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HUMAN ABUSE POTENTIAL STUDIES

The importance of an expert Drug Development Solution partner in human abuse potential evaluation

"Human Abuse Potential (HAP) studies are procedurally intense, requiring the simultaneous collection of pharmacodynamic, pharmacokinetic, and safety data, such as pupillometry, nasal exams, capnography, and continuous telemetry. Our extensive experience with all aspects of HAP studies, from protocol development to clinical operations, and our robust database of recreational drug users, have allowed us to provide sponsors with high quality data."

Debra Kelsh, M.D.
Senior Principal Investigator,
Altasciences

FDA TAKES STEPS TO LIMIT THE MISUSE AND ABUSE OF PRESCRIPTION DRUGS

Prescription drugs, including opioid analgesics, are an important component of modern pain management; however, their tendency to produce euphoria in addition to pain relief, allows for misuse and abuse, which can lead to addiction, overdose, and death. Misinformation about the addictive properties of such medications, and the perception that prescription drugs are less harmful than illicit drugs, are additional contributors to the problem.

The FDA has undertaken efforts to help clinicians manage this widespread issue by instating guidelines to better understand the abuse potential of new drugs, and ensure drugs currently on the market are less likely to be abused through the use of abuse-deterrent formulations (ADFs).

The 2017 FDA guidance, Assessment of Abuse Potential of Drugs, states that a broad range of CNS drugs require human abuse potential (HAP) studies, also known as human abuse liability (HAL) studies, to evaluate the abuse liability of drugs in development and to determine the relative risk of abuse before a drug comes to market. HAP studies are clinical pharmacology studies and play a key role in the overall abuse potential assessment of a new chemical entity (NCE) or of a marketed drug if the route of administration is being changed in a manner that may affect its abuse potential. This assessment involves a comprehensive analysis of chemistry, pharmacology, clinical data, and the public health risk associated with the drug. It is conducted on drugs that affect the central nervous system, that are chemically or pharmacologically similar to other drugs with known abuse potential, or that produce psychoactive effects, such as sedation or euphoria. HAP studies are also conducted as proof-of-concept studies to evaluate novel drug formulations that are developed with properties to deter abuse.

Sponsors are encouraged to proactively interact with the FDA and the Controlled Substance Staff (CSS) when conducting such studies by submitting protocols for review, often by the end of Phase II, to obtain advice on design and safety issues, before beginning the study. The CSS evaluates the investigational new drug (IND) information relating to abuse and dependence potential as determined in clinical studies. This includes evaluating the methodology and data from both preclinical and clinical studies. From this information, the CSS determines whether the IND requires additional preclinical or clinical studies designed to address questions about the abuse potential of the drug. Altasciences' recognized experts help clients collate relevant data to determine if such studies are needed or can be waived.

Abuse potential evaluation is also required to evaluate novel formulations designed to specifically reduce or deter abuse of a drug. According to the National Center for Drug Abuse Statistics, 16 million, or 6% of Americans over the age of 12, abuse prescription drugs every year. In addition, many individuals misuse their prescription medications by tampering with the formulation. The FDA has worked to address this problem by encouraging the development of ADFs for opioids and other drugs that are associated with a high risk of abuse. These products are formulated with properties that are expected to meaningfully deter certain types of abuse and/or make abuse more difficult or less rewarding. This allows patients who are in chronic pain to have appropriate access to drugs, such as opioid analgesics, with significantly less risk of abuse through unintended routes, such as intranasal insufflation or injection.

The objective of ADF trials is to assess the ability of the new formulation to be tampered with and abused, by crushing or dissolving traditional medications for the purpose of chewing, snorting, smoking, or injecting the drug to increase exposure and rate of onset, resulting in a more potent high. One potentially important step toward the goal of creating safer opioid analgesics, for example, has been the development of opioid drug products with ADFs.

The FDA's two guidances for the industry, Abuse-Deterrent Opioids – Evaluation and Labeling and General Principles for Evaluating the Abuse Deterrence of Generic Solid Oral Opioid Drug Products, are excellent resources to assist manufacturers who plan to develop and submit an Abbreviated New Drug Application (ANDA) to seek approval of a generic version of a solid oral opioid drug product that references an opioid drug with abuse-deterrent properties described in its labeling. They recommend studies, including comparative in vitro and pharmacokinetic (PK) studies, that the potential ANDA applicant should conduct and submit to the FDA, to demonstrate that a generic solid oral opioid drug product has the same abuse liability as its Reference Listed Drug (RLD), with respect to all potential routes of abuse. The results of such studies help the FDA and the sponsor determine risk management strategies to mitigate risks and help in the determination of the product's schedule.

