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"Human Abuse Potential (HAP) studies are procedurally intense, requiring the simultaneous collection of pharmacodynamic, pharmacokinetic, and safety data, such as pupillometry, nasal exams 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."

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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, because they tend to produce euphoria in addition to pain relief, they can be misused and abused, 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 contributors to the problem as well.

The FDA has undertaken several efforts to help clinicians manage this widespread issue by instating guidelines to better understand the abuse potential of new drugs being developed, and make drugs currently on the market less likely to be abused through the approval 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). 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. Sponsors are encouraged to proactively interact with 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 the potential for abuse and dependence in clinical studies. This includes evaluating the methodology and data in a preclinical or clinical protocol or study report. From this information, the CSS determines whether a drug under review requires additional preclinical or clinical studies designed to address questions about the abuse potential of the drug.

In other instances, sponsors are required to evaluate the effectiveness of an ADF. According to the Academy of Integrative Pain Management, over 95% of patients are using their medications appropriately, while others are tampering with standard formulations to achieve heightened psychological or physiological effects. 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 in an ANDA, to demonstrate that a generic solid oral opioid drug product is no less abuse deterrent than 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.

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.

To date, the FDA has approved seven extended-release/long-acting (ER/LA) opioids with labeling that describes abuse-deterrent properties and has an additional thirty in the pipeline for approval, including ADF generics.

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

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, 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 Services

Altasciences' full-service capabilities for abuse potential studies provide a one-stop solution in support of HAP studies for NCEs or ADFs. We have conducted close to 40 HAP/substance abuse studies for pharmaceutical/biotech companies in both the U.S. and Canada in the last 5 years. Our research includes studies for stimulants, opioids, cannabinoids, and sedative hypnotics.

In order to deal with the more challenging subject populations involved in HAP studies, we have designed and built Clinical Pharmacology Units (CPUs) that allow for reconfigurable and adaptable space. For example, one of our CPUs consists of a 30-bed, locked, limited-access, self-contained unit incorporated into the overall footprint of the 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), or 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.

In support of the FDA's increasingly strict regulations on tobacco products, our facilities are also ideally suited for studies on smoking behavior, including abuse liability and the pharmacokinetic analysis of nicotine. We have built rooms designed to support studies using the human laboratory model of smoking behavior, which allow us to test combustible or vaped cannabis, or cannabinoids, and ensure that we are uniquely qualified to conduct all types of specialized HAP studies.

Our clinical research pharmacists have been trained at the Professional Compounding Centers of America and have specialized abuse-deterrent preparation and manipulation training, as well as experience in formulating and dosing via several routes of administration (including oral, sublingual, intranasal, and parenteral). Their capabilities also include 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	
Amphetamine Mixed Salts	Naloxone
Buprenorphine/Norbuprenorphine	Naloxone 3-glucuronide
Codeine (and metabolites)	Naltrexone
Hydrocodone	Naltrexone/6β-naltrexol
Hydromorphone	Tetrahydrocannabinol (THC)
Lorazepam	11-OH-THC
Methylphenidate (chiral method also available)	Cannabidiol
Morphine Noroxycodone	Tramadol/O-desmethyltramadol
M6G	Carbamazepine
Oxycodone/Noroxycodone/Oxymorphone	Eslicarbazepine
Zolpidem	Oxcarbazepine/2H
Chiral Amphetamine (R and S)	OH Carbamazepine
Methadone	Alprazolam
Apomorphine	Midazolam/1-Hydroxymidazolam

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 allows 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, and over 50,000 smokers) 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 very intense, as they are very 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 any changes in mood states.

At Altasciences, we validate our studies by assessing the abuse potential of the test drug by comparing responses of that 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.

In addition, we work with specialized organizations like Altreos Research Partners to provide sponsors with scientific and regulatory input on abuse liability assessments for novel and ADFs, and ensure we meet the specific individual requirements of each sponsor. The latter can help save months of time dedicated to reviews and revisions.

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	2-3 weeks
Timing	Usually initiated in Phase II.
FDA Review Timeline	Up to 4 months for the CSS to review outlines or protocols.
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 – cigarette and marijuana smokers should be discussed.
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 2 doses of the active control.
Dose Selection: Treatment Phase	Typically 2-3 doses of the test drug are selected, ranging from a therapeutic dose to supratherapeutic dose.
Positive Control	Typically 2-3 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.

Supporting Case Study — Evaluating the Abuse Potential of Mirogabalin

The current standard in the management of neuropathic pain (as per the International Association for the Study of Pain) includes a range of pharmacological interventions, including selective ligands for the $\alpha_2\delta$ subunit of voltage-gated calcium channels, such as gabapentin and pregabalin. While both these compounds are effective, they have been shown to exhibit the potential for abuse and misuse, especially in individuals with a history of opioid or benzodiazepine use. In addition, they have been associated with a high incidence of AEs, particularly dizziness and somnolence.

