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PSFC Psychedelic Science Funders Collaborative

To: Psychedelic Science Funders Collaborative (PSFC)

From: Atul Pande (Verity BioConsulting)

Dated: March 25, 2020

Re: Independent evaluation of the reforecast budget for the MDMA phase 3 studies

Executive Summary

MAPS Public Benefit Corporation (MAPS PBC) has made substantial revisions to the budget for their phase 3 program on MDMA-assisted psychotherapy for the treatment of post-traumatic stress disorder (PTSD). At the request of the Psychedelic Science Funders Collaborative (PSFC), I have examined this revised budget. In order to complete this review, I have relied on the detailed revised budget provided by MAPS, supplemented by discussions with Ryan Hudgins, MAPS PBC's Director of Financial Planning, and Amy Emerson, MAPS PBC's Executive Director.

This report summarizes my observations and judgment on the adequacy of the proposed budget revisions, the likelihood of technical success in achieving the goal of positive clinical data, and the probability of regulatory success. After probing the assumptions used for the revised budget, I am comfortable that the forecast is as accurate as possible for typical industry-sponsored clinical trials.

Further, based on the conduct of the first phase three (MAPP1) trial, the agreements with the FDA on the data to be generated, and a more precise estimate of the funding needed up to New Drug Application (NDA) submission, my assessment of the combined probability of technical and regulatory success for the trial is upward of 70 percent. In my pharmaceutical industry experience, this level of confidence in the program would be considered a positive trigger for full investment in the program.

About the Author

I am a psychiatrist and have spent the past 30 years in the pharmaceutical and biotechnology industry. My expertise is in the development of drugs and medical devices, with a primary focus on neuropsychiatric conditions. I am experienced in designing and executing clinical trials broadly across many diseases (depression, anxiety, schizophrenia, bipolar disorder, smoking cessation, Alzheimer's disease, traumatic brain injury, epilepsy, restless legs syndrome, etc.). Over the years I have been involved in the development of many products (e.g., Prozac, Zyprexa, Neurontin, Lyrica, Chantix, Geodon, Trobalt/Potiga, Lamictal XR, Requip XR, Horizant, Breo/Relvar, Tivicay, Tykerb, etc.), and earlier stage development candidates that did not reach the market.

Further, I have held senior executive positions at large and small companies with accountability for executing development programs within time and budget limits set a priori by the company. I currently serve as an independent director on the boards of five biotech companies (three of them publicly traded companies). Therefore, I have the benefit of broad and deep visibility into industry practices regarding clinical trial planning, operational execution, and budget-building.

Scope of this Memo

This report was commissioned by PSFC, a 501(c)3 nonprofit that supports research on and clinical trials of physician-prescribed psychedelic medicines and patient access to these treatments. In 2019, MAPS PBC engaged me as an outside consultant at the suggestion of and with the financial support of PSFC, and I have been working with the MAPS PBC team to review their clinical program and advise on the phase 3 trial, staffing, and other areas. In late 2019, MAPS PBC reassessed and updated their phase 3 budget: The budget for the first and second phase 3 trials (MAPP1 and MAPP2) increased from $11.5 million to $18.9 million. Additionally, MAPS increased overall staffing, spending on FDA compliance and drug approval and initial drug commercialization expenses in anticipation of regulatory approval. MAPS has asked PSFC to partner with them on a $30 million fundraising capstone campaign to support this revised budget. PSFC wanted to have an independent review of this revised budget by a drug development expert who was familiar with MAPS PBC, and they asked me to address three key questions:

1. Is the new budget likely to be sufficient?
2. Why was the new budget needed and what has been learned?
3. Given the new budget, what are the odds of achieving a successful New Drug Application (NDA) submission, and what additional risks remain?

Introduction to MAPS Clinical Trials

Post-traumatic stress disorder (PTSD) is a serious and prevalent psychiatric condition that is the cause of significant morbidity and mortality. Although commonly misunderstood as a condition that primarily affects military veterans, PTSD is in fact more common among individuals in the civilian population who have been exposed to extraordinary (e.g. living in war zones) or repeated (e.g. physical or sexual abuse) traumatic experiences. PTSD causes subjective distress, often leads to alcohol or drug abuse, impairs social and familial relationships, and stunts academic and occupational achievement. Even worse, PTSD increases the risk for other psychiatric conditions such as depression. All-causes mortality, and mortality from suicide, are both higher among PTSD patients than the general population.

