Greenleaf Health

MEMORANDUM

TO: Mind Medicine (MindMed) Board of Directors

FROM: Greenleaf Health, Inc.

DATE: May 24, 2023

SUBJECT: Expert Regulatory Assessment of MindMed's MM-120 Development Strategy

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Background

Greenleaf Health, Inc. (Greenleaf) was engaged on behalf of the MindMed Board of Directors (Board) to conduct a clinical and regulatory assessment of MindMed's MM-120 product candidate (lysergic acid diethyl amide D-tartrate or LSD D-tartrate) under development in the U.S. to treat the symptoms of anxiety in patients with generalized anxiety disorder (GAD). In particular, the Board requested Greenleaf's expert perspective on the appropriateness of completing a Phase 2b dose-ranging study prior to initiating a Phase 3 program.

As part of Greenleaf's assessment, the team reviewed the following material:

- Code of Federal Regulations
- FDA guidance documents and Agency commentary
- Regulatory correspondence between FDA and MindMed on the MM-120 program
- Published reports of investigator-initiated trials
- MM-120 Phase 2 protocol
- MM-120 Phase 3 plans
- MM-120 Investigator's Brochure
- Regulatory approval precedents
- Overview of known competitor programs

This memo summarizes Greenleaf's views on FDA clinical data expectations and standards for clinical trials, particularly with respect to the importance of identifying an optimal safe and effective dose. It should be noted that while the Greenleaf team members are not scientific experts in LSD nor clinical experts in the field of psychiatry, we have extensive experience in supporting clients developing new drugs regulated by the FDA Division of Psychiatry. The assessment provided is specific to our understanding of the FDA drug development and approval process as applied to the MM-120 development program.

About Greenleaf Health
Greenleaf is a full-service regulatory consulting firm comprised of experts who draw on a combined total of more than 300 years of Food and Drug Administration (FDA) experience to provide best-in-class strategic and technical guidance to companies navigating the evolving FDA regulatory environment. Specifically, Greenleaf provides regulatory guidance to clients in the healthcare community facing issues related to product development, product approval, manufacturing and compliance, marketing practices, labeling, and more. With experience in both the private and public sectors, Greenleaf uses its sophisticated analytical capabilities, subject matter expertise, and institutional knowledge of the FDA to interpret recent or pending regulatory actions and applies these skills to assist clients in making real-time business decisions.

The Greenleaf expert team for this engagement was led by:

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I. Executive Summary

- After review of the MM-120 regulatory history, relevant regulatory precedent, and applicable regulations and guidance, Greenleaf believes MindMed's ongoing Phase 2b dose-ranging clinical trial is an essential component to the development program for MM-120. The effectiveness and safety of a drug are determined, in large part, on a comprehensive understanding of relationships around dose, drug concentration in the blood (pharmacokinetics), and clinical response. A program to pursue first approval for a novel therapy is highly complex, requiring a stepwise process to explore and refine knowledge about the investigational agent to support the ultimate goal of generating the pivotal data regarding effectiveness and safety required to support approval. The ongoing MM-120 Phase 2b trial is designed to address fundamental questions about dose-response, target population, preliminary evidence of efficacy on accepted FDA endpoints for anxiety, and safety that will provide clarity and confidence in designing a Phase 3 program. To initiate Phase 3 trials before these foundational issues have been adequately addressed would substantially increase the chances of a failed trial and/or uninterpretable results. It also risks FDA placing the program on clinical hold if the FDA determines that "the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives."[1]

[1] 21 CFR 312.42(b)(2)(ii).

- MM-120 is a new molecular entity (proposed drug product that contains an active moiety that FDA has not previously approved, either as a single ingredient drug or as part of a combination product). MM-120 is also a Schedule I substance under the Controlled Substances Act, the most restrictive classification indicative of a substance that is classified as having no currently accepted medical use and a high potential for abuse. The FDA has and will continue to be cautious in how MindMed advances the asset into larger cohorts of patients. That caution serves to confirm FDA's feedback on the need for controlled, dose-ranging data in a well-defined target population using endpoints validated for regulatory purposes before agreeing to the design and execution of a larger Phase 3 program. The FDA's feedback on the proposed developed program in no way suggests that it would accept a development program that skips important learnings from a well-designed and conducted Phase 2b trial in favor of moving directly to a large Phase 3 pivotal program.

