Methods for Prospectively Evaluating Potential Abuse-related Adverse Events in Clinical Studies: Implementation in a Phase 1 Study of S1-221, a Novel Cannabinoid Drug Product in Development for the Acute Treatment of Migraine

Authors: Ryan K. Lanier, PhD,[1*] Sarah Thayer,[2] Joe Seroogy,[2] Terrance Ocheltree, PhD, RPh,[2] Alan M. Rapoport, MD,[2,3] George Pappas[2]

Affiliations: [1]Pinney Associates; [2]Delphian Therapeutics; [3]The David Geffen School of Medicine at UCLA

***Presenting Author: Ryan K. Lanier, PhD (rlanier@pinneyassociates.com)**

Connect with Ryan

Background

Per the United States Food and Drug Administration (FDA's) 2017 abuse potential guidance document, all drugs with central nervous system (CNS) activity under development should be evaluated for abuse potential.[1] A full abuse potential assessment (APA) includes identifying potential abuse-related adverse events (ARAEs) in all clinical safety and efficacy studies. S1-221 is a combination cannabidiol (CBD) and Δ9-tetrahydrocannabinol (THC) product being developed for the acute treatment of migraine. A Phase 1 single ascending dose (SAD) study (DLP-S-0-1.01) was conducted to evaluate the safety, tolerability, and pharmacokinetics (PK) of different doses and ratios of orally administered S1-221 in healthy participants. A total of 8 cohorts consisting of 8 participants each (randomized 6:2, active:placebo) has been completed and data analysis is ongoing. The study evaluated ratios of CBD:THC ranging from 25:1 to 300:1 and doses ranging from 250 to 1000 mg CBD and 2.5 to 10 mg THC. As part of the overall APA strategy for S1-221, potential ARAEs were prospectively evaluated as AEs of special interests (AESIs) using a prespecified list of adverse event (AE) terms recommended by FDA.[1,2]

The objectives of this presentation are to:

(1) Provide background information about the importance of collecting ARAE data as part of an overall APA of a drug in development, and

(2) Summarize the methods used to monitor for AESIs in study DLP-S-0-1.01 and present results of the evaluation in the form of AESI narratives

What is Abuse Potential & Why Assess It?

*"**Drug abuse** is defined as the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desired psychological or physiological effect. Therefore**, abuse potential refers to the likelihood that abuse will occur with a particular drug product or substance with CNS activity.**"*[1]

Why assess it?[3,4]

- Required by law per the Controlled Substances Act (CSA) (1970) to assist with scheduling and labeling of approved medications
- Part of the overall safety assessment of a drug in development
- Scheduling is intended to protect the public health by controlling the prescribing and use of drugs that may have addictive potential, but not limit their access by patients who need them
- All Schedule I (CI) drugs subsequently approved by FDA require rescheduling by the Drug Enforcement Administration (DEA) to CII to CV

Abuse Potential Assessment During Drug Development

Data on the drug's abuse potential can be obtained at critical times throughout the drug development process:[5]

Assessing Abuse Potential in Clinical Studies

*"All clinical safety and efficacy studies should be evaluated for **CNS-related AEs** that may suggest the test drug produces effects that will be sought out **for abuse purposes**."*[1]

Key recommendations from FDA:[1,2]

- Develop a **prespecified list of potential abuse-related AEs** that will be closely monitored
- **Phase 1 studies are of particular importance**, especially analysis of supratherapeutic doses which tend to produce a greater degree of abuse-related AEs
- Phase 2 and 3 studies in patients may produce different signals (e.g., dose differences, duration of dosing, effects of disease state or use of concomitant medications)
- If available, analyze **PK data** to better understand if there is a relationship between drug exposure and abuse-related AEs
- Collect data on the timing of the event in relation to drug administration, duration of the event, severity of the event, and co-occurrence with other events
- The presence of a **euphoria-like response** is a key observation in the clinical assessment of whether a test drug has abuse potential, although absence of euphoria does not indicate absence of abuse potential