Mirogabalin is a novel $\alpha_2\delta$ ligand that has been shown to have effective analgesic properties. This is based on a recently completed Phase II proof-of-concept study in patients with diabetic peripheral neuropathic pain. Our clinical site in Kansas (Vince & Associates) was selected to work with Daiichi Sankyo in evaluating mirogabalin as a well-tolerated $\alpha_2\delta$ ligand with low abuse potential.

The human abuse potential study was designed as 2 independent studies intended to evaluate the abuse potential of mirogabalin versus a) placebo and diazepam, and b) placebo and pregabalin, in recreational drug users. Each study was divided into 2 parts: a qualification phase intended to enrich the study population with subjects that could provide accurate subjective assessments (reducing the number of false positives and negatives), and an assessment phase where mirogabalin was formally evaluated against the corresponding positive and negative controls.

The study comparing mirogabalin to diazepam was conducted as a randomized, placebo and active-controlled crossover study involving recreational polydrug users who had a history of CNS depressant use. Subjects fulfilling the inclusion/exclusion criteria entered a qualification phase where they were assessed for their ability to discriminate 20 mg of diazepam from a matching placebo in a crossover design.

A validated electronic VAS was used to measure Drug Liking and determine eligibility to enter the assessment phase. The assessment phase was designed as a 5-way crossover study in which subjects were randomized to either a 15 or 45 mg dose of mirogabalin, a 15 or 30 mg dose of diazepam, or matching placebo tablets, in each treatment period. Subjective VAS ratings on the likeability and general effects of the treatment were recorded at specific times in each period.

Safety and pharmacokinetics were also assessed. To ensure subject compliance and safety, all participants were confined in the clinic for the duration of the assessment phase (approximately 30 days). Of the 38 subjects who entered the assessment phase, 32 completed the study.

In evaluating the abuse potential of mirogabalin against pregabalin, a single ascending dose study in 24 subjects was first conducted to evaluate 3 doses of mirogabalin. The data from this study was used to select the doses to be used in the abuse potential study, which had a similar design

to the diazepam study. Subjects that were successfully able to discriminate between 300 mg of pregabalin and the matching placebo during the qualification phase were entered into the assessment phase of the study, which was conducted as a 6-way crossover design. In each period, subjects were randomized to a 15, 60, or 105 mg dose of mirogabalin, a 200 or 450 mg dose of pregabalin, or matching placebo tablets. Subjective VAS ratings on the likeability, similarity, and general effects of the treatment were recorded at specific times in each treatment period. As in the diazepam study, safety monitoring, pharmacokinetic sampling, and a long confinement period were incorporated into the study design. Of the 56 subjects who entered the assessment phase, 44 received all 6 treatments, and 41 completed the study.

In both studies, the planned therapeutic dose of mirogabalin (15 mg) did not have maximal Drug Liking scores different from the placebo. These scores were also found to be significantly less than therapeutic doses of diazepam and pregabalin. At supratherapeutic doses of 45 mg, the maximal effects of mirogabalin on Drug Liking, Positive Effects High, and Good Drug Effects were not significantly different from the placebo and markedly less than either dose of diazepam. In comparison to 200 mg pregabalin, doses of greater than 4 times the therapeutic dose of mirogabalin were required to achieve a similar level of abuse potential. The overall incidence of AEs of 15 or 45 mg of mirogabalin was comparable to, or lower than the placebo in both studies. The incidence of AEs of mirogabalin was comparable to 200 mg of pregabalin, only at supratherapeutic doses.

Overall, these studies showed that a therapeutic dose of mirogabalin is a safe and well-tolerated $\alpha_2\delta$ ligand with low potential for abuse in recreational polydrug users.

Pioneering Future Research

To protect the public's health, the FDA has made it one of its top priorities to reevaluate 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 will continue 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 recently awarded a 5-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 cements 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, 5-year contract with the FDA, 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 pharmacokinetic study of opioids manipulated via milling procedures.

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About Altasciences

Altasciences is a forward-thinking, mid-size contract research organization offering pharmaceutical and biotechnology companies of all sizes a proven, flexible approach to preclinical and early phase clinical studies, from lead candidate selection to proof of concept. For over 25 years, Altasciences has been integrating into clients' projects to help support educated, faster, and more complete early drug development decisions. Altasciences' full-service solutions include preclinical safety testing, clinical pharmacology, bioanalysis, program management, medical writing, biostatistics, data management and more, all of which can be tailored to specific sponsor requirements.

Altasciences… helping sponsors get better drugs to the people who need them, faster.

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