Pilot, Dose-Finding Study of Kratom Alkaloids: Study Design Updates

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Disclaimer

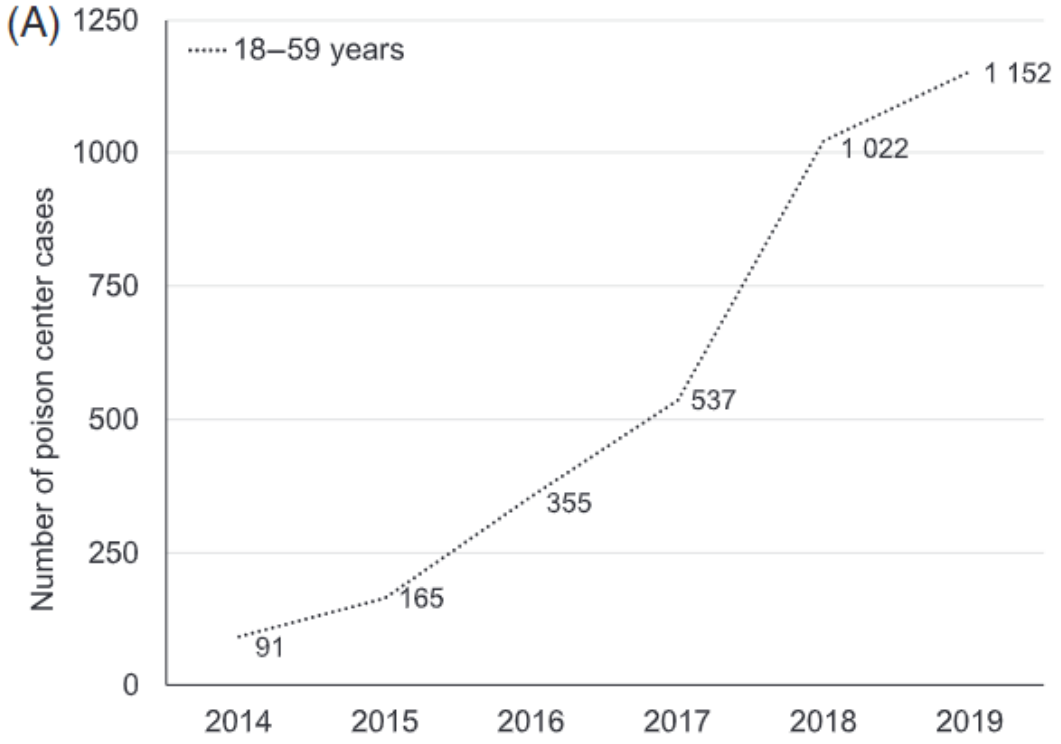
Opinions expressed in this presentation are my own and do not necessarily reflect the views and policies of the FDA

I have no conflicts of interest to report

Kratom

- According to the 2021 National Survey on Drug Use and Health (NSDUH), an estimated 0.6% of individuals (~1.7 million people) reported using kratom in the past 12 months

- Reports of kratom exposures to poison control centers have also increased 2014-2019
  - Graves et al., 2021 J. Am Geriatr Soc 69 (8): 2176-2184



Clinical Kratom Research

- Controlled, well-designed human studies of kratom are sparse despite increasing interest and use of kratom
  - e.g., Trakulsrichai et al. (2015), Balasingam et al. (2020), Tanna et al. (2022)
- A pilot, dose-ranging and safety study was desired by FDA to gain preliminary data on kratom's effects in humans
  - Contract was awarded to AltaSciences on 9/30/2021
  - Study conducted by Vince and Associates

Study Design

- Single, ascending dose (SAD) design
  - Orally administered, botanical kratom (i.e., encapsulated, raw leaf)
  - The kratom material used in our study was from a single source and well-characterized as to composition and impurities
  - The kratom used did not have alkaloid levels found to be present in *some* marketed kratom products
  - Thus, the results might not be representative of drug effects associated with other kratom-related products in the marketplace
- Primary objective: evaluate the safety and tolerability of single, ascending, oral doses of kratom relative to placebo
- Secondary objectives:
  - To evaluate the pharmacokinetics (PK) of mitragynine, 7-hydroxy-mitragynine, paynantheine, speciogynine, mitraciliatine, corynantheidine, and speciociliatine
  - To evaluate the pharmacodynamics (PD) of kratom

