future investments in Therapeutics. This is the critical first step in a broader ACT-A portfolio investment strategy that will play a crucial role in ensuring global and equitable access to COVID-19 therapeutics.

EXPECTED IMPACT

These treatment modalities will likely provide the first opportunity to reduce mortality, morbidity and hospitalizations across treatment settings (both inpatient, as well as the severely underserved outpatient segment). For mAbs alone, this investment can avert 350,000+ deaths, at a cost of $1000 per death-averted and $60 per disability-adjusted life year (DALY) in high-risk patients (based on 50% effectiveness).

Expected allocation will be defined in due course following WHO guidance, though it is likely health-care workers and other high-risk/vulnerable populations could be the first recipients of the aforementioned therapies.

RISK ASSESSMENT AND THE COUNTERFACTUAL

The key risks inherent in this investment proposal are outlined below, with pre-emptive steps and proposed mitigations:

- **Clinical/regulatory risk**: Trials which are yet to read-out will ultimately determine the effectiveness of these novel therapeutics, and treatments must prove to be effective at doses low enough to render affordable pricing. These risks can be partially mitigated by the product-agnostic nature of the investment; reserved capacity can be redeployed to novel candidates as efficacy data emerges from the therapeutic landscape, which will continually be monitored by ACT-A.
- **Execution risk**: To facilitate rapid global deployment, ACT-A needs to install a robust allocation, procurement and distribution mechanism. In response, ACT-A is actively developing an in-depth implementation roadmap and risk mitigation strategy in collaboration with all ACT-A Tx Partners. In addition, WHO is leading all allocation efforts across ACT-A (see addendum 2).
- Financial risk: While financial exposure is limited due to the staggered nature of the investment, the Tx Partnership risks losing part of the upfront reservation fees if development timelines are severely delayed (~est. 10% of the total investment).

At the same time, the cost of inaction is immense. If we don't invest, we risk forfeiting our opportunity to realize rapid and equitable access to the most promising COVID-19 treatment modalities. For LMIC specifically, access will be severely delayed or never achieved:

- The expected timeline on which new chemical entities (e.g., novel antivirals) achieve scale in LMIC after successful approval is 5+ years.
- For mAbs, we likely forego the opportunity to realize access for LMIC in the next year. Today, there is limited to no access to these treatment modalities.

However, securing access for LMIC to effective Therapies is crucial to solve the pandemic on a global level. If the most promising treatment modalities are only available in targeted geographies, we risk continued spread and further outbreaks in the near-future.

While mAbs and novel antivirals represent the most efficacious near-term therapeutic options to treat patients with COVID-19, obtaining global access to these therapies presents an immense challenge. The proposed investments will ensure that ACT-A can meaningfully accelerate access for millions of individuals in order to save lives, protect health systems and restore societal and economic activity.

Addendum 1

BREAKDOWN OF TOTAL INVESTMENT NEED

Table 1 – Investment need for Monoclonal Antibodies manufacturing capacity reservation

INVESTMENT TYPE	$mm	Recipient	Deadline
Volume guarantee to CMO	~65	Unitaid	9/30/2020
Volume guarantee to mAb Developer	~55-100	UNICEF	9/30/2020
Total investment need 2021 for 4M doses in 2021	**~120-165**		
Manufacturing capacity reservation fee	~20	Unitaid	9/30/2020
Volume guarantee to CMO	~65	Unitaid	Q1/2 2021
Volume guarantee to mAb Developer	~55-100	UNICEF	Q1/2 2021
Total investment need 2021 for 4-5M doses in 2022	**~140-200**		

Table 2 – Investment need for Novel antivirals manufacturing capacity reservation

INVESTMENT TYPE	$mm	Recipient	Deadline
Capacity reservation and service fee to CMO	~10-20	Unitaid	8/30/2020[1]
Volume guarantee to Developer	~10-20	UNICEF	10/30/2020
Investment need H1 2021 CMO capacity (10 metric ton)	**~20-40**		
Capacity reservation and service fee to CMO	~5-10	Unitaid	Q1/2 2021[1]
Volume guarantee to Developer	~10-20	UNICEF	Q2/3 2021
Investment need H2 2021 CMO capacity (10 metric ton)	**~20-40**		
Capacity reservation and service fee to CMO	~5-10	Unitaid	Q3/4 2021[1]
Volume guarantee to Developer	~10-20	UNICEF	Q4 2021
Investment need H1 2022 CMO capacity (10 metric ton)	**~20-40**		

Addendum 2

IMPLEMENTATION ROADMAP - OPERATIONAL PATHWAY OUTLINED ACROSS TX PARTNER ORGANIZATIONS (BMGF, WELLCOME, UNITAID, UNICEF, GLOBAL FUND AND WHO)