- As for any novel study drug, the FDA is likely to view the prior published literature around LSD use for the treatment of anxiety as informative and hypothesis generating but not of sufficient detail to allow for an independent review or for regulatory decision making. This is particularly true for LSD given the lack of dose-finding in patients with anxiety and given that the various dosage forms utilized in the published studies do not match what MindMed has developed or intends to use as its to-be-marketed formulation. Therefore, the studies from the published literature are not sufficient to support a proposal for streamlining the MM-120 program directly into Phase 3. Such a plan, if presented to the FDA by MindMed would likely trigger a clinical hold.

- In a review of the last 10-years of new molecule entity (NME) approvals within the Division of Psychiatry, a sample set that Greenleaf believes is most relevant and informative to the MM-120 program (i.e., an NME within the Division of Psychiatry), the FDA has been consistent in its clinical expectations, which include extensive clinical pharmacology assessments, robust Phase 2 development including dose ranging, and multiple Phase 3 trials. Absent from any of these precedents are the use of published literature as a replacement for Phase 2 clinical trials.

II. Background on Regulations & Guidance for Drug Development

The phases of drug development are defined in 21 CFR 312.21 as follows:

> (a) Phase 1. (1) Phase 1 includes the initial introduction of an investigational new drug into humans. Phase 1 studies are typically closely monitored and may be conducted in patients or normal volunteer subjects. These studies are designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. During Phase 1, sufficient information about the drug's pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid, Phase 2 studies. The total number of subjects and patients included in Phase 1 studies varies with the drug but is generally in the range of 20 to 80.
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> (b) Phase 2. Phase 2 includes the controlled clinical studies conducted to evaluate the effectiveness of the drug for a particular indication or indications in patients with the disease or condition under study and to determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well controlled, closely monitored, and

conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

(c) Phase 3. Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase 3 studies usually include from several hundred to several thousand subjects.

As noted above, Phase 2 and Phase 3 studies share many of the same design features and objectives, but Phase 3 studies are performed once there is preliminary evidence of effectiveness and additional information is needed to establish effectiveness, provide an adequate safety database, and to evaluate the overall benefit-risk framework.

To supplement the regulations, FDA published "Drug Development and Review Definitions" where it provides the following overview of Phase 2 and Phase 3 trials:[2]

Phase 2 Clinical Studies
Phase 2 includes the early controlled clinical studies conducted to obtain some preliminary data on the effectiveness of the drug for a particular indication or indications in patients with the disease or condition. This phase of testing also helps determine the common short-term side effects and risks associated with the drug. Phase 2 studies are typically well-controlled, closely monitored, and conducted in a relatively small number of patients, usually involving several hundred people.

Phase 3 Clinical Studies
Phase 3 studies are expanded controlled and uncontrolled trials. They are performed after preliminary evidence suggesting effectiveness of the drug has been obtained in Phase 2 and are intended to gather the additional information about effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug. Phase 3 studies also provide an adequate basis for extrapolating the results to the general population and transmitting that information in the physician labeling. Phase 3 studies usually include several hundred to several thousand people.

In both Phase 2 and 3, CDER can impose a clinical hold if a study is unsafe (as in Phase 1), or if the protocol is clearly deficient in design in meeting its stated objectives. Great care is taken to ensure that this determination is not made in isolation, but reflects current scientific knowledge, agency experience with the design of clinical trials, and experience with the class of drugs under investigation.

The definitions more directly link the role of Phase 2 trials in providing the "preliminary evidence" needed to move into Phase 3 trials where larger numbers of patients are exposed to the investigational agent thereby warranting a greater degree of confidence around the safety and effectiveness of the drug. The safety and effectiveness of a drug is determined, in large part, on a comprehensive

[2] https://www.fda.gov/drugs/investigational-new-drug-ind-application/drug-development-and-review-definitions

understanding of the relationships around dose, drug concentration in the blood (pharmacokinetics), and clinical response.

These fundamental principles are recognized, not just by the FDA, but by regulatory bodies around the world. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) generates consensus guidelines that are followed by regulators "worldwide to ensure that safe, effective and high quality medicines are developed, and registered and maintained in the most resource efficient manner whilst meeting high standards."[3]

One of the core ICH-developed guidelines for industry is "ICH-E4 Dose-Response Information to Support Drug Registration."[4] The guidance, endorsed and adopted by the FDA, includes the following key tenants for drug development:

> Assessment of dose-response should be an integral component of drug development with studies designed to assess dose-response an inherent part of establishing the safety and effectiveness of the drug.[5]
>
> Conducting dose-response studies at an early stage of clinical development may reduce the number of failed Phase 3 trials, speeding the drug development process and conserving development resources.[6]
>
> It is prudent to carry out dose-ranging or concentration-response studies early in development as well as in later stages in order to avoid failed Phase 3 studies or accumulation of a database that consists largely of exposures at ineffective or excessive doses.[7]
>
> Dose-response data for both beneficial and undesirable effects may provide information that allows approval of a range of doses that encompass an appropriate benefit-to-risk ratio. A well-controlled dose-response study is also a study that can serve as primary evidence of effectiveness.[8]

III. FDA Guidance on Psychiatry Drug Development

While the FDA has not issued drug development guidance specific to the treatment of anxiety symptoms, it has done so for other disease areas within the jurisdiction of the Division of Psychiatry.[9]

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[3] https://www.ich.org/

[4] https://www.fda.gov/media/71279/download

[5] Ibid. at 5.

[6] Ibid. at 7.

[7] Ibid. at 13.

[8] Ibid. at 14.

[9] The Division of Psychiatry regulates and reviews Investigational New Drug (IND) applications and marketing applications for products for the treatment of psychiatric diseases and conditions, such as bipolar disorder, schizophrenia, schizoaffective disorder, major depressive disorder, attention deficit hyperactivity disorder, obsessive-compulsive disorder, panic attacks, posttraumatic stress disorder, generalized anxiety disorder, autism spectrum disorder, and insomnia.

In both its draft guidance, "Major Depressive Disorder: Development Drugs for Treatment,"[10] and "Attention Deficit Disorder: Developing Stimulant Drugs for Treatment,"[11] the FDA stresses the importance of dose-finding.

In its Major Depressive Disorder (MDD) guidance, the FDA notes the following clinical pharmacology considerations:

> Characterization of a drug's pharmacokinetics and pharmacodynamics in early phase development is critical to assist identification of rational doses and dosing intervals for the phase 3 trials, and to develop drug switching strategies. Different types of antidepressants, such as the rapid-acting drugs under development, are likely to have different pharmacokinetic and pharmacodynamic properties that may involve specific studies and methods of analysis.
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> For all antidepressants, sponsors should conduct pharmacodynamic studies, such as in vivo receptor binding studies or biomarker studies, to initially identify appropriate dosage ranges, and these should be followed by clinical endpoint dose-response studies. Sponsors generally should include at least one dose-finding trial using a fixed-dose design with at least three doses. Sponsors can apply dose-response or exposure-response modeling and simulation to integrate the information obtained in early phase clinical trials and to inform dosing regimen selection for phase 3 trials.[12]

Depression and anxiety share many commonalities in terms of the subjective nature of the endpoints utilized for assessing efficacy, the importance of understanding duration of drug effect, and the target patient population as many individuals with depression have generalized anxiety as a comorbidity. As such, many of the underlying PK/PD considerations for depression drug development are also relevant for development of new drugs for treatment of anxiety. As discussed later in this memo, there is less precedent for novel therapies conducting these fundamental clinical pharmacology studies in anxiety specifically because many of the approved therapies for anxiety were first approved for different indications. As such, subsequent label expansion in indications like GAD have relied on the previous findings from the initial approval, which makes the anxiety indication itself seem far more streamlined from a clinical data perspective than it is in reality for a novel drug seeking its first indication in the disease area.

This has been less of the case in Attention Deficit Disorder (ADD), where novel therapies have come to market with ADD as the lead approved indication (see discussion below on regulatory precedents for novel CNS drugs). The FDA's ADD guidance shares many of the same clinical pharmacology principals as the MDD guidance:

> In general, central nervous system stimulant drugs demonstrate a strong concentration-response relationship for efficacy and safety (Kimko et al. 2012; Li et al. 2017). Therefore, sponsors can develop formulations using the same active moiety with the objective of creating drug product-specific release features intended to affect the shape of the pharmacokinetic (PK) profile and the onset or duration of effect. Various clinical and clinical pharmacology trials may

[10] https://www.fda.gov/media/113988/download
[11] https://www.fda.gov/media/124334/download
[12] MDD Guidance, 3-4.

be of value in the clinical development program based on the characteristics of the active moiety, formulation features, and clinical experience.

IV. Assessment of FDA Feedback on MM-120 to Date

Greenleaf conducted a clinical and regulatory assessment of the MM-120 development program with a focus on the steps MindMed has taken to advance the asset based on the broader framework outlined above and the specific guidance the company has received from the FDA.

