CLINICAL CONSIDERATION OF 5-MeO-DMT

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BACKGROUND

5-MeO-DMT Research Interest

- **Potent Naturally Occurring Psychoactive Alkaloid**
  - Potential to induce acute and profound altered consciousness[1]
  - Found in parotid gland secretions of *Incilius alvarius*
  - Present in virola resin, peregrina seeds, *Dictyoloma incanescens*
    - 5-MeO-DMT-containing snuff used as an entheogen by indigenous South American peoples for centuries
- **Mechanism of Action Not Well Described**
  - Interacts with many CNS receptors (polypharmacology)
  - Uniquely selective for 5-HT_{1A} receptor subtype[2]
  - Potentially active metabolite (bufotenine)
  - Promotes neurogenesis and reduces inflammation *in vitro*[3,4]
- **Subjectively Unique Psychedelic**
  - Short duration, typically less than 1h; poor oral bioavailability
  - Reported to induce a unique state of altered consciousness and awareness which may support a number of potential therapeutic utilities.[5,6]

Initiating 5-MeO-DMT Clinical Study

5-MeO-DMT has unique pharmacology and a history of anecdotal human use suggesting potential psychotherapeutic utility. To empirically determine measures of safety and efficacy, controlled studies to support human clinical trials are necessary.

5-MeO-DMT vs. Psilocybin (psilocin)

Clinical trials to evaluate the therapeutic efficacy of psilocybin are currently underway. Despite similarity in structure, several key differences distinguish 5-MeO-DMT from psilocybin (or its active metabolite psilocin).

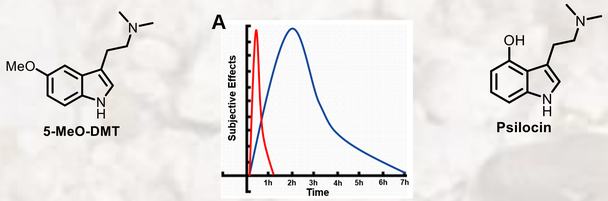

Figure 1 **A)** Approximate subjective experience time course for 5-MeO-DMT (red) versus psilocybin (blue). **B)** Normalized CNS receptor binding affinity profile for 5-MeO-DMT (top) versus psilocin (bottom).[2]

DESIGN

FDA Investigational New Drug (IND) Application Enabling Activities

Drug-related

- ✓ Identify Scalable Synthetic Route
- ✓ Develop Analytical Methods
- ✓ Fully Characterize Compound
- ✓ Identify Route of Administration and Formulation

Preclinical Studies

- Toxicology
- Safety Pharmacology
- Genotoxicity
- Primary / Secondary Pharmacodynamics
- ADME / Drug-drug Interactions

Synthetic Design

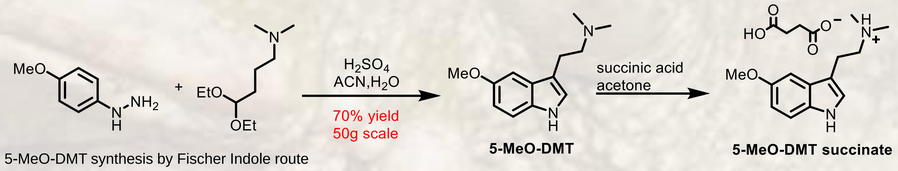

Figure 2: 5-MeO-DMT synthesis by Fischer Indole route

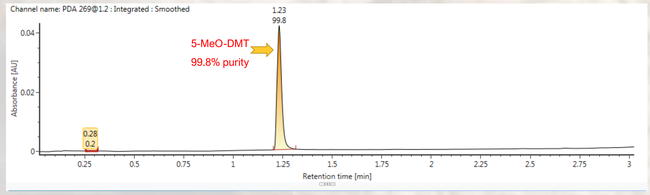

Figure 3: UPLC chromatogram and high-purity 5-MeO-DMT crystal

Route of Administration Selection

5-MeO-DMT is subject to rapid first-pass metabolism by monoamine oxidase and is not orally active. The most commonly reported route of administration is by vaporization of the freebase drug, which is not a pharmaceutically acceptable approach. An intramuscular injection of 5-MeO-DMT has been identified as the most preferable dosage form.

Route / Dosage Form	Pros	Cons
Intramuscular Injection	• Avoid first pass metabolism • High bioavailability • Precise control of dosage • Gentle onset, slightly longer duration of effects	• Additional burden on manufacturing sterile product
Intravenous Injection	• Avoid first pass metabolism • Complete bioavailability • Precise control of dosage	• Additional burden on manufacturing sterile product • Very rapid onset • High dose-sensitivity
Metered Dose Inhalation	• Favorable route for patient acceptance • Ease of administration • Avoid first pass metabolism • Similar route / exposure compared to anecdotal use	• More complex drug delivery systems • Very rapid onset • Challenging to control dosage
Dry Powder Inhalation		
Buccal / Sublingual	• Ease of administration • Avoid first pass metabolism	• Intrinsic dose/absorption limits • Absorption may not be rapid enough
Oral	• Ease of administration • Ease of formulation	• First pass metabolism – 5-MeO-DMT not orally active • Elongated PK curve

PLAN

Pre-clinical Studies to Determine Safety

Toxicology	• Safe Dose (animal)
Safety Pharmacology	• Respiratory • CNS • hERG • ECG/CV
Genotoxicity	• LeadScope/DEREK • Ames • Micronucleus • Chromosomal aberration
Primary PD	• Target binding/affinity
Secondary PD	• Off-target binding
Absorption, Distribution, Metabolism, Excretion (ADME)	• Plasma protein binding • Blood partitioning • Pharmacokinetic Study • Transporter substrate • Hepatocyte met ID
Drug-Drug Interactions (DDI)	• CYP induction • CYP inhibition • Transporter inhibition

"First-in-Man" Clinical Study Approach

Patient Population	Experienced psychedelic users
Objectives	1. *Determine the human safety of 5-MeO-DMT* 2. *Determine the human PK & metabolic profile of 5-MeO-DMT* 3. *Determine the mystical experience occasioned by 5-MeO-DMT* 4. *Determine the 5HT receptor binding of 5-MeO-DMT*
Safety	Physical Examination, Vital Signs, Labs (CBC, CMP, Urinalysis), UPT, Holter ECG
Pharmacokinetics	Serial blood and urine sampling
PD-biomarker	5-HT_{1A} and/or $5HT_{2A}$ PET imaging
Pharmacodynamic Activity	PROs: Hallucinogen Rating Scale, revised 5-Dimension Altered States of Consciousness questionnaire, Mystical Experience Questionnaire, Challenging Experiences Questionnaire, and Psychological Insight Questionnaire. Investigator-Completed: Brief Psychiatric Rating Scale, the Scale for Assessment of Negative Symptoms, Scale for Assessment of Positive Symptoms
Doses	*tbd*
Controls	Randomized (5:1), Double-Blind

Conclusion and Direction

- **5-MeO-DMT may hold potential as a novel psychotherapeutic tool**
- **Initiation of human clinical trials with 5-MeO-DMT will require a multi-pronged effort to:**
  - **1) Provide consistent high-quality cGMP 5-MeO-DMT**
  - **2) Formulate 5-MeO-DMT appropriately for intramuscular injection**
  - **3) Conduct preclinical experiments to rigorously ensure patient safety**
  - **4) Effectively design the clinical program to assess safety, PK/PD and clinical activity**

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