Assessing Abuse Potential in Phase 1 SAD Study DLP-S-0-1.01

Overview of Methods for Assessing ARAEs:

- Investigators and site staff were trained prior to study start to identify ARAEs using a prespecified list of MedDRA AE terms based on FDA recommendations[1,2] and to collect sufficient information so narratives could be written
- Combined AESI/Serious Adverse Event (SAE) case report forms (CRFs) were developed and included a section for collecting additional event information required for narratives
- Event-related information from participants and study staff was collected in real-time (or near real-time) to allow for more comprehensive, detailed narratives
- Narratives were written like medical discharge summaries or SAE reports

Sample Case Report Forms:

Pre-Specified List of AEs[2] Used to Assess Abuse Potential in Phase 1 Study DLP-S-0-1.01

- ***Euphoria-related terms:***
  - Elevated mood, euphoria, euphoric mood, feeling drunk, feeling of relaxation
- ***Dissociative/psychotic-related terms:***
  - Abnormal behavior, amnesia, delirium, delusion, delusion of grandeur, delusional perception, mixed delusion depersonalization, derealization, disturbance in attention, hallucination, hypnagogic hallucination, hypnopompic hallucination, hallucination auditory, hallucination gustatory, hallucination olfactory, hallucination synesthetic, hallucination tactile, hallucination visual, hallucinations mixed paranoia, psychotic disorder, acute psychosis, transient psychosis, substance-induced psychotic disorder, sensory disturbance, thinking abnormal
- ***CNS stimulation terms:***
  - Affect liability, aggression, agitation, anxiety, disinhibition, energy increased, feeling jittery, flight of ideas, hypervigilance, irritability, psychomotor hyperactivity, restlessness
- ***CNS depression terms:***
  - Bradyphrenia, depression, dysphoria, hypersomnia, hypersomnia related to another mental condition, sedation, infant sedation, neonatal oversedation, post-injection delirium sedation syndrome, sedation complication, sedative therapy, somnolence, somnolence neonatal, stupor
- ***General terms:***
  - Drug abuse, drug abuser, substance abuser, substance abuse, drug use disorder, drug use disorder antepartum, drug use disorder postpartum, substance use disorder, drug diversion, drug dependence, dependence, drug dependence antepartum, drug dependence postpartum, substance dependence, drug withdrawal syndrome, drug withdrawal convulsions, drug withdrawal headache, drug withdrawal maintenance therapy, drug withdrawal syndrome neonatal, withdrawal arrhythmia, withdrawal catatonia, withdrawal hypertension, withdrawal syndrome
- ***Terms not captured elsewhere:***
  - CSSR abnormal, confusional state, disorientation, emotional disorder, feeling abnormal, homicidal, inappropriate affect, overdose, logorrhea, mania, memory impairment, mental disorder, mood altered, mood disorder, mood disorder due to a general medical condition, substance induced mood disorder, substance-induced mood disorder, mood swings, suicidal ideation, intentional misuse of drug delivery system, intentional product misuse, prescription form tampering, product tampering, suspected product tampering

Narratives for Potential Abuse-related AEs

- Narratives were written for certain abuse-related AEs according to FDA recommendations[2] (see list below)

Narratives are recommended for Certain Abuse-Related AEs (MedDRA PTs)

1. Affect Lability
2. Aggression
3. Delusion
4. Depersonalisation
5. Derealisation
6. Disinhibition
7. Drug abuse
8. Drug diversion
9. Drug dependence, drug withdrawal syndrome
10. Elevated mood
11. Energy increased
12. Euphoria, euphoric mood
13. Feeling drunk
14. Feeling jittery
15. Feeling of relaxation
16. Flight of ideas
17. Hallucinations
18. Hypersomnia
19. Hypervigilance
20. Intentional overdose
21. Intentional product misuse
22. Psychomotor hyperactivity
23. Psychotic disorder
24. Sedation
25. Somnolence

Study DLP-S-0-1.01 AESI Narratives Include:

- Age and sex of participant
- Medical history
- Signs and symptoms of AE being discussed
- Verbatim information from participants and observations from Investigators and study staff
- Timing of the event in relation to drug administration
- Duration, relationship, and severity of the event
- If >1 AE was reported, information on all events
- PK measures to determine if there was a correlation between onset and duration of the event and drug exposure
- Concomitant meds with relative start dates to AE
- Treatments provided (if any)
- Pertinent clinical data (e.g., key physical exam findings or lab results)
- Subjective drug effects visual analog scale (VAS) results
- Outcomes and resolution

Results

- Commonly reported ARAEs included "feeling of relaxation" and "somnolence"
- All ARAEs were mild & transient and most occurred within 1-4 hours after dosing, when maximum plasma concentrations of THC were expected to occur
- Narratives included verbatim descriptions of symptoms, contextual information regarding the nature of the events, examinations when performed, and details about potentially positive vs negative experiences
- Narratives for participants with multiple ARAEs allowed for a better understanding of time course and the evolving nature of events and effects post-dose

Examples of Detailed Narratives from Phase 1 Study DLP-S-0-1.01

Study Title: A Phase 1 Double-blind, Randomised, Placebo-controlled Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses of S1-221 Following Oral Administration
Sponsor: Delphian Therapeutics
Protocol Number: DLP-S-0-1.01
Subject ID: 1-200
AESI ID(s): DLPS0101-2026-1200-AESI-22
Investigator: Dr Philip Ryan, Nucleus Network, Melbourne, Australia

Event/s: Feeling of relaxation

A 31-year-old white non-Hispanic or Latino male weighing 79.4 kg (height 178.4 cm) was consented for this study on 17/Feb/2026. At the time of enrolment, the participant was a healthy volunteer with no ongoing medical history conditions. The participant was assigned to study Part A, Cohort 8.

On 11/Mar/2026 at 09:00 hrs, following an overnight fast of 10 hours duration, a single dose of blinded study treatment (10 ml) was administered.

On 11/Mar/2026 at 11:21 hrs (approximately 2 hours after administration of study drug), the participant experienced the AESI event 'feeling of relaxation'. On the visual analog scale (VAS) assessment at 2 hours post-dose, he reported feeling "relaxed" and "tired". Regarding the tiredness, he reported poor sleep overnight with multiple overnight disruptions and early start for assessments. The relaxation was not reported at the 30 minutes and 1 hour post-dose assessments. Other than feeling relaxed, he reported no other symptoms and no distress. On examination, he was comfortable with GCS 15, and was holding conversations although appeared tired. Cranial nerve examination was normal, there was full range of neck motion, and power assessment was rated 5/5. At 6 hour post-dose, VAS score was 'not at all' for study drug effect, and the participant reported still feeling tired, generally calm but not feeling
effects of relaxation. He denied other symptoms. His mood was settled and calm without excessive relaxation. The participant reported that he felt the tiredness was in keeping with poor sleep overnight. On examination, he appeared comfortable.
No action was taken in relation to study drug as a result of this event, and no medication or other action was taken for treatment of the relaxed event. No laboratory testing or other investigations were performed for the event. The event 'feeling of relaxation' was resolved
on 11/Mar/2026 at 19:00 hrs, and was mild (Grade 1) in severity.

Concomitant Medications:
None

Relevant Medical History:
None

INVESTIGATOR AND SPONSOR ASSESSMENT OF CAUSALITY
The investigator considered the event 'feeling of relaxation' to be possibly related to study drug, and not related to other study treatments. The Medical Monitor/Sponsor assessed the relationship of the event 'sensory disturbance' to be possibly related to study drug, and not related to other study treatments.

