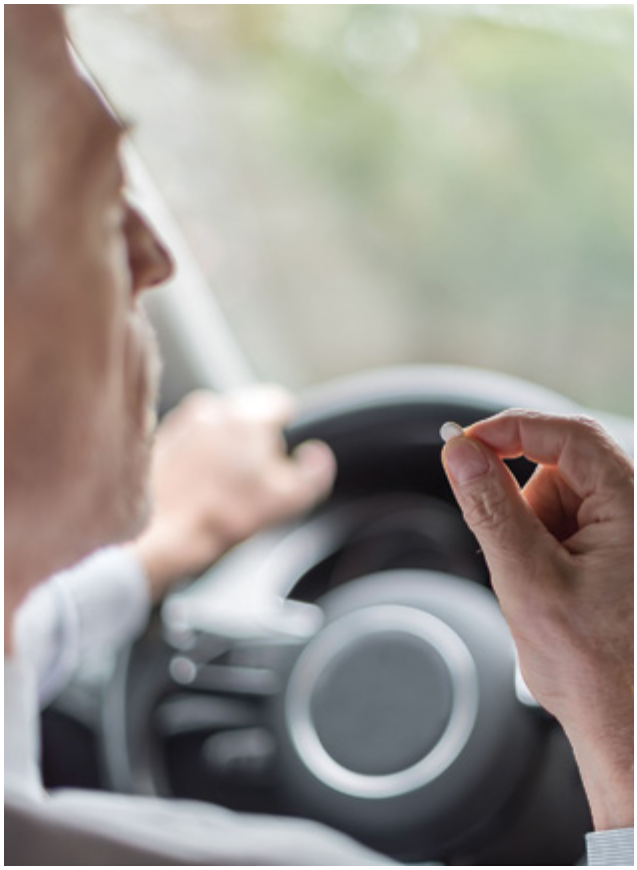
ALTASCIENCES

The Altascientist

ISSUE NO. 1

FDA Finalizes Drug-Impaired Driving Guidance, Leading to Additional Studies on the Effects of Drugs on Driving

Reducing the incidence of motor vehicle accidents (MVAs) that occur because of drug-impaired driving is a public health priority. With more than 6,800 FDA-approved drugs, many of which contain psychoactive or sedative pharmaceutical ingredients which could alter the ability to operate a motor vehicle, it is crucial to put in place a systematic effort to identify the drugs that increase the risk of MVAs. This is a critical component in assessing drug risk and designing strategies to reduce this risk.



In 2015, the draft guidance detailing the FDA's current thinking and expectations around how and when to assess a new drug's ability to affect driving was released to address this concern. In November of 2017, after receiving industry feedback, the FDA finalized the guidance entitled *Evaluating Drug Effects on the Ability to Operate a Motor Vehicle* and maintained all of the key aspects of the draft guidance. Namely, the guidance proposes a tiered approach consisting of pharmacological/toxicological, epidemiological, and standardized behavioral assessments to evaluate possible drug effects on driving, starting early in clinical development. The inclusion of these assessments represents a dramatic shift in the current design of early phase studies as most early clinical studies currently only assess self-reported adverse events related to cognition instead of directly measuring them.

This is not to say that every drug will have to undergo this tiered evaluation. The first considerations in determining whether the effect of a drug on driving should be evaluated are the conditions for use of the drug and the intended patient populations. As an example, an anesthetic used for surgery will not need to undergo in-depth cognitive assessments, as long as the time course of the pharmacokinetics shows that drug levels are minimal by the time patients leave the hospital. On the other hand, drugs intended for chronic (including chronic-intermittent) outpatient use by adults who drive will most likely need to be evaluated to assess their effects on driving, whether they are psychoactive or non-psychoactive. Although there is a focus on psychoactive drugs in the new guidance, there is also clear indication that special care is needed during the development of non-psychoactive drugs, since they can also indirectly impair the ability to drive.

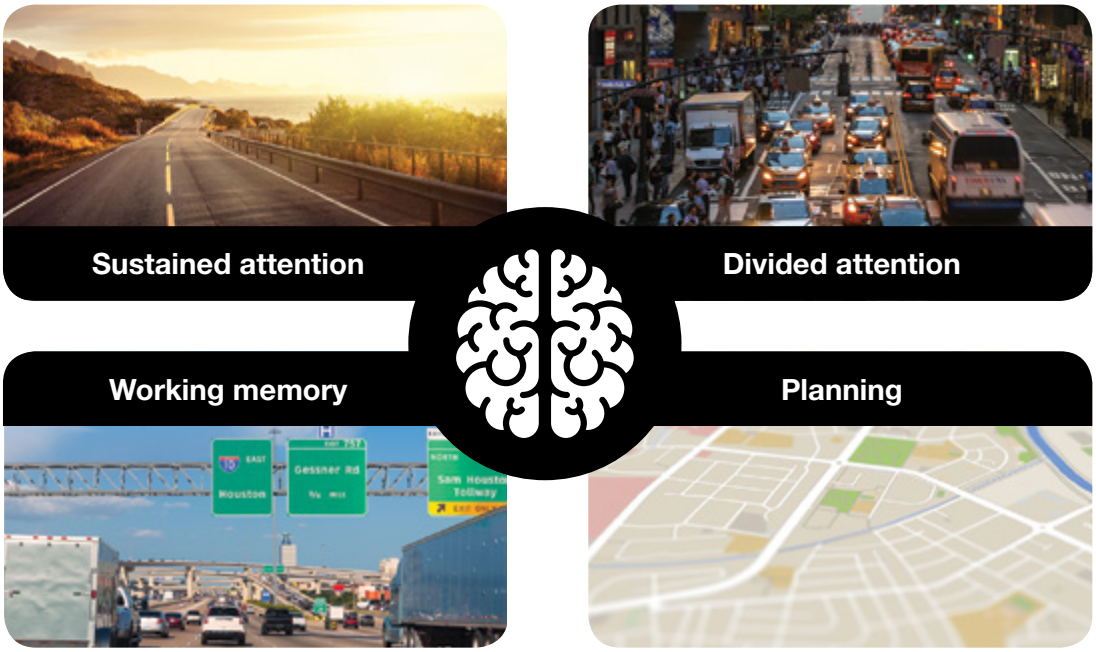
Driving Simulation Testing and CNS Side Effect Specificity