Current treatments for PTSD are hampered by limited efficacy, frequent relapse and treatment non-adherence. Various psychotherapeutic approaches, sometimes in combination with medicines, remain the mainstay of treatment.

Several small clinical studies have suggested that PTSD patients treated with psychotherapy augmented with an exposure to MDMA can produce large and enduring relief of symptoms. Based on this observation, MAPS PBC is developing MDMA-assisted psychotherapy as a treatment for PTSD. Designed in consultation with the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), the development program aims to seek approval of MDMA as a regulated treatment for PTSD.

The key components of the development program involve two phase 3 clinical trials (MAPP1 and MAPP2) and a pharmaceutical product development effort to meet regulatory standards. The MAPP trials are similar studies intended to be run in series to satisfy the regulatory standard of at least two positive clinical studies to support the filing of an NDA for the US FDA, Israeli Ministry of Health, and Health Canada. Another Phase 3 study is needed for EMA.

MAPP1 was initiated in 2018 and is currently enrolling subjects. The study is comparing PTSD subjects who are randomly assigned to receive either MDMA and psychotherapy or placebo and psychotherapy. Efficacy is assessed using standardized clinical rating scales. As the medications are given in a double-blind fashion, neither the subjects nor the clinical raters are aware of the treatment assignment.

Since there was only limited efficacy information available at the time the MAPP trials were designed, and there was a desire to achieve maximum utility with the MAPS funds, the MAPP1 study planned to conduct an interim data analysis. An interim analysis, a common feature in clinical trials, aims to determine whether the actual efficacy data being gathered in the study are following the treatment difference (active versus control) predicted at the start of the study. The data from this analysis are reviewed by an independent expert panel and the only direction conveyed to the study team is either (1) continue the study unchanged, (2) add more subjects to increase the statistical power of the study, or (3) stop the study either because there is a concerning safety issue or because it is highly unlikely the study goal will be achieved. If the interim analysis indicates the study should be continued unchanged, it can be concluded that the actual data in the study are consistent with the original assumptions of the expected treatment effect. This is commonly interpreted as a confidence booster for the trial's positive outcome.

Factors Necessitating a Budget Revision

Clinical trials for psychiatric disorders entail many uncertainties, especially when little is known about the pattern of help-seeking behavior and the receptivity for the treatment approach that is under study. The MAPS program made optimistic assumptions at the outset of the program about medical need, the desire for new treatments, willingness of participants, ability of clinical sites to run trials, and so forth.

Trials of medical treatments for PTSD have been few and far between, thus only limited, if any, historical costing information was available to the team. In contrast, the typical industry practice for estimating clinical trial costs relies heavily on commercially available historical databases, such as the Medidata Grants Manager (PICAS database). PICAS provides industry-wide negotiated site cost information. It is a database of negotiated investigator grants, and includes more than 250,000 grants and contracts and 27,000 protocols in over 1,400 indications. The repository of benchmarked costs is extremely useful for clinical trial budget planning.

In the absence of such guidance, the program budget appears to have been developed based on a mind-set of using financial resources sparingly, thereby compelling optimistic assumptions about the time and cost of the clinical endeavor. The actual conduct of the MAPP1 study has revealed that the amount of effort required at the sites, and within MAPS, is considerably greater than originally planned, and the pace of subject enrollment has been slower than projected.

Moreover, the "scarcity" mindset, and the relative inexperience of the organization, led the MAPS team to incompletely anticipate all of the activities necessary to reach an NDA submission. They maintained a narrow focus only on the costs of completing the trials, and did not account for the full costs of ancillary activities that commonly occur in parallel with phase 3. This falls short of industry standards.

In addition to the phase 3 clinical study costs, pharmaceutical companies invariably also incorporate into the budget the costs associated with compiling the new drug application, and its submission and review

by the regulators. Most companies tend also to fold in initial commercialization costs (fuller pharmacovigilance and medical affairs capability, market preparation, commercial scale product manufacturing, etc.) in order that, should the NDA be successful, the time to market launch is minimized. In contrast, none of these activities were included in the original MAPS budget.

Key Changes in the Revised Budget

The revised budget is based upon learnings from the initial conduct of MAPP1 and the additional input sought by MAPS during 2019 from drug development and commercialization experts.