Study Title: A Phase 1 Double-blind, Randomised, Placebo-controlled Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses of S1-221 Following Oral Administration
Sponsor: Delphian Therapeutics
Protocol Number: DLP-S-0-1.01
Subject ID: 1-133
AESI ID(s): DLPS0101-2025-1133-AESI-12
Investigator: Dr Philip Ryan, Nucleus Network, Melbourne, Australia

Event/s: Feeling of Relaxation; Closed Eye Visual Imagery

A 34-year-old mixed race Hispanic or Latino male weighing 83 kg (height 170.1 cm) was consented for this study on 21/Nov/2025. At the time of enrolment, the participant was a healthy volunteer with no ongoing medical history conditions. The participant was assigned to study Part A, Cohort 5.

On 02/Dec/2025 at 09:50 hrs, following an overnight fast of 10 hours duration, a single dose of blinded study treatment (10 ml) was administered.

On 02/Dec/2025 at 13:55 hrs (approximately 4 hours after administration of study drug), the participant experienced the AESI event 'feeling of relaxation', which was reported as a pleasant, positive feeling of relaxation. He described feeling "peaceful". On examination he appeared clinically well, with GCS 15. No action was taken in relation to study drug as a result of this event, and no medication or other action was taken for treatment of the event. No laboratory testing or other investigations were performed for the event. The event was resolved on 03/Dec/2025 at 09:32 hrs. The event 'feeling of relaxation' was mild in severity.

On 02/Dec/2025 at 21:55 hrs (approximately 12 hours post-dosing), the participant reported that he had started to develop closed-eye visual imagery, described as seeing colourful buildings on closing his eyes. He reported that the imagery was not disturbing him or negatively impacting him in any way. On examination he appeared calm and settled, with GCS 15. The symptoms were ongoing until approximately 24 hours later, when during medical review both symptoms had fully resolved. No action was taken in relation to study drug as a result of this event, and no medication or other action was taken for treatment of the event. No laboratory testing or other investigations were performed for the event. The event was resolved on 03/Dec/2025 at 14:00 hrs. The event 'closed eye visual imagery' was mild in severity.

Concomitant Medications:
None reported

Relevant Medical History:
None

INVESTIGATOR AND SPONSOR ASSESSMENT OF CAUSALITY
The investigator considered the event 'feeling of relaxation' to be probably related to study drug, and not related to other study treatments. The Medical Monitor/Sponsor assessed the relationship of the event 'feeling of relaxation' to be probably related to study drug, and not related to other study treatments.
The investigator considered the event 'closed eye visual imagery' to be probably related to study drug, and not related to other study treatments. The Medical Monitor/Sponsor assessed the relationship of the event 'closed eye visual imagery' to be probably related to study drug, and not related to other study treatments.

Study Title: A Phase 1 Double-blind, Randomised, Placebo-controlled Study Evaluating the Safety, Tolerability, and Pharmacokinetics of Single Ascending Doses of S1-221 Following Oral Administration
Sponsor: Delphian Therapeutics
Protocol Number: DLP-S-0-1.01
Subject ID: 1-218
AESI ID(s): DLPS0101-2026-1218-AESI-21
Investigator: Dr Philip Ryan, Nucleus Network, Melbourne, Australia

Event/s: Sensory Disturbance; Energy Increased

A 24-year-old white, non-Hispanic or Latino male weighing 74.2 kg (height 183.5 cm) was consented for this study on 26/Feb/2026. At the time of enrolment, the participant was a healthy volunteer with no ongoing medical history conditions except hay fever. The participant was assigned to study Part A, Cohort 8.

On 11/Mar/2026 at 09:15 hrs, following an overnight fast of 10 hours duration, a single dose of blinded study treatment (10 ml) was administered.