Program Background & Utility of Prior Investigator-Initiated Studies

MM-120 is a semisynthetic product of lysergic acid. The prior published human and nonclinical experiences with LSD to date have primarily been with a LSD free base solution, while MindMed is developing the tartrate salt of D-lysergic acid diethylamide for solid oral administration.

LSD was first synthesized in 1938 and the psychoactive effects of the drug were discovered in 1943. While there is a long history of recreational use and academic study of LSD in various diseases and clinical settings, it has never been formally studied under a US industry-sponsored IND in clinical trials overseen by the FDA. Additionally, LSD is a Schedule I substance under the Controlled Substances Act, which is a classification indicating it has no currently accepted medical use and a high potential for abuse.[13] As such, any studies of LSD require a Schedule I research license and compliance with all Drug Enforcement Administration regulations for the use, manufacturing, handling, and storage of a Schedule I drug.[14]

In recent years, there have been some promising findings around use of LSD as a treatment for anxiety.

In 2014, the Journal of Nervous and Mental Disease published results from a double-blind, randomized, active placebo-controlled pilot study of LSD-assisted psychotherapy in 12 patients with anxiety associated with life-threatening diseases. Treatment included drug-free psychotherapy sessions supplemented by two LSD-assisted psychotherapy sessions 2 to 3 weeks apart.[15] The participants received either 200 μg of free-base (LSD (n = 8) or 20 μg of LSD (n =4), which was intended to serve as an active placebo. Three of the four patients on 20 μg crossed over to 200 μg of LSD after the initial blinded treatment was unmasked. At the 2-month follow-up, there were positive trends in reduction in trait anxiety reported in the 200 μg arm vs the active placebo arm as measured by the State-Trait Anxiety Inventory (STAI). The study also reported no acute or chronic adverse effects persisting beyond 1 day after treatment or treatment-related serious adverse events. STAI reductions were sustained for 12 months without further dosing in those patients on the 200 μg dose, however these assessments occurred after the treatment assigned for the two LSD assisted psychotherapy sessions had been unblinded. The authors acknowledged the limits of the study including the small sample size and imperfect blinding (all patients accurately guessed their dose assignment).

In 2022, the Society of Biological Psychiatry published the results of an investigator-initiated 2-center trial that used a double-blind, placebo-controlled, 2-period, random-order, crossover design with 2

[13] https://www.dea.gov/drug-information/drug-scheduling
[14] 21 CFR part 1301-1301.18 Research protocols.
[15] Gasser, *J Nerv Ment Dis 2014;202: 513-520.*

sessions with either LSD in solution (200 μg) or placebo per period.[16] The primary endpoint was anxiety symptoms 16 weeks after the last treatment session, assessed by the STAI score in 42 patients. LSD treatment resulted in significant reductions of STAI scores up to 16 weeks with similar effects observed for ratings of comorbid depression.

Neither of the clinical trials referenced above were dose-ranging studies and we are aware of no modern data demonstrating clinical response to doses of LSD other than 20 or 200 μg.

There have been dedicated PK studies of LSD in healthy volunteers, with a 2021 publication in *Neuropsychopharmacology* exploring the same four doses that MindMed has included in its ongoing Phase 2b clinical trial.[17] The study was a double-blind, randomized, placebo-controlled, crossover design in 16 healthy subjects who underwent six 25-hour dosing sessions and received placebo, LSD (25, 50, 100, and 200 μg), or 200 μg LSD 1 hour after administration of ketanserin (40 mg). In this study, LSD was administered as a free base in solution. The study reported that LSD showed dose-proportional pharmacokinetics and first-order elimination and dose-dependently induced subjective responses starting at the 25 μg dose. A ceiling effect was observed for "good drug effects" at 100 μg. The 200 μg dose of LSD induced greater ego dissolution than the 100 μg dose and also induced significant anxiety during the dosing session. The average duration of subjective effects increased from 6.7 to 11 hours with increasing doses of 25–200 μg. LSD moderately increased blood pressure and heart rate. Ketanserin, administered to confirm the expected mechanism of action of LSD, was reportedly effective in preventing the perceptual response to 200 μg LSD. The LSD dose–response curve showed a ceiling effect for subjective good effects, and ego dissolution and anxiety increased further at a dose above 100 μg. The authors concluded that these results may assist with dose finding for future LSD research.