Study Design - Key Inclusion Criteria

- Healthy adult male or female subjects
- Current nondependent, polydrug recreational users
  - Used opioid drugs for recreational (nontherapeutic) purposes (i.e., for psychoactive effects) at least 10 times in the subject's lifetime and at least once in the last 12 weeks from screening; and has a history of recreational use of at least 2 or more of any of the perception-altering (e.g., lysergic acid diethylamide [LSD], kratom, cannabis, dronabinol, ketamine, phencyclidine [PCP], dextromethorphan, 3,4 methylenedioxymethamphetamine [MDMA], mescaline, psilocybin, tryptamine derivatives or ring-substituted amphetamines with perception altering effects) or stimulant drugs (e.g., cocaine, amphetamine, methamphetamine, methylphenidate, methcathinone, and other synthetic cathinones) on at least 5 occasions in the subject's lifetime
- Other, standard criteria (e.g., signed ICF, use of appropriate contraceptives etc.)

Study Design - Key Exclusion Criteria

- Difficulty swallowing capsules
- Sensitivities to kratom
- Significant disease (e.g., history of significant hepatic, renal, cardiovascular, pulmonary, hematologic, neurological, psychiatric, gastrointestinal, endocrine, immunologic, ophthalmologic, or dermatologic disease)
- History of substance or alcohol moderate to severe use disorder (excluding nicotine and caffeine) within the past 2 years, as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)

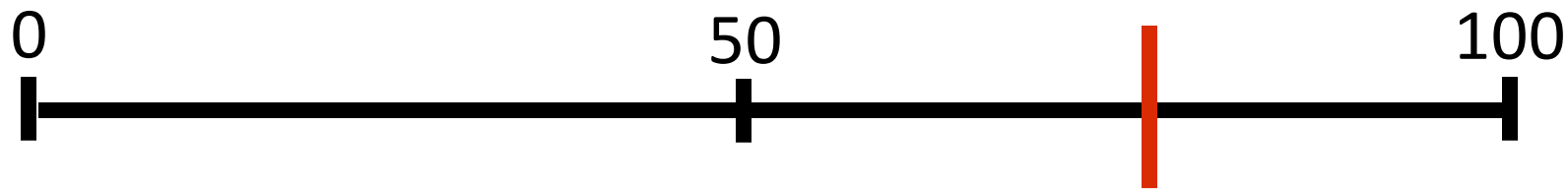
Study Design

- Study was performed under an Investigational New Drug (IND) application
  - Botanical kratom was obtained from Sun Distribution, Super Organics
  - Subjects were dosed using 500 mg, light blue, gelatin capsules (size 00) manufactured under GMP
  - Kratom was administered under “fed” conditions after a high fat meal

Study Design - Pharmacodynamic endpoints

- Drug liking VAS including maximum (peak/Emax) ratings

Do you like the drug effect?



Neither like nor dislike

No, not at all

Yes, very much

Study Design - Pharmacodynamic endpoints

- Drug liking VAS including maximum (peak/Emax) ratings
- Overall Drug Liking VAS (12 and 24 hr)
- Take Drug Again VAS (12 and 24 hr)
- High VAS
- Various other PD effects:
  - Good effects, bad effects, any effects, feeling drunk, drowsiness, relaxation/agitation, Bowdle VAS
- ARCI
- Pupillometry
- PD endpoints were assessed repeatedly after capsule administration

Study Design - Safety Endpoints

- Safety will be evaluated through the assessment of adverse events (AEs), vital signs (blood pressure, pulse, respiratory rate, oxygen saturation, and body temperature), electrocardiogram (ECG), physical examination findings, and Columbia Suicide Severity Rating Scale (C-SSRS)

Study Design - Pharmacokinetic endpoints

- A total of 15 blood plasma samples were obtained
- Timepoints: baseline and 0.25, 0.5, 1, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 8.0, 10, 12.0, 24, 48 hours
- Samples are being processed; no data currently available