TYPES OF ABUSE-DETERRENT FORMULATIONS	
Physical/Chemical Barriers	May prevent chewing, crushing, cutting, grating and grinding
Agonist/Antagonist Combinations	Added to release upon manipulation and possibly interfere, reduce or defeat euphoria associated with abuse
Aversion Effects	Added substances to produce unpleasant effects upon manipulation or if taken at higher doses (e.g., nasal irritant)
Delivery System	Drug release designs or methods of drug delivery can offer resistance to abuse (e.g., sustained-release depots)
New Molecular Entities and Prodrugs	NME and prodrugs with different receptor binding profiles that lack opioid activity until transformed in the gastrointestinal tract, or prevent oral overdose by novel means

In addition, the Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy (ER/LA REMS) is a program required by the FDA for all manufacturers of these types of drugs. The goal of the ER/LA REMS is to reduce serious adverse outcomes of inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications.

CONTROLLED SUBSTANCE DRUG SCHEDULING	
DRUG SCHEDULES	**EXAMPLES**
Schedule I	
Drugs with no currently accepted medical use and a high potential for abuse.	Heroin, lysergic acid diethylamide (LSD), marijuana (cannabis), 3,4-methylenedioxymethamphetamine (ecstasy), methaqualone, psilocybin, and peyote.
Schedule II	
Drugs with a high potential for abuse, with use potentially leading to severe psychological or physical dependence.	Combination products with less than 15 milligrams of hydrocodone per dosage unit (Vicodin), cocaine, methamphetamine, methadone, hydromorphone (Dilaudid), meperidine (Demerol), oxycodone (OxyContin), fentanyl, Dexedrine, Adderall, and Ritalin.
Schedule III	
Drugs with a moderate to low potential for physical and psychological dependence. Schedule III drugs abuse potential is less than Schedule I and Schedule II drugs, but more than Schedule IV.	Products containing less than 90 milligrams of codeine per dosage unit (Tylenol with codeine), ketamine, anabolic steroids, testosterone.
Schedule IV	
Drugs with a low potential for abuse and low risk of dependence.	Xanax, Soma, Darvon, Darvocet, Valium, Ativan, Talwin, Ambien, Tramadol.
Schedule V	
Drugs with lower potential for abuse than Schedule IV and consist of preparations containing limited quantities of certain narcotics. Schedule V drugs are generally used for antidiarrheal, antitussive, and analgesic purposes.	Cough preparations with less than 200 milligrams of codeine or per 100 milliliters (Robitussin AC), Lomotil, Motofen, Lyrica, Parepectolin.

ALTASCIENCES' HUMAN ABUSE POTENTIAL STUDY SOLUTIONS

Altasciences' full-service capabilities provide a comprehensive solution in support of HAP studies for NCEs or ADFs. We have conducted close to 50 HAP/substance abuse studies in both the U.S. and Canada. Our research includes studies for stimulants, opioids, cannabinoids, nicotine, and sedative hypnotics.

In order to deal with the specific needs of the subject populations involved in HAP studies, we have designed and built clinical pharmacology units that allow for reconfigurable and adaptable space, including a 30-bed, locked, limited-access, self-contained unit incorporated into the overall footprint of a 140-bed general population research campus – the perfect size and scale to conduct a single clinical trial, especially when managing critical endpoints, monitoring adverse events (AEs), and performing complex medical procedures. It allows sponsors to control every aspect of the study environment as it relates to the special needs of the unique study population or the specific requirements of the protocol.

Our facilities are also ideally suited for studies on addiction behavior, including assessments for craving and withdrawal, abuse liability and the pharmacokinetic analysis of the drugs being studied.

Our clinical research pharmacists have specialized abuse-deterrent preparation and manipulation training, as well as vast experience in formulating and dosing via all routes of administration (including oral, sublingual, intranasal, and parenteral). Their capabilities also include handling and storage of controlled substances, over-encapsulation, manipulation and usability processing of abuse-deterrent oral dosage forms, and the blinding of referenced and comparator products.