As for any novel study drug, the FDA is likely to view the prior published literature around LSD use for the treatment of anxiety as informative and hypothesis generating but not of sufficient detail to allow for an independent review or for regulatory decision making. This is particularly true for LSD given the lack of dose-finding in patients with anxiety and given that the various dosage forms utilized in the published studies do not match what MindMed has developed or intends to use as its to-be-marketed formulation. For the FDA to rely on data from a study(ies) described in published literature would be difficult. As a first step in such reliance, the FDA would require the sponsor to establish a "bridge" between the drug product proposed for approval and that described in the published literature to demonstrate that such reliance is scientifically appropriate. This would likely be conducted as new studies by the sponsor comparing the freebase form of LSD to the LSD D-tartrate in capsules used in the Phase 2b and then again to the to-be-marketed formulation. Even with such bridging studies, data on clinical response to doses other than 20 or 200 μg are not available, thus the need for dose-ranging studies in the target population (i.e. GAD) would remain.

Thus, as currently presented, the published studies are not adequate to establish efficacy or dose-finding for LSD and do not directly bridge to the form/formulation of LSD being developed by MindMed. Since MindMed is developing a new form/formulation of LSD, these published studies are at best hypothesis generating.

[16] Holze, *Biological Psychiatry February 1, 2023; 93:215–223*

[17] Holze, *Neuropsychopharmacology (2021) 46:537–544*

Phase 2 Study Design & FDA Feedback

MindMed has an ongoing Phase 2b, multi-center, randomized, placebo-controlled, double-blind, parallel-group, dose-finding clinical trial to assess 4 doses of MM-120 (25, 50, 100 or 200 µg freebase-equivalent) for the treatment of anxiety symptoms in subjects diagnosed with GAD.[18] The study is enrolling approximately 200 subjects, 18 years to < 75 years of age, who met certain criteria for GAD based on symptom severity. MindMed has reported that over 100 patients have enrolled to date, and it anticipates completion of enrollment and topline readout by the end of 2023.

In the trial, eligible subjects are randomized in a 1:1:1:1:1 ratio to receive a single dose of either investigational drug (25, 50, 100 or 200 µg MM-120 freebase-equivalent) or placebo in a controlled clinical setting. The primary efficacy endpoint is change in Hamilton Anxiety Rating Scale (HAM-A) Total Score from Baseline to Week 4 with a key secondary of change in HAM-A Total Score from baseline to Week 8. The study is also collecting safety data on adverse events, vital signs (heart rate, blood pressure, respiration rate, temperature), and electrocardiogram readings.

This is a well-designed Phase 2b trial that will provide important dose ranging efficacy data using a primary endpoint that has been previously utilized for regulatory approval in GAD, HAM-A, as opposed to the STAI endpoints used in the published literature. The trial will also provide important safety data at several dose/exposure levels in patients and serve as part of the safety database that will be necessary to support FDA approval for this Schedule 1 NME. Given the limited range of LSD doses studied in prior investigator studies of patients with anxiety (i.e., Gasser study examined only 20 µg and 200 µg, and Holze was a single 200 µg dose), the ongoing Phase 2b clinical trial will generate critical dose-response data over a wide dose range. It will also inform on the hypothesized functional mechanism of action of LSD, specifically the extent to which psychedelic effects mediate anxiety-related clinical outcomes. For each dose, MindMed has been thoughtful in seeking data that could inform future pivotal development:

- 25ug: Threshold dose – minimum dose at which psychoactive effects are perceivable by patients on average.
- 50ug: Dose that is above the psychoactive threshold but unlikely to result in significant "psychedelic effects"
- 100ug: Lower of the two doses that reliably results in a "psychedelic effect" while minimizing side effects
- 200ug: Higher of two doses that reliably results in a "psychedelic effect"[19]

Prior to opening the IND and initiating this study, MindMed obtained formal guidance from the FDA Division of Psychiatry on two separate occasions – a Type B Pre-IND meeting in December 2020, and a Type C Written Response Only (WRO) meeting in May 2021. During these engagements the FDA provided extensive feedback to MindMed on their overall proposed development program (e.g., CMC, toxicology, clinical plans) and raised a number of issues for further consideration and refinement. Despite this, subsequent to these interactions and following submission of the IND, the FDA placed the program on Full Clinical Hold on December 22, 2021, and provided additional feedback on the proposed Phase 2 protocol.

[18] Greenleaf notes that Phase 2a and Phase 2b descriptors are not official regulatory terms but are generally employed to describe early versus later studies in Phase 2 of development.

[19] Phase 2 Clinical Study Protocol.