Driving, a complex activity involving a wide range of cognitive, perceptual, and motor skills helps to facilitate everyday life, with Americans reportedly driving more than three trillion miles in 2015. Consequentially, the impact drugs have on driving is an integral consideration with regard to designing medication regimens.

The FDA guidance indicates that testing in the early stage of clinical development should emphasize sensitivity over specificity in CNS effects. While driving or driving simulations do not need to be tested early in development, the cognitive domains that are important for driving should be examined. As such, various psychomotor and neuropsychological tests, including measures of reaction time, divided attention, selective attention, and memory may be appropriate.

If accumulating data suggests a potential for driving impairment, then more general CNS function tests may be needed to refine the assessment of the clinical effect of impairment. Such studies can be carried out with either actual motor vehicles or driving simulators, on patient populations likely to use the drug, including the elderly, instead of healthy volunteers.

It is important that studies of driving impairment assess drug effects at the highest exposures expected to be encountered in clinical use. Generally, studies should be conducted to evaluate both the initial effects of drug exposure and the effects after chronic exposure, as it is important to determine the time course and extent of any tolerance that develops in order to instruct patients adequately about the safe use of the drug in question.



The occurrence of adverse CNS events in even a small number of Phase I subjects can indicate the need for more focused studies of CNS effects. If there is initial evidence of impairing effects, additional Phase I studies should examine CNS impairment over the full range of drug exposures that may occur in Phase II and III studies. For drugs identified in early development as having a high potential to cause impairment, patients should be monitored in Phase II and III studies for signs and symptoms of psychoactive effects that could place the individual at unacceptable risk.

For certain drugs intended to be dosed at night, including drugs for sleep disorders, adverse CNS effects cannot be assumed to be absent at the lower levels expected during the following day, especially in the morning. Focused studies of CNS effects during the day after dosing, as guided by blood levels, may be needed to identify the risk of driving.

Generating accurate and reliable data for such studies is undoubtedly a challenge for any contract research organization (CRO). Altasciences has overcome the challenge with the use of an advanced driving simulator that has proven to be a game-changer in the course of these types of complex studies.

Cognitive Studies with State-of-the-Art Driving Simulator

Altasciences and Cognitive Research Corporation (CRC) have partnered to provide sponsors with a leading-edge driving simulator study solution to test the impairing effects of a wide variety of drugs on driving abilities in both normal and patient populations. The simulator provides accurate driving performance data comparable in sensitivity to over-the-road-testing, but in less time, for less cost, and with no risk of property damage or injuries. This customized driving simulator can also be used to evaluate the effects of age, trauma, neurologic disease, alcohol and fatigue on driving performance. Data from the simulator developed by CRC has been used to support applications that were approved by the FDA and EMA.

Some of the simulator's key features, which can be used to detect cognitive changes in categories such as sustained attention, divided attention, working memory, and planning, include the following:

Automated Measurements

The simulator provides automated measurements of psychomotor functioning, divided attention, situational awareness and other cognitive behaviors.

Three-Dimensional Graphics

The simulator utilizes advanced three-dimensional (3D) graphics to generate realistic representations of various driving environments.

Auditory Feedback

Auditory feedback is provided for engine speed, acceleration limits, and for indication of excessive cornering speed, or excessive deceleration when braking.

These data point assessments culminate to provide accurate and detailed accounts in Standard Deviation of Lateral Position (SDLP) during simulated driving, which measure the ability of drivers to stay in the center of their lane; a task that has been shown to be impaired by alcohol or drugs.

Altasciences Supportive Case Studies

Clinical Study Planning Challenges of Driving Studies: A Case Study

The release of the FDA guidance on the impact of drugs on driving abilities has highlighted the importance of delivering reliable cognitive assessment programs with regard to potential driving impairment risks.