Preliminary (blinded) Results

Results

- Kratom composition
  - 6 month stability data

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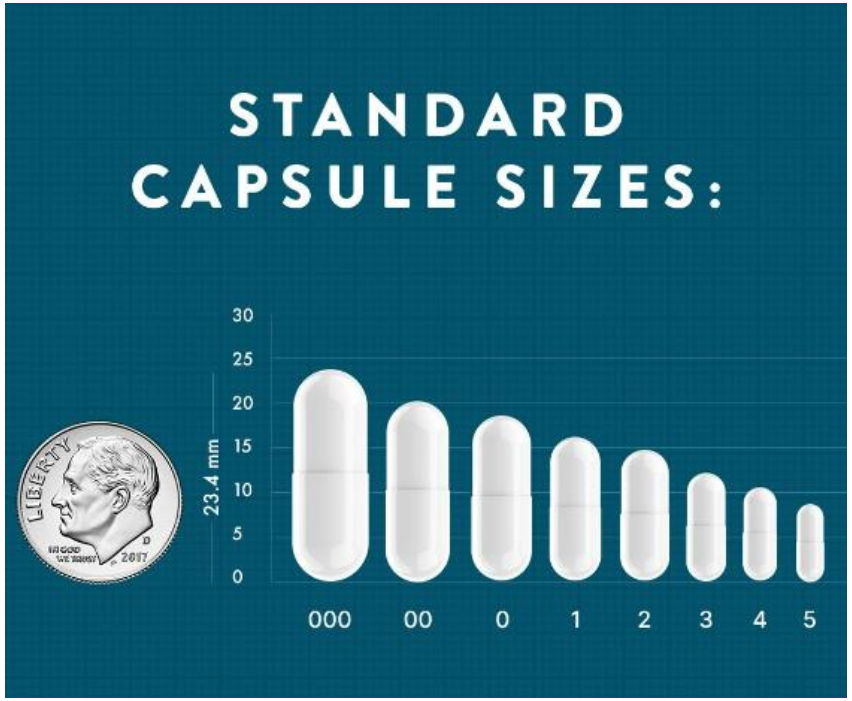
FDA

Alkaloid	Capsule content (mg)#
Mitragynine	5.07 ± 0.71
Speciogynine	0.92 ± 0.13
Speciociliatine	1.98 ± 0.26
Mitraciliatine	0.29 ± 0.04
7-Hydroxymitragynine	BLLOQ
Paynantheine	1.28 ± 0.18
Corynantheidine	0.13 ± 0.02
Corynoxine A	0.04 ± 0.01
Corynoxine B	BLLOQ
Mitraphylline	BLLOQ

*BLLOQ = below the lower limit of quantification (1 ng/mL equivalent to 32 ng/capsule)

Results

- Five (5) cohorts (n=8/cohort) were completed (**2 subjects in each cohort received placebo**)
  - Last subject(s) completed dosing on Jan 17th 2024
- Final dosing regimen was: **1, 3, 8, 10, and 12g** (500 mg capsules)



Results

- This SAD was substantially different than a traditional human abuse potential (HAP) study
- Considerations:
  - Data are still blinded
  - Small sample size
  - No qualification phase
  - No positive control comparator
  - Between-subject design

Safety

- No serious adverse events occurred in dosed subjects
- Nausea and vomiting were observed, but no more than 2 events/dose have been recorded
  - No significant changes in vital signs, ECG, or laboratory evaluations
- No study subject(s) reached "stopping criteria" that were defined as:
    - 1 kratom-related SAE
    - Moderate or severe AEs in 50% of the subjects in the cohort or more

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Preliminary Conclusions

Conclusions

- Data are still blinded but…
- At the doses tested, no SAEs occurred and kratom appeared to be well-tolerated in this study
  - The kratom material used in our study was taken from a single source and well-characterized as to composition and impurities. The kratom used did not have alkaloid levels found to be present in some marketed kratom products
  - Thus, the results might not be representative of drug effects associated with other kratom-containing products in the marketplace
- Further studies are need to determine kratom's comprehensive safety and tolerability profile

Next Steps…

- These pilot data are informative for future studies of kratom
- The PK data may provide additional insight on the time course effects of various kratom alkaloids
- FDA has announced a cooperative agreement for a human abuse potential (HAP) study of kratom
  - Announced 1/16/24: grants.gov/search-results-detail/351644.
  - These pilot data compliment other research activities currently ongoing by FDA; see web page at https://www.fda.gov/news-events/public-health-focus/fda-and-kratom


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