Below is Greenleaf's assessment of each of these interactions, but as a whole the level of FDA engagement and feedback on the proposed indication, target population, efficacy endpoints, study design, and study conduct indicate an expectation by the FDA for a measured approach in the development of MM-120. This is to be expected for a novel medical product generally, and especially for a Schedule I NME drug substance. FDA's feedback on the proposed development program in no way suggests that the FDA would accept a development program that skips important learnings from a well-designed and conducted Phase 2b trial in favor of moving directly to a large Phase 3 pivotal program.

Indication & Target Population

In MindMed's correspondence with FDA prior to submission of its IND, FDA provided extensive feedback on the need for definition of the target treatment population. FDA's feedback was consistent with their general concern about narrowly limiting the proposed indication for a drug, particularly a drug likely to be used in a broader patient population if subsequently approved. FDA also emphasized "the need for a well-defined, clinically meaningful, and reliable construct when determining an appropriate indication for a drug."[20]

FDA additionally gave feedback with respect to the inclusion of multiple populations in a single clinical trial (as were included in the academic studies of LSD) noting that a single study would "introduce an unacceptable degree of variability and may yield results that are difficult to interpret."[21]

We point out these exchanges not for the purpose of providing a particular perspective on the most appropriate indication for development, but to highlight the complexities and stepwise process required in drug development to define a program's objectives prior to generating the pivotal data required for approval. To enter Phase 3 without a well-articulated target population and indication could result not only in misalignment with the FDA, but more importantly the potential for a Phase 3 program that is difficult to interpret and thus more likely to fail. It could also result in a Phase 3 trial that the FDA could place on clinical hold (i.e., suspension of any ongoing investigation of a therapy) if "the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives."[22]

With these considerations having been addressed, it appears that the ongoing Phase 2b clinical trial is designed to answer key questions and provide clarity and confidence in designing a Phase 3 program that, if executed properly, will increase the chances for a successful regulatory outcome.

Efficacy Endpoints & Study Design

Similar to the process for defining a target population and proposed indication, reaching alignment with FDA on the design of the initial IND study for a novel therapy is a critical step to the future success of the program. In the pre-IND meeting, MindMed and FDA discussed study blinding considerations and primary efficacy endpoints. FDA provided further feedback in the Type C WRO minutes around avoidance of functional unblinding in the Phase 2 study and strategies to address those concerns to preserve data interpretability.

[20] Ibid. Question 1 Discussion.
[21] Type C WRO Minutes, FDA Response to Question 2.
[22] 21 CFR 312.42(b)(2)(ii).

As noted above, upon submission of the IND, the MM-120 program was placed on a full clinical hold. The hold issue itself was relatively straightforward and easily remediated through protocol revisions around the need to ensure proper dosing session monitoring of patients. However, included in the hold letter were a number of non-hold issues that highlight the range of clinical data expectations that the FDA wants addressed prior to Phase 3. The clinical pharmacology and clinical issues/recommendations, included:

- Collection of PK samples around expected Tmax on Day 1 to facilitate future exploration of dose/exposure-response for acute effects
- The need to evaluate food effect on the final to-be marketed formulation
- Justification for enrolling and randomizing 200 patients in the Phase 2 dose-finding study
- Considerations around use of the HAM-A over the Structured Interview Guide for the Hamilton Anxiety Rating Scale (SIGH-A) as the primary efficacy endpoint
- Considerations around the potential use of niacin as an active comparator in the Phase 2 study
- Inclusion/exclusion criteria for subject enrollment

While all of these variables are addressable by MindMed as part of the development program, each has the potential to impact data interpretability and to inform subsequent trial design. Additionally, the clinical hold itself coupled with the extensive protocol feedback from the FDA indicates to us that the FDA would have had serious reservations about proceeding directly into a large Phase 3 pivotal trial before preliminary efficacy and safety data were generated across the doses proposed.

FDA Requirements for Substantial Evidence of Effectiveness & Safety Database

"Substantial evidence" of effectiveness is a statutory standard that refers to both the quality and the quantity of evidence required for approval. FDA guidance, "Demonstrating Substantial Evidence of Effectiveness for Human Drugs and Biological Products," outlines the potential pathways to provide "substantial evidence" in a development program – (1) "two adequate and well-controlled trials; (2) one adequate and well-controlled trial plus confirmatory evidence; or (3) reliance on a previous finding of effectiveness of an approved drug when scientifically justified and legally permissible (i.e., no new effectiveness or pharmacodynamic data would be needed)."[23]