We work with clients who are developing CNS compounds to incorporate critical regulatory decisions and requirements as early as possible into their clinical development programs. Our proactive approach and frequent communication with regulatory agencies keep us updated on the latest requirements and allow us to effectively advise our clients on their study design and execution, as well as all matters pertaining to guidances and regulations on abuse potential. Our regulatory team is experienced with IRB requirements for HAP trial approvals, and our various regulatory consulting strategies can provide guidance from the in vitro stage of ADFs through the post-approval process and pharmacovigilance monitoring.

OUR VALIDATED BIOANALYTICAL ASSAYS		
Alprazolam	Diazepam	Naltrexone/6β-naltrexol
Amphetamine Mixed Salts	Doxepin	Nicotine
Asenapine	Eslicarbazepine	OH Carbamazepine
Buprenorphine/Norbuprenorphine	Fentanyl	Olanzapine
Bupropion (and metabolites)	Haloperidol	Oxcarbazepine/2H
Butalbital	Hydrocodone	Oxycodone/Noroxycodone/Oxymorphone
Carbamazepine	Hydromorphone	Quetiapine
Cannabichromene	Lorazepam	Tetrahydrocannabinol (THC)
Cannabidiol	Methylphenidate (chiral method also available)	Tramadol/O-desmethyltramadol
Cannabigerol	Midazolam/1-Hydroxymidazolam	Trazodone
Chlordiazepoxide	Morphine Noroxycodone	Triazolam
Citalopram	M6G	Trimipramine
Clobazam/N-Desmethylclobazam	Naloxone	Zaleplon
Cocaine (and metabolites)	Naloxone 3-glucuronide	11-OH-THC
Codeine (and metabolites)	Naltrexone	

Additional assays can be developed and tailored to your program upon request.

OUR STUDY DESIGN AND PROTOCOL

As per the FDA's guidance, Altasciences' HAP studies are conducted with participants who have experience with recreational drug use in the same pharmaceutical class as the NCE, or with drugs with similar psychoactive properties. These types of participants are enrolled because they are better able to identify subtle differences in the drug effects that are known to be relevant to abuse assessment, such as likability and euphoric effects.

Our inclusion/exclusion criteria for HAP trials also allow cigarette smokers because many recreational drug users are smokers, and excludes individuals with a history of substance or alcohol dependence.

Altasciences' robust database of participants (both recreational drug users and substance abusers) has made rapid enrollment and retention some of our greatest strengths. We are able to overcome recruitment challenges, which is one of the major obstacles for studies of this nature due to the unique patient populations and confinement periods.

The medical oversight for these trials is particularly intense, as the protocols are assessment-heavy, and all participants are required to be seen by an investigator each day they are in-house, even if no assessments are being performed, simply to ensure patient safety and quickly identify AEs.

Data is collected by measuring subjective effects, using visual analog scales (VAS) or other measures, by looking at physiological effects, such as pupillometry, and through the evaluation of safety and pharmacokinetics. Measures include ratings of liking ("at the moment" and "overall") and other participant-rated effects, such as the disposition to take the drug again, drug similarity, price-value assessment, as well as other behavioral and cognitive assessments, and changes in mood states.

Abuse potential studies are assessed by comparing responses to the test drug to those of a placebo and to those of a positive control. AEs, particularly abuse-related AEs of special interest, are collected throughout the trial and provide important information about abuse potential of the test drug in comparison to the positive control and placebo.

Sponsors benefit from our in-house team of recognized experts in abuse potential evaluation. We have a psychiatrist and clinical psychologist who are trained at facilitating the administration and evaluation of various CNS compounds, including psychedelics. Our team of experts is highly versed in the unique attributes of CNS-active drugs and the regulatory requirements for successful drug approvals, including 8-Factor analysis as required by the FDA.

Psychedelics have become increasingly of interest for development in the treatment of several psychiatric illnesses and mental health disorders, and our experts will help guide a clinical development strategy that enables comprehensive evaluation of safety, and pharmacokinetic and pharmacodynamic drug profiles.

Our team of internationally recognized experts in the fields of pharmacology, abuse and addiction, drug development, and regulatory can provide the integral support to build your target product profile and clinical development plan to ensure that comprehensive studies and data are collected early in drug development to help support regulatory milestones and key meetings with the FDA. Ensuring appropriate data collection will help determine whether dedicated studies evaluating QT prolongation, abuse potential, driving impairment, and other studies will be required, or may be waived by regulators. Our team will help strategically evaluate your program to ensure efficiency and timely decision making for drug development and drug approval.