As detailed by the guidance, these studies require the same participant to perform multiple drives with double-blinded administration of the test drug (sometimes at two different doses), a positive control group and placebo arms. An important factor to take into account in the dosing schedule is the use of the same simulator for the on-study testing at approximately the same time of day (same period of time after dosing) for all subjects, in an effort to reduce variability. These three or four-way crossover studies require thorough planning to ensure success during the execution phase.

In a recent study that required 80 subjects to be assessed while using the driving simulator, Altasciences had to recruit enough participants to screen over 260 potential subjects. The two-stage screening process resulted in a 45% screen fail rate in Stage 1, which focused on demographics and medical history, and a 22% rejection rate in Stage 2, which evaluated motion sickness caused by the simulator and participants' baseline driving abilities.

The four-way crossover study offers a good example of how careful planning can reduce the overall timelines. First, eight rooms were built at Altasciences' clinical facility to house the driving simulators, as each simulator needed to be isolated so there would be no distractions for the subjects. In addition, having more simulators set up allowed us to test larger groups of subjects in a given time.

With the desire to keep the time between First Patient First Visit (FPFV) to Last Patient Last Visit (LPLV) as short as possible, two scheduling scenarios using the eight simulators were assessed: a non-overlapping seven-day wash-out design, and an overlapping 15-day wash-out, in conjunction with a dosing/driving regimen involving in-house dosing, driving tests, home dosing, and wash-out periods. The 15-day wash-out scenario demonstrated study timeline improvements of 16% (from 107 days to 89 days from FPFV to LPLV), delivering the best overall results to reduce total study duration when compared to seven-day wash-out scenarios.

Overall, the analysis showed that a flexible screening process, an efficient dosing schedule, and sufficient clinical space and availability of a closed room to install the driving simulators are all critical aspects to ensure the reliability of the data, and the executional success of the studies. In addition, the number of available driving simulators is an important element to consider in the study planning based on the study design, sample size and expected timeline.

Driving Assessment: Flibanserin (Addyi) Case Study

Flibanserin is a centrally-acting, multifunctional serotonin agonist/antagonist that was developed for the indication of hypoactive sexual desire disorder (HSDD) in premenopausal women. During development, the most common adverse effects (AEs) reported after dosing were dizziness (11.4%), somnolence (11.2%), nausea (10.4%) and fatigue (9.2%). Therefore, to prevent these AEs from having an impact on the ability to drive, chronic bedtime oral dosing was suggested.

Altasciences conducted novel endpoint research to determine the extent of next-day impairment in cognition and alertness, and determine if nighttime dosing was the correct approach and if a warning would be necessary.

A randomized, double-blind, placebo-controlled, four-way crossover study was performed to evaluate the potential next-morning residual effects after bedtime dosing in 72 healthy premenopausal women. Treatment arms included a placebo administration group (acute and chronic), a positive control zopiclone group (7.5 mg qhs; acute only), and two separate dosage groups of flibanserin, which included 100 mg qhs (acute and chronic) or 200 mg qhs (acute after 100 mg chronic). Assessments were based on simulated driving, a Symbol Digit Coding Test (SDCT), and the Karolinska Sleepiness Scale (KSS).

Evaluation of next-day impairment during simulated driving revealed bedtime administration of flibanserin (up to 200 mg) did not impair next-day cognitive function or driving performance, while improving symptoms of HSDD. Women dosed with 100 mg qhs flibanserin before bed were found to have significantly ($p<0.01$) lower ΔSDLP values compared to acute and chronically dosed placebo groups. No statistically significant differences were found between groups dosed with 100 mg flibanserin versus 200 mg.

Altasciences was able to demonstrate that there was no impairment to driving the morning after nighttime dosing of flibanserin in premenopausal women. The study, sponsored by Sprout Pharmaceuticals, was described as “reassuring” by the FDA.

Regulatory Recommendations and Requirements

Early clinical cognitive testing and dedicated driving simulation studies can help in assessing cognitive functions for safety and efficacy in drug development. Altasciences has the expertise and experience to meet all the FDA guidance requirements with regards to dedicated driving studies and assessment of clinical effect impairments. Our innovative and intuitive driving simulation studies provide the ultimate in CNS side-effect investigation, including detailed driving performance data comparable in sensitivity to over-the-road-testing, but with much faster timelines.

References:

- Evaluating Drug Effects on the Ability to Operate a Motor Vehicle Guidance for Industry (Online). Available: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm430374.pdf
- Fortier, A., Sicard, E., Tupper, S., Legault, E. and Lefebvre, M. (2005). What are the Clinical Study Planning Challenges of Driving Studies: A Case Study (Online). Available: http://abstracts.aaps.org/Verify/NBC15/PosterSubmissions/T2086.pdf
- Important Details about the FDA Draft Guidance (Online). Available: http://www.algopharm.com/microsites/driving_simulator_FDA.html
- Natarajan, K., Sicard, E., Kay, G.G. and Kim, N.N. (2017). Evaluation of Efficacy & Sedation-Related Safety of Flibanserin in Premenopausal Women. *Human Psychopharmacology: Clinical and Experimental, 32*(4).

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.

ALTASCIENCES

altasciences.com
contact@altasciences.com
Tel: 514 246-4191

Follow us
LinkedIn @altasciences