In the pre-IND meeting minutes, the FDA noted the following, "LSD has no prior approval history. You should plan to provide substantial evidence of effectiveness based on two adequate and well-controlled trials."[24]

To support FDA approval, the MM-120 program will need at least one, and more likely two, positive, adequate and well-controlled trials. The decision by MindMed to first initiate a dose-ranging Phase 2b study is appropriate and sound from a clinical and regulatory perspective. Further, it should be noted that the substantial evidence guidance does not differentiate between Phase 2 and Phase 3 trials when discussing the need for adequate and well-controlled trials. The ongoing Phase 2b dose-ranging trial, depending on the robustness of its findings, might ultimately be considered one of the two adequate and well-controlled trials, or confirmatory evidence, needed for approval if coupled with an equally

[23] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/demonstrating-substantial-evidence-effectiveness-human-drug-and-biological-products

[24] Pre-IND Meeting Minutes, FDA Response to Question 2.

robust and clinically meaningful Phase 3 trial. This would, of course, be a topic for discussion with FDA as development progresses.

Additionally, the FDA will expect MM-120 to have robust safety data in patients treated with MM-120 at or above the to-be-marketed dose. Safety requirements will also be influenced by how the MM-120 program continues to evolve (i.e., as a one-time acute therapy or a drug that patients will continue to receive episodically). The FDA expectations regarding the required safety database to support approval directly align with MindMed's plans to explore dose ranging for efficacy and safety in the ongoing Phase 2b trial.

Regulatory Considerations related to MM-120 Status as a New Molecular Entity

As noted above, an MM-120 approval would represent the first time an LSD derived therapy has been approved for any indication and would thus be considered an NME. The proposed drug product contains an active moiety that FDA has not previously approved, either as a single ingredient drug or as part of a combination product. While the substantial evidence criteria for an NME is technically not different from the requirements for new indications of previously approved products, the level of comprehensiveness required for the New Drug Application (NDA) and corresponding regulatory scrutiny is heightened because there are no prior findings of safety or effectiveness to rely on or leverage as supporting evidence.

As noted above, there have been very few NMEs approved for anxiety. For reference, the last novel drug to receive its initial FDA approval for treatment of anxiety was Buspar (buspirone hydrochloride) in 1986.

The following table represents other NME approvals within the Division of Psychiatry over the past 10 years. All of the programs required multiple adequate and well-controlled studies to support approval, whether it be two or more adequate and well-controlled Phase 3 studies or a Phase 3 study plus confirmatory evidence from Phase 2 studies and PK bridging. For the Phase 2b trials, all included multiple doses of investigational drug.

Approval Date	**Product**	**Indication**
01/07/22	Quviviq (daridorexant)[25]	Treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.
05/28/21	Lybalvi (olanzapine and samidorphan)[26] Note: Samidorphan was added to previously approved olanzapine to prevent weight gain, not as an active treatment for schizophrenia itself.	Treatment of: - schizophrenia in adults - bipolar I disorder in adults - Acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate

[25] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/214985Orig1s000IntegratedR.pdf
[26] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213378Orig1Orig2s000MultidisciplineR.pdf

Approval Date	Product	Indication
		- Maintenance monotherapy treatment
03/02/2021	Azstarys (serdexmethylphenidate and dexmethylphenidate)[27] Note: Serdexmethylphenidate is a prodrug of previously approved methylphenidate. Both are dosed on a patient-driven flexible dosing schedule, limiting the need for a dedicated dose ranging study.	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in patients 6 years of age and older.
12/20/19	Caplyta (lumateperone)[28]	Treatment of schizophrenia in adults.
03/19/2019	Zulresso (brexanolone)[29] Note: Designated as a Breakthrough Therapy	Treatment of postpartum depression (PPD) in adults.
12/20/19	Dayvigo (lemborexant)[30]	Treatment of adult patients with insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.
04/29/16	Nuplazid (pimavanserin)	Treatment of hallucinations and delusions associated with Parkinson's disease psychosis.
10/05/15	Aristada (aripiprazole lauroxil)[31] Note: A prodrug of previously approved aripiprazole	Treatment of schizophrenia
09/17/15	Vraylar (cariprazine)[32]	Treatment of schizophrenia and acute treatment of manic or mixed episodes associated with bipolar I disorder.
07/10/15	Rexulti (brexpiprazole)[33]	- Adjunctive treatment of major depressive disorder (MDD). - Treatment of schizophrenia.
08/13/14	Belsomra (suvorexant)[34]	Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