On 11/Mar/2026 at 10:08 hrs (approximately 45 minutes after administration of study drug), the participant experienced the AESI event 'sensory disturbance'. On 11/Mar/2026 at 11:15 hrs, the participant experienced the AESI event 'energy increased'. On the visual analog scale (VAS) assessment at 30 minutes and 1 hour post dose, he reported whole body "tingling" and "clear head". Ther were no pins and needles, or pains. He described his muscles as "vibrating outwards", particularly in his arms and legs. There was no dizziness, headache or nausea. The "clear head" was described as opposite of a headache. Neurological examination was normal. At the 2 hours post-dose VAS assessment, he reported feeling "more alert" and having "more energy"; this peaked at 2 hours post-dose. This was despite poor sleep overnight and feeling tired pre-dose. He denied any restlessness or flight of ideas. On examination he was holding a conversation well. The sensory disturbance and increased energy improved throughout the day. By 10 hours post-dose, he reported feeling calmer with no signs of agitation or restlessness on review. No other abnormal sensory, mood or psych symptoms were described. The sensory disturbance was also resolved by 12 hours post-dose.
No action was taken in relation to study drug as a result of this event, and no medication or other action was taken for treatment of the relaxed event. No laboratory testing or other investigations were performed for the event. The event 'sensory disturbance' was resolved on 11/Mar/2026 at 20:06 hrs, and was mild (Grade 1) in severity. The event 'energy increased' was resolved on 11/Mar/2026 at 19:00 hrs, and was mild (Grade 1) in severity.

Concomitant Medications:
None

Relevant Medical History:
Hay Fever since Unk/Unk/2013

INVESTIGATOR AND SPONSOR ASSESSMENT OF CAUSALITY
The investigator considered the event 'sensory disturbance' to be probably related to study drug, and not related to other study treatments. The Medical Monitor/Sponsor assessed the relationship of the event 'sensory disturbance' to be probably related to study drug, and not related to other study treatments.
The investigator considered the event 'energy increased' to be probably related to study drug, and not related to other study treatments. The Medical Monitor/Sponsor assessed the relationship of the event 'energy increased' to be probably related to study drug, and not related to other study treatments.

Note: Narratives shown here are **drafts** and unblinded dosing information, PK results, and other pertinent details are not yet available for inclusion.

Conclusions

- Evaluating ARAEs can provide critical data as part of the overall APA of a drug to aid in labeling and scheduling decisions
- Monitoring and reporting of ARAEs needs to be well-planned, prospective, and systematic
- Narratives of ARAEs provide important context to help determine whether a drug is likely to be sought out for rewarding effects
- Methods and recommendations from FDA for evaluating ARAEs were successfully implemented in a Phase 1 study of S1-221
- All ARAEs in this study were mild, transient, and expected based on the pharmacology of S1-221 (CBD & THC combination)
- While none of the ARAEs reported in the study met the reporting criteria for seriousness (SAE), the ICH E3 standard for SAE narrative writing was applied to provide a comprehensive, chronological accounting of each event (or combined events) to inform the assessment of severity, causality, and criteria for abuse potential
- ARAE data and narratives from this study provide detailed insight into the initial safety and abuse potential of a novel and promising acute treatment for migraine and suggest that the product is optimized for further development

References: 1) Food and Drug Administration. Assessment of Abuse Potential of Drugs. (2017, January). Guidance for Industry, U.S. Department of Health and Human Services, Center for Drug Evaluation and Research, Washington, DC. 2) Galati S. Identifying relevant adverse events of interest and recommendations for analysis and presentation of data in the NDA submission. Presented at: Advancements and Challenges in Abuse Potential Evaluation Cross-Company Abuse Liability Council Meeting; September 27, 2023; Rockville, MD, USA. 3) Calderon SN, Bonson KR, Reissig CJ, et al. Considerations in assessing the abuse potential of psychedelics during drug development. *Neuropharmacology*. 2023;224:109352. 4) Henningfield JE, Comer SD, Banks ML, et al. Abuse potential assessment of novel central nervous system active and psychedelic substances for controlled substances act scheduling recommendations. *J Psychopharmacol*. 2025:2698811251378511. 5) Figure adapted from Dr. Mike Klein, FDA at DIA 2008.

Disclosures: Delphian Therapeutics sponsored this clinical study. Delphian is developing S1-221 for the acute treatment of migraine attacks, supported by NIH/NIDA under Award Number R44DA051309. Pinney Associates provides consulting support to developers of CNS-active drugs, including Delphian.