The key assumptions that have been revised are (1) the MAPP2 study will run longer (~5 months more than assumed for MAPP1) to recruit the sample of 100 subjects, (2) conduct of the study at the sites will require more hours by the site staff (therapists and administrative), and (3) demand greater effort from internal MAPS-PBC staff to continue the follow-up phase of MAPP1 in parallel with executing MAPP2, and planning for NDA submission. Consistent with industry practice, the costs for the clinical studies now also include a 10 percent contingency.

Anticipating that the phase 3 studies will have positive outcomes, the new budget incorporates approximately $3.3 million for the costs of compiling and submitting the NDA, and potential costs of iterative interactions with the FDA during the review process until approval is achieved. Because MDMA is a scheduled drug, it is conceivable that the review process could be protracted, and there is the possibility that last minute issues or concerns will be raised by the FDA or DEA that need to be addressed either through marshalling of expert panels, or by conducting additional studies.

The budget revision now also includes the initial costs for commercial preparation of approximately $9.9 million. This will cover the cost of producing commercial-grade drug product, fund the training and supervision of therapists who will administer the therapy, and support general commercial activities such as market planning, pricing and reimbursement activities, pharmacy benefit management, etc.

All of these enhancements have brought the program budget in line with what a pharmaceutical company would plan for.

Conclusions

During the course of the past year, I have had the opportunity to interact with the MAPS team on multiple occasions. Though the team members are early in their experience as clinical drug developers, they are an extremely dedicated and talented team. It is to their credit that with single-minded focus and determination they have brought the program to this stage, while operating on what is a shoe-string budget by industry standards. The proposed revisions to the budget are an appropriate response by the team to what they have learned from the MDMA program to date.

Upon completing my review, I offer the following responses to the questions that were posed by PSFC.

1. After probing the assumptions used for the revised budget, I believe that the current forecast sufficiently accounts for the foreseeable costs up to NDA. The final overall spend should land within the 10 percent contingency.

2. I believe the original under-estimate of the resources (money and people) needed for the MAPP program were driven by a combination of:
    a. Working in a novel area for clinical trials (medication + psychotherapy has not often been subjected to clinical trials) so that there were fewer precedents to rely on in judging study costs,
    b. The relative inexperience of the MAPS team in running a phase 3 program, and
    c. A desire by MAPS leadership to maximally stretch the limited funding that was available to them at the outset.

3. Successful submission of an NDA depends on several factors of which the key components are achieving technical success (do the studies produce data indicating the treatment is safe and effective), and navigating the regulatory process (has the statutory standard for approval of therapeutics been met). The proposed budget revisions, which will permit more appropriate internal staffing and fairer reimbursement for study sites, are essential to increasing the probability of technical success, which I estimate in the 80 percent range (both studies positive).

    Assuming the MAPP studies are both positive, I believe the likelihood of regulatory success is likely to be in the 80-90 percent range. I base my opinion on the interactions the MAPS team has already had with the FDA and with EMA advisors. The tone and gist of the exchanges with the FDA, including written agreements on the MAPP protocols, all point towards a favorable outcome provided the clinical studies meet their endpoint. Thus, the combined probability of technical AND regulatory success would be in the 70 percent range, which by industry standards would be considered a positive signal for further investment.

    During the preparation of this report, I was made aware that the interim analysis of MAPP1 was completed and the study will close enrollment at the planned target of 100 subjects. With a sample size of 100 participants, this study has a 90 percent or greater probability of achieving statistically significant results. Needless to say, a positive MAPP1 study would increase the probability of a positive MAPP2 study.

    Since the interim analysis for MAPP1 indicated no change in study sample size, a smooth transition into the start of MAPP2 is anticipated. Therefore, it is even more imperative to implement the budget revisions now to allow a timely completion of the phase 3 program.

    As with any drug development program, some risks remain until late in the game. Once a positive data read-out from the MAPP studies is achieved, there can still be regulatory delays and unexpected regulatory demands for additional data. The previous agreements with the FDA notwithstanding, it is always possible for the NDA reviewers to identify new issues and questions that require additional time and money to answer. This is the only scenario in which there may be further stress on the budget as the MAPS overhead will need to continue running while the regulatory aspects are sorted out.