[27] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/212994Orig1s000MultidisciplineR.pdf
[28] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/209500Orig1s000MultidisciplineR.pdf
[29] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211371Orig1s000MultidisciplineR.pdf
[30] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/212028Orig1s000MultidisciplineR.pdf
[31] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/207533Orig1s000MedR.pdf
[32] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/204370Orig1Orig2s000MedR.pdf
[33] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/205422Orig1Orig2s000MedR.pdf
[34] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/204569Orig1s000MedR.pdf

Approval Date	Product	Indication
09/30/13	Trintellix (vortioxetine)[35]	Treatment of major depressive disorder (MDD)

We also note the 2018 FDA approval of Spravato (esketamine) for treatment resistant depression (TRD). While not an NME by definition, as ketamine was previously approved by FDA in 1970 as a rapid-acting general anesthetic, it further illustrates the clinical expectations of a psychiatric therapy. As FDA noted in its Medical Review, "TRD is a life-threatening, severely impairing and, by definition, difficult-to-treat condition; in this instance, we must strongly consider the public health benefit to providing this medication without further delay to the population of patients who may improve."[36] Against that backdrop, the FDA still required substantial evidence of effectiveness and a robust safety database in the form of the following clinical trials:

- Phase 2 randomized, placebo-controlled, sequential parallel comparison design dose-response study of two doses of esketamine (n=40)
- Phase 2 two-panel, double-blind, placebo-controlled study to assess safety and efficacy in treatment-resistant depression (n=108)
- Phase 2 double-blind, randomized, placebo-controlled study to evaluate the efficacy and safety of IN esketamine for rapid reduction of symptoms of major depressive disorder (n=68)
- Five Phase 3 trials -- 3001 (TRANSFORM-1, fixed-dose, adult, parallel-group study), 3002 (TRANSFORM-2,flexible-dose, adult, parallel-group study), 3003 (SUSTAIN-1, adult randomized withdrawal maintenance study), 3005 (TRANSFORM-3, flexible-dose, geriatric, parallel-group study), and 3004, a long-term (>1 year) open-label study
- The combined cumulative exposure to esketamine in the five completed Phase 3 studies was 601 patient-years.

In a disease that FDA acknowledged as serious and life-threatening, and for which it granted esketamine breakthrough therapy designation, the clinical data package for approval still required multiple Phase 2 trials (which included dose-ranging) and five Phase 3 trials.

Competitive Landscape

Psilocybin is another Schedule I product undertaking a formal clinical development program in the pursuit of FDA approval. Compass Pathways completed a Phase 2b trial in n=233 subjects testing three different doses of psilocybin in MDD. It is now being investigated in a single dose monotherapy Phase 3 trial and a fixed repeat dose monotherapy Phase 3 trial in n=255 and n=568 patients, respectively.[37]

While in a different indication, psilocybin provides further support for the regulatory strategy being employed by MindMed of a well-constructed Phase 2b trial to inform the design and execution of a Phase 3 program.

[35] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/204447Orig1s000MedR.pdf
[36] https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211243Orig1s000MedR.pdf
[37] https://ir.compasspathways.com/static-files/3fc3f186-4732-4f08-b8d6-67ce9a84b3f9

Conclusion

After review of the MM-120 regulatory history, relevant regulatory precedent, and applicable regulations and guidance, Greenleaf believes MindMed's ongoing Phase 2b dose-ranging clinical trial is an essential component to the development program for MM-120. The effectiveness and safety of a drug are determined, in large part, on a comprehensive understanding of relationships around dose, drug concentration in the blood (pharmacokinetics), and clinical response. A program to pursue first approval for a novel therapy is highly complex, requiring a stepwise process to explore and refine knowledge about the investigational agent to support the ultimate goal of generating the pivotal data regarding effectiveness and safety required to support approval.

The ongoing MM-120 Phase 2b trial is designed to address fundamental questions about dose-response, target population, preliminary evidence of efficacy on accepted FDA endpoints for anxiety, and safety that will provide clarity and confidence in designing a Phase 3 program. FDA's feedback on the proposed development program in no way suggests that the FDA would accept a development program that skips important learnings from a well-designed and conducted Phase 2b trial in favor of moving directly to a large Phase 3 pivotal program. To initiate Phase 3 trials before these foundational issues have been adequately addressed would substantially increase the chances of a failed trial and/or uninterpretable results. It also risks FDA placing the program on clinical hold if the FDA determines that "the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives."[38]

[38] 21 CFR 312.42(b)(2)(ii).