TIPS FOR DESIGNING A HAP STUDY	
Study Objective	To provide information on the relative abuse potential of a new drug in humans, compared with a placebo and an active comparator (controlled substance)
Protocol Preparation	2 to 3 weeks
Timing	Usually initiated in Phase II
FDA Review Timeline	Initiated following the End of Phase II meeting
Study Design Considerations	
Number of Subjects	25 to 50 subjects
Primary Inclusion Criteria	Subjects that have experience with recreational drug use in the same pharmaceutical class, or with using drugs with similar psychoactive properties.
Primary Exclusion Criteria	Subjects that have substance dependence or are in treatment for substance disorders — nicotine and marijuana users may be considered for inclusion, depending on protocol requirements.
Dose Selection: Qualification Phase	Doses are selected based on literature, which shows that the selected dose was previously associated with a positive response in recreational users. Typically, the dose is the same that will be administered in the treatment phase if it is only one dose, or a mid-range dose if administering two doses of the active control.
Dose Selection: Treatment Phase	Typically 2 to 3 doses of the test drug are selected, ranging from a therapeutic dose to supratherapeutic dose.
Positive Control	Typically 2 to 3 doses are selected (high or supratherapeutic). They should have measurable abuse potential previously shown, should be the same class of drug as the drug being studied, and should have known effects on the parameters of abuse potential that are being investigated.
Primary Endpoints	Drug Liking and Drug High assessments
Other Important Endpoints	Good Effects, Bad Effects, Overall Drug Liking, Take Drug Again, Class-specific effects such as alertness/drowsiness VAS, as well as other cognitive assessments, such as choice reaction time.

ALTASCIENCES' CASE STUDY:

Abuse Potential Assessment of the New Dual Orexin Receptor Antagonist (DORA) Daridorexant in Recreational Sedative Drug Users as Compared to Suvorexant and Zolpidem

The high prevalence of insomnia together with the shortcomings of existing therapies highlight a major unmet clinical need for safe, effective, and well-tolerated pharmacological treatments of insomnia or related symptoms. To this end, the orexin receptor has evolved as a promising druggable target for development of sleep-promoting agents with a presumably more favorable benefit/risk profile. In contrast to benzodiazepines or non-BZRAs, DORAs appear essentially devoid of withdrawal effects as reflected in the U.S. labeling information of the approved DORAs suvorexant and lemborexant.

Daridorexant (ACT-541468) is a new, selective, and potent competitive antagonist of the orexin-1 and orexin-2 receptor currently in late-stage clinical development. In healthy participants, favorable PK/PD properties, including quick absorption and elimination, have been determined to lead to absence of next-morning residual effects. In phase II, daridorexant demonstrated dose-dependent efficacy in adult and elderly patients with insomnia. Following treatment cessation, no withdrawal effects were detected based on the Benzodiazepine Withdrawal Symptom Questionnaire after a 30-day treatment period.

Altasciences conducted a randomized, double-blind, double-dummy, placebo- and active-controlled HAP study in recreational sedative drug users, comparing drug-liking and other abuse-related parameters with those of placebo and two positive control drugs, namely suvorexant and zolpidem.

Healthy male and female participants aged 18 to 55 years with a body mass index of 18.0 to 33.0 kg/m^2 were enrolled. Each participant had to be a recreational user of sedatives, defined as at least 10 lifetime occasions of using CNS depressants. Some key study-specific exclusion criteria included a positive urine drug screen at admittance (except for cannabinoids) and a history or presence of substance or alcohol dependence, any treatment of substance- or alcohol-related disorders, or prior participation in a substance or alcohol dependence rehabilitation program.

The core phase of this study had a six-period, crossover design. In each period, a single, oral dose of either daridorexant (50, 100, or 150 mg), suvorexant (150 mg), zolpidem (30 mg), or placebo was administered in the morning. The treatment sequence was randomized applying a 6 × 6 Williams square design to mitigate potential first-order carry-over effects.

Each dosing occurred in the morning under fasted conditions, followed by computerized PD assessments up to 24 hours post each dosing and applying a washout period of ≥72 hours. Participants remained domiciled for the entire duration of the core phase, i.e., until at least 24 hours after last dosing and returned for an end-of-study visit ≥72 hours after last dosing.

The primary PD endpoint was the E_{max} of the bipolar "at-the-moment" drug-liking VAS ranging from 0 (maximum disliking) to 100 points (maximum liking). The drug-liking VAS was assessed at 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 12, and 24 hours post dosing.

Several secondary PD endpoints were collected. The balance of positive and negative effects was assessed based on bipolar and unipolar scales. Perceptual/psychedelic and any effects were assessed based on the unipolar Bowdle VAS and Any Effects VAS, respectively. Sedative effects were measured based on the bipolar Alertness/Drowsiness VAS and the Observer's Assessment of Alertness/Sedation (OAA/S). The drug similarity VAS was determined at 12 hours post each dosing to assess how similar the perceived effects were compared to drugs or drug classes previously used by the study participants for recreational purposes.

Objective cognitive function tests were also applied at 0.5, 1, 2, 4, and 8 hours post dosing using the validated Cambridge Cognition cognitive assessment software.

PK Assessments

Blood samples were taken predose and at 0.25, 0.5, 1, 1.5, 2, 3,4, 5, 6, 8, 12, and 24 h post dosing. Plasma was stored at −70 °C and protected from light. Concentrations of daridorexant were determined using a validated liquid chromatography–tandem mass spectrometry assay with a lower limit of quantification of 0.5 ng/mL.

Safety Assessments

Safety and tolerability were monitored based on repeated assessments of AEs, vital signs, clinical laboratory, 12-lead ECG, and Columbia-Suicide Severity Rating Scale (C-SSRS) data until 24 hours post dosing, and at the end-of-study visit.

Overall, in this large, valid human abuse potential study, daridorexant showed dose-related drug-liking among recreational sedative drug users with lower effects at the highest phase III dose, and similar effects at higher doses compared to supratherapeutic doses of suvorexant and zolpidem.

PIONEERING ONGOING RESEARCH

To protect the public's health, the FDA has prioritized the evaluation of how drugs that are already on the market are used, both for legitimate purposes, and misuse and abuse. Consequently, more research is required to identify factors that predispose some patients to addiction and to develop measures to prevent abuse.

In support of this mandate, Altasciences continues to conduct research on HAP studies for NCEs or ADFs, to broaden the understanding of the abuse potential of certain classes of drugs. As a testament to our knowledge and quality in the conduct of HAP studies, Altasciences was awarded a five-year, $9.5-million contract with the National Institute on Drug Abuse (NIDA) to conduct clinical pharmacology studies to support the development of new medications for the treatment of substance abuse disorders. This contract further confirms the existing relationships we have with regulatory agencies, having previously been awarded approximately $10 million for a multi-year contract with NIDA (2012-2017), a $5-million, five-year contract with the FDA's Center for Drug Evaluation and Research (CDER) to conduct bioequivalence studies of innovator and generic drugs, and a contract in 2015 with the FDA's Office of Generic Drugs (OGD) to conduct a clinical pharmacology and PK study of opioids manipulated via milling procedures.

ALTASCIENCES' RESOURCES

Webinars

Amphetamine to Zoldipem - Navigating the ABCs of CNS Drug Development

Cracking the Pill, a Journey of Exploring Abuse-Deterrent Methods

Strategic Considerations for a Successful CNS Clinical Development Pathway

Navigating Early Phase CNS-Active Drug Development

Assessing Cognition and Driving Ability in Clinical Pharmacology Studies

To Control or Be Controlled, Navigating the Abuse Potential Evaluation of CNS-Active Drugs

The Strategic Use of Cognitive Measures and Biomarkers in Early Phase CNS Drug Studies

The Many Facets of Early Phase Evaluation of Psychedelics in Psychiatry

Podcasts

Developing the Second Generation of Psychedelics and Their Analogues for Targeted Medical Use

The Many Faces of Recreational Drug Use

J Episode 1 J Episode 2

Blog

Psychedelics - Regulatory Environment Challenges

Fact Sheets

Human Abuse Potential Studies for Innovator Medicines

Human Abuse Potential Studies for Generic Medicines

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ABOUT ALTASCIENCES

Altasciences is an integrated drug development solution company offering pharmaceutical and biotechnology companies a proven, flexible approach to preclinical and clinical pharmacology studies, including formulation, manufacturing, and analytical services. For over 25 years, Altasciences has been partnering with sponsors to help support educated, faster, and more complete early drug development decisions. Altasciences' integrated, full-service solutions include preclinical safety testing, clinical pharmacology and proof of concept, bioanalysis, program management, medical writing, biostatistics, clinical monitoring, and data management, all customizable to specific sponsor requirements. Altasciences helps sponsors get better drugs to the people